Contents

[Overview and Recommendations 2](#_Toc170372784)

[Background 2](#_Toc170372785)

[Evaluation 3](#_Toc170372786)

[Management 3](#_Toc170372787)

[General Information 6](#_Toc170372788)

[Description 6](#_Toc170372789)

[Definitions 6](#_Toc170372790)

[Types 7](#_Toc170372791)

[Epidemiology 8](#_Toc170372792)

[Who Is Most Affected 8](#_Toc170372793)

[Incidence/Prevalence 8](#_Toc170372794)

[Risk Factors 16](#_Toc170372795)

[Associated Conditions 27](#_Toc170372796)

[Etiology and Pathogenesis 27](#_Toc170372797)

[Causes 27](#_Toc170372798)

[Pathogenesis 28](#_Toc170372799)

[History and Physical 31](#_Toc170372800)

[Clinical presentation 31](#_Toc170372801)

[History 31](#_Toc170372802)

[Physical 33](#_Toc170372803)

[Performance status scales 35](#_Toc170372804)

[Diagnosis and Staging 35](#_Toc170372805)

[Making the Diagnosis 35](#_Toc170372806)

[Differential Diagnosis 36](#_Toc170372807)

[Testing Overview 37](#_Toc170372808)

[Staging System(s) 37](#_Toc170372809)

[Blood Tests 41](#_Toc170372810)

[Imaging Studies 41](#_Toc170372811)

[Biopsy and Pathology 64](#_Toc170372812)

[Tumor Subtyping, Hormone Receptor and HER2 Testing 77](#_Toc170372813)

[Prognostic Assessment and Predictive Factors for Treatment Decision-making 84](#_Toc170372814)

[Other Diagnostic Testing 90](#_Toc170372815)

[Diagnostic Evaluation During Pregnancy or Lactation 92](#_Toc170372816)

[Management 95](#_Toc170372817)

[Management of early or operable breast cancer 95](#_Toc170372818)

[Management of inoperable locally advanced noninflammatory breast cancer 100](#_Toc170372819)

[Management of inflammatory breast cancer 102](#_Toc170372820)

[Management of locoregional recurrence of breast cancer 103](#_Toc170372821)

[Management of metastatic breast cancer 104](#_Toc170372822)

[Management of breast cancer during pregnancy 111](#_Toc170372823)

[Management of breast cancer in older women 113](#_Toc170372824)

[Complications and Prognosis 120](#_Toc170372825)

[Complications 120](#_Toc170372826)

[Prognosis 122](#_Toc170372827)

[Prognosis 168](#_Toc170372828)

[Survival and Mortality 168](#_Toc170372829)

[Prognostic Tools 173](#_Toc170372830)

[Prognostic Factors 175](#_Toc170372831)

[Recurrence Risk 201](#_Toc170372832)

[BRCA Mutations 208](#_Toc170372833)

[Pregnancy-Associated Breast Cancer 210](#_Toc170372834)

[Pregnancy After Breast Cancer 212](#_Toc170372835)

[Quality of Life 213](#_Toc170372836)

[Prevention and Screening 214](#_Toc170372837)

[Prevention 214](#_Toc170372838)

[Screening 233](#_Toc170372839)

Overview and Recommendations

Overview and RecommendationsOverview and Recommendations

Background

* Breast cancer is a malignancy of the breast tissue and is the most common malignancy diagnosed in women worldwide.
* Early or operable breast cancer is considered potentially curable and includes stage I-IIB and some stage IIIA cancers, specifically T3, N1 tumors.
* Noninflammatory locally advanced inoperable breast cancer is considered potentially curable and includes stage IIIA-C breast tumors with the exception of some stage IIIA, specifically T3, N1 tumors.
* Inflammatory breast cancer is a rare, aggressive subtype of locally advanced breast cancer characterized by a substantial area of breast skin that is red in color, warm, and thickened or swollen (referred to as peau d'orange).
* Advanced (metastatic) breast cancer encompasses disease that has spread beyond the breast and regional lymph nodes and is either de novo stage IV (metastatic at the time of initial diagnosis) or a metastatic recurrence. Common sites of metastases include bone, liver, lung, and brain.
* [Risk factors](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#LIKELY_RISK_FACTORS) for breast cancer include genetic causes, increased age, reproductive history and hormone exposure, lifestyle factors, medical history, and radiation exposure.
* Women with breast cancer may present with breast abnormalities detected during screening, without any other signs or symptoms. [Common signs and symptoms](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#CLINICAL_PRESENTATION) of breast cancer include palpable breast mass, axillary mass, nipple discharge, skin changes on breast or nipple, asymmetric thickening or nodularity, breast pain, or signs and/or symptoms due to metastatic disease.
* The [5-year survival after diagnosis of breast cancer](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#TOPIC_SB4_F3T_1MB__LI_NWV_MV1_4BC) is 99% for women with localized disease, 85% for women with regional spread, and 27% for women with distant metastases in the United States. Factors affecting [prognosis](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-4EBC37FC-4F61-4104-BEE2-8F0DFCB6492C) include tumor and disease characteristics, age, response to therapy, race and ethnicity, and body mass.

Evaluation

* [Diagnosis](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#MAKING_THE_DIAGNOSIS) is based on examination of the breast and axillary lymph nodes with clinical [exam](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#BREAST_EXAM) and [imaging](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#IMAGING_FOR_DIAGNOSIS), and confirmed by the pathological assessment of [biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#BIOPSY_AND_PATHOLOGY).
* Perform imaging including either or both [diagnostic mammogram](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#DIAGNOSTIC_MAMMOGRAPHY) and [ultrasound](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#ULTRASOUND) ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)); [magnetic resonance imaging (MRI)](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#BREAST_MAGNETIC_RESONANCE_IMAGING__MRI_) of breast may also be used in specific circumstances. Recommendations for specific imaging tests vary based on [presentation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#IMAGING_FOR_DIAGNOSIS).
* Pathological assessment of breast is generally performed using [core needle biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#CORE_NEEDLE_BIOPSY), preferably with ultrasound or stereotactic guidance ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)); also perform ultrasound-guided [fine needle aspiration](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#FINE_NEEDLE_ASPIRATION__FNA_) or core needle biopsy of suspicious lymph nodes ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
* Consider testing to assess for distant metastatic disease in patients with inoperable breast cancer and in symptomatic or [high-risk](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#RECOMMENDATIONS_IMAGING_METASTATIC__ANC_441764537) patients with operable breast cancer including [blood tests](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#BLOOD_TESTS), [chest computed tomography (CT)](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#COMPUTERIZED_TOMOGRAPHY__CT_), abdominal ultrasound or abdominal with or without pelvic CT with contrast or magnetic resonance imaging, [bone scan](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#BONE_SCAN), or [fluorodeoxyglucose positron emission tomography (PET)/CT](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#POSITRON_EMISSION_TOMOGRAPHY__PET__AND_PET_CT) ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).

Management

Management of Early and Locally Advanced Noninflammatory Breast Cancer

* [Management](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-FB70B819-89CD-415D-9940-AEA1D4521F31) of breast cancer is based on the disease stage and characteristics, comorbidities, and patient preferences; treatment may include neoadjuvant and/or adjuvant systemic therapy, surgery, and radiation therapy.
* For patients with [early or operable breast cancer](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#MANAGEMENT_OF_EARLY_BREAST_CANCER):
  + Neoadjuvant systemic therapy, using endocrine therapy or chemotherapy (either alone or in combination with human epidermal growth factor receptor 2 [HER2]-targeted therapy), may be indicated for:
    - patients who desire breast-conserving surgery but mastectomy would be required due to tumor size ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF))
    - patients with clinically positive lymph nodes that are likely to become negative with neoadjuvant systemic therapy ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF))
    - patients who may benefit from additional or different adjuvant (post-operative) therapy based on assessment of response to neoadjuvant therapy
  + Locoregional therapy includes surgery to the breast and axilla as well as radiation therapy; offer either
    - breast-conserving therapy by lumpectomy with surgical axillary staging ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)), followed by radiation therapy according to lymph node status:
      * surgical axillary staging may be omitted in select older women with clinically negative lymph nodes
      * radiation may be omitted in select older women with estrogen positive breast cancer who receive adjuvant endocrine therapy
    - total mastectomy with surgical axillary staging ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)) with or without breast reconstruction ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)) and with or without postmastectomy radiation therapy according to lymph node status, tumor size and surgical margins
  + Adjuvant systemic therapy is determined based on tumor size, nodal status, tumor histology, hormone receptor (HR) status, HER2 status, and multigene assays.
* For patients with [inoperable locally advanced noninflammatory breast cancer](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#MANAGEMENT_OF_LOCALLY_ADVANCED_BREAST_CANCER):
  + Neoadjuvant systemic therapy is recommended for all patients with inoperable locally advanced breast cancer ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
  + For most patients with response to neoadjuvant systemic therapy, locoregional therapy follows and includes surgery to the breast and axilla and radiation therapy. Options include:
    - breast-conserving therapy by lumpectomy plus level I/II axillary dissection plus whole breast radiation therapy with or without boost radiation to tumor bed, plus radiation to infraclavicular region, supraclavicular area, internal mammary nodes, and any part of axillary bed at risk ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF))
    - total mastectomy plus level I/II axillary dissection plus radiation therapy to chest wall, infraclavicular region, supraclavicular area, internal mammary nodes and any part of axillary bed at risk, with or without breast reconstruction ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF))
  + Adjuvant systemic therapy should include:
    - adjuvant chemotherapy if not already completed in the neoadjuvant setting ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)); patients with triple-negative tumor and residual invasive cancer after neoadjuvant therapy with taxane, alkylator, and anthracycline based chemotherapy, may receive adjuvant capecitabine ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF))
    - adjuvant endocrine therapy should be offered to patients with HR positive (estrogen receptor and/or progesterone receptor positive) breast cancer ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF))
    - adjuvant HER2 targeted therapy with trastuzumab up to 1 year should be offered to patients with HER2 positive breast cancer ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)), with or without pertuzumab ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).

Management of Inflammatory Breast Cancer

* The management of [inflammatory breast cancer](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#MANAGEMENT_OF_INFLAMMATORY_BREAST_CANCER) consists of trimodality therapy starting with neoadjuvant systemic therapy followed by mastectomy with axillary dissection and postmastectomy radiation therapy.
* Neoadjuvant (preoperative) systemic therapy
  + An anthracycline plus taxane is the preferred combination for neoadjuvant chemotherapy ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
  + If the cancer is HER2 positive, add HER2 targeted therapy to the neoadjuvant chemotherapy ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
* Following neoadjuvant therapy, assess the treatment response with a physical examination and repeat imaging of abnormal findings at the time of initial tumor staging ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
* For patients with cancer response to neoadjuvant therapy:
  + Perform total mastectomy with level I/II axillary lymph node dissection ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
    - Delayed breast reconstruction is an option for women who desire breast reconstruction ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
    - Immediate breast reconstruction is contraindicated ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
  + Provide postmastectomy radiation therapy ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
  + Adjuvant (postoperative) systemic therapy:
    - Complete planned chemotherapy regimen if not completed preoperatively and give endocrine therapy following completion of chemotherapy if the cancer is HR positive ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
    - Complete up to 1 year of HER2 targeted therapy if the cancer is HER2 positive ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)); it should be given concurrently with radiation therapy and with endocrine therapy if indicated ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
* For patients with cancer unresponsive to neoadjuvant chemotherapy:
  + Consider treating with additional neoadjuvant chemotherapy and/or preoperative radiation therapy to achieve response, or enrollment in a clinical trial ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
  + For patients with cancer unresponsive to additional neoadjuvant chemotherapy or preoperative radiation therapy, consider individualized treatment, or enrollment in a clinical trial ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
  + Mastectomy is generally not recommended if there is no response ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).

Management of Locoregional Recurrence of Breast Cancer

* Before treatment, assessment for evidence of metastatic disease is necessary to differentiate isolated locoregional recurrences from those associated with synchronous distant metastatic disease ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
* For women with [local only recurrence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#MANAGEMENT_OF_LOCOREGIONAL_RECURRENCE):
  + In women initially treated with breast-conserving surgery and radiation therapy, offer total mastectomy plus axillary lymph node staging if level I/II axillary dissection was not done previously ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
  + In women initially treated with mastectomy, offer surgical resection if possible ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
  + In women without previous radiation therapy, offer locoregional radiation therapy ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)); if the initial treatment included radiation therapy, consider reirradiation to all or part of chest wall in select cases ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF))
  + Offer systemic therapy if HR negative disease ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)) and consider systemic therapy if HR positive disease ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)) , especially if initially unresectable or in women who are not candidates for surgical resection.
  + In women who are not candidates for surgical resection, options include systemic therapy followed by surgical resection ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)), definitive radiation therapy, or systemic therapy alone.
* For the management of [regional or local and regional recurrence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#MANAGEMENT_OF_LOCOREGIONAL_RECURRENCE__ANC_1963694348):
  + When possible, treat locoregional recurrence with curative intent ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)). Treat areas of local recurrence based on recommendations under management of local only recurrence and areas of regional recurrence based on location of recurrence.
  + In women with axillary recurrence:
    - Perform surgical resection if possible, plus radiation therapy if possible ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
    - If initially unresectable or in women who are not candidates for surgical resection, consider systemic therapy to best response followed by surgical resection, if possible ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
  + In women with supraclavicular or internal mammary node recurrence, if no previous radiation therapy, offer locoregional radiation therapy ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)); if initial treatment included radiation therapy, consider reirradiation to all or part of chest wall in select cases ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
  + Offer systemic therapy if HR negative disease ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)) and consider systemic therapy if HR positive disease ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF))

Management of Metastatic Breast Cancer

* Consider for all patients with [metastatic breast cancer](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#ADVANCED_BREAST_CANCER) enrollment in a clinical trial ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
* Palliative and supportive care should be offered to all patients throughout the course of metastatic disease ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
* Treatment typically involves systemic therapy with endocrine therapy, chemotherapy, and/or targeted/biologic therapy based on HR status, HER2 status, *BRCA1/2* mutation status, programmed cell death ligand 1 (PD-L1) status, status of other biomarkers, comorbidities, and severity of disease.
  + For HR positive, HER2 negative breast cancer:
    - Offer endocrine therapy with or without a cyclin dependent kinase (CDK) 4/6 inhibitor for first-line therapy unless there is a visceral crisis ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)). Offer ovarian ablation or suppression in addition to endocrine therapy for premenopausal women ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)). May consider a selective estrogen receptor modulator without ovarian suppression or ablation in select women who have not been on endocrine therapy for a year ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)). If there is a visceral crisis, consider chemotherapy or targeted therapy for first line therapy ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
    - Continue therapy until disease progression or intolerable toxicity ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)), then, weighing benefits and harms, consider a different line of endocrine therapy, targeted therapy, and/or chemotherapy while continuing supportive care ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)). Most patients are candidates for multiple sequential lines of systemic therapy.
    - May consider single agent poly adenosine diphosphate ribose polymerase (PARP) inhibitors for patients with a germline *BRCA1/2* mutation after progression on endocrine therapy plus CDK4/6 inhibitor ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
  + For HR positive, HER2 positive breast cancer:
    - Offer chemotherapy plus HER2 targeted therapy ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)). May consider endocrine therapy plus HER2 targeted therapy for maintenance therapy following completion of chemotherapy and continued until progression or unacceptable toxicity ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)). In select patients, may consider endocrine therapy, with ovarian suppression or ablation for premenopausal women, with or without HER2 targeted therapy as first-line therapy ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)). For select premenopausal women, may consider a selective estrogen receptor modulator (SERM) plus HER2 targeted therapy without ovarian oblation or suppression ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
    - Continue therapy until progression or intolerable toxicity ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)), then, weighing benefits and harms, offer a different line of chemotherapy plus HER2 targeted therapy, other HER2 targeted therapy, or endocrine therapy with or without HER2 targeted therapy ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)). Most patients are candidates for multiple sequential lines of systemic therapy.
  + For HR negative, HER2 positive breast cancer:
    - Offer chemotherapy plus HER2 targeted therapy ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
    - Therapy should be continued until progression or intolerable toxicity ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)), then, weighing benefits and harms, offer a different line of chemotherapy plus HER2 targeted therapy, other HER2 targeted therapy, or other targeted therapy ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)). Most patients are candidates for multiple sequential lines of systemic therapy.
    - May consider single agent poly adenosine diphosphate ribose polymerase (PARP) inhibitors for patients with a germline *BRCA1/2* mutation, although they are not FDA-approved for HER2 positive breast cancer ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
  + For HR negative, HER2 negative (triple negative) breast cancer:
    - Offer chemotherapy and/or targeted therapy ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)) until progression or intolerable toxicity ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)), then, weighing benefits and harms, offer a different line of chemotherapy and/or targeted therapy ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)). Most patients are candidates for multiple sequential lines of systemic therapy.
* For [bone metastases](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#MANAGEMENT_OF_ADVANCED_BREAST_CANCER__LI_XQD_2CD_LPB), a multidisciplinary treatment approach may include systemic therapy, surgery, radiation and supportive care. Offer bone-modifying agents such as bisphosphonates or denosumab, with calcium and vitamin D supplement, for all patients with bone metastases ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
* For [brain metastases](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#MANAGEMENT_OF_ADVANCED_BREAST_CANCER__LI_W3K_2CD_LPB), a multimodal treatment approach is based on performance status, prognosis, number, size, and location of brain metastases. Consider steroids for patients who are symptomatic due to brain metastases or spinal cord compression ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)). Do not offer routine prophylactic antiseizure medications ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)), although they may be considered perioperatively ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
* Surveillance includes periodic assessment of symptoms, physical exam findings, laboratory tests, imaging studies, and blood biomarkers where appropriate ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)). The optimal frequency of testing is unknown, but generally consider every 2-4 months for endocrine therapy and every 2-3 cycles for chemotherapy ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)) For patients with brain metastases, consider following with brain MRI every 2-3 months for 1-2 years, and then every 4-6 months thereafter ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).

Management of Breast Cancer During Pregnancy

* For [pregnant women](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#MANAGEMENT_OF_BREAST_CANCER_IN_PREGNANCY) with confirmed breast cancer diagnosis, considerations and selection of optimal local and systemic therapy are similar to those in nonpregnancy associated breast cancer; however, the timing and selection of chemotherapy, endocrine therapy, and radiation therapy is different for pregnant and nonpregnant women.
* Maternal fetal medicine consultation should include a review of treatment options and the possibility of pregnancy termination.
  + In the first trimester, discuss nontherapeutic pregnancy termination ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)). For women who choose to continue pregnancy:
    - consider mastectomy plus axillary staging as surgical treatment ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF))
    - if late in first trimester, may consider neoadjuvant chemotherapy to begin in the second trimester; otherwise, offer adjuvant chemotherapy in second trimester ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF))
  + In second trimester or early third trimester, options include:
    - mastectomy or breast-conserving surgery plus axillary staging, followed by adjuvant chemotherapy ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF))
    - neoadjuvant chemotherapy followed by mastectomy or breast-conserving surgery plus axillary staging ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF))
  + In late third trimester, consider mastectomy or breast conserving surgery plus axillary staging, followed by adjuvant chemotherapy if indicated ([Conditional recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).
* Chemotherapy should not be given after week 35 of pregnancy or within 3 weeks of planned delivery to avoid potential hematologic complications during delivery.
* HER2 targeted therapy is contraindicated in pregnancy.
* Adjuvant endocrine therapy and radiation therapy should not be used during any trimester of pregnancy, but may be offered in postpartum period if indicated by disease status ([Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-AB58B260-1753-4538-BF37-4EAF1FF7B5BF)).

General Information

Description

* breast cancer is a malignancy of the breast tissue and is the most common malignancy diagnosed in women worldwide[1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF5142),[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF6778)

Definitions

* breast cancer classified as carcinoma in situ or invasive breast cancer
  + defined as carcinoma in situ (noninvasive carcinoma, stage 0) if cancer cells have not invaded past the basement membrane of the duct or lobule; breast carcinoma in situ not covered in this topic; see also [Ductal carcinoma in situ](https://dpa-pde-oxford.shinyapps.io/condition/ductal-carcinoma-in-situ-dcis) and [Lobular carcinoma in situ](https://dpa-pde-oxford.shinyapps.io/condition/lobular-carcinoma-in-situ)
  + defined as invasive breast cancer (infiltrating breast cancer, stages I-IV) if cancer cells have invaded beyond basement membrane of duct or lobule into adjacent breast parenchyma
  + Reference - [18457192Cleve Clin J Med 2008 Mar;75 Suppl 1:S10](http://pubmed.ncbi.nlm.nih.gov/18457192?dopt=Abstract)
* invasive breast cancer further classified as[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF6778),[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__ANC_1607337114),[4](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF4502)
  + early breast cancer (includes stages I, IIa, IIb)
    - no tumor extension to chest wall or skin
    - may include movable ipsilateral axillary lymph node metastases
    - no distant metastases
  + locally advanced breast cancer (includes stages IIIa, IIIb, IIIc)
    - metastases in ipsilateral axillary lymph nodes that are clinically fixed or matted
    - metastases in clinically detected internal mammary lymph nodes
    - tumor > 5 cm and metastases in movable ipsilateral axillary lymph nodes
    - tumor with direct extension to chest wall or skin
    - no distant metastases
  + advanced (metastatic) breast cancer includes stage IV tumors which encompass disease that has spread beyond the breast and axilla; common sites of metastases include bone, liver, lung, and brain
* inflammatory breast cancer is a rare, aggressive subtype of locally advanced breast cancer that is characterized by a substantial area of breast skin that is red in color, warm, thickened due to edema (referred to as peau d'orange), and usually without underlying breast mass ([25459672Crit Rev Oncol Hematol 2015 Feb;93(2):116](http://pubmed.ncbi.nlm.nih.gov/25459672?dopt=Abstract))
* locoregional recurrence is the development of new tumor in breast or chest wall/mastectomy site and/or regional lymph nodes on side previously affected by cancer ([mnh28396099pcxh126821927pmdc28396099pClin Breast Cancer 2017 Nov;17(7):493](http://pubmed.ncbi.nlm.nih.gov/28396099?dopt=Abstract) )
* pregnancy-associated breast cancer (also called gestational breast cancer) includes breast cancer that occurs in any of the following settings
  + during pregnancy
  + during the first postpartum year
  + during lactation
  + PubMed30392595Journal of the American College of Radiology : JACRJ Am Coll Radiol201811011511SS263-S275S263Reference - [J Am Coll Radiol 2018 Nov;15(11S):S263](http://pubmed.ncbi.nlm.nih.gov/30392595)[PDF](https://acsearch.acr.org/docs/3102382/Narrative/)

Types

* immuno/pathological subtypes determined by receptor status
  + hormone receptor (HR)-positive (that is, estrogen receptor [ER]-positive and/or progesterone receptor [PR]-positive), and human epidermal growth factor receptor 2 [HER2]-negative
  + HER2-positive and HR-negative (both ER-negative and PR-negative)
  + triple-negative (ER-negative, PR-negative, and HER2-negative)
  + triple-positive (ER-positive, PR-positive, and HER2-positive)
  + Reference - [mnh21965335pcxh67241334pmdc21965335pJ Clin Invest 2011 Oct;121(10):3789](http://pubmed.ncbi.nlm.nih.gov/21965335?dopt=Abstract) [full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3195465/)
* intrinsic molecular subtypes of breast cancer
  + luminal A
    - reportedly 28%-31% prevalence
    - mostly ER-positive and HER2-negative
    - proliferation status generally low and thus lower risk of recurrence
    - generally chemoresistant but endocrine sensitive
  + luminal B
    - reportedly 19%-23% prevalence
    - mostly ER-positive and HER2-negative, although about 20% may be HER2-positive
    - proliferation status generally high and thus higher risk of recurrence
    - may benefit more from chemotherapy than luminal A subtype but less endocrine sensitive
  + HER2-enriched (also called HER2-positive)
    - reportedly 12%-21% prevalence
    - about 51% ER-negative and HER2-positive and 15% ER-positive and HER2-positive
    - about 16% are ER-positive and HER2-negative and 18% are triple-negative by clinical definition of HER2 overexpression, but are considered HER2-enriched based on gene expression array
  + basal-like
    - reportedly 11%-23% prevalence
    - mostly triple-negative tumors, but 11%-19% may be ER-positive and 9%-13% may be HER2-positive
  + claudin-low
    - reportedly about 7%-14% prevalence
    - mostly high-grade and triple-negative tumors, although about 12%-33% are reportedly HR-positive
  + normal breast-like, reportedly 3%-10% prevalence
  + Reference - [21147047Mol Oncol 2011 Feb;5(1):5](http://pubmed.ncbi.nlm.nih.gov/21147047?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5528267/)
* histologic types, see 2019 [WHO classification](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#PATHOLOGY_REPORTING__LI_M3Z_5BQ_2MB) of malignant breast tumors, 5th edition

Epidemiology

Who Is Most Affected

* women > 40-50 years old[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF6778),[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__ANC_1607337114)
  + 95% of new cases occur in women > 40 years old
  + about 20% are reported to occur in women < 50 years old
  + Reference - [American Cancer Society (ACS) Breast Cancer Facts & Figures and 2022-2024 PDF](https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/2022-2024-breast-cancer-fact-figures-acs.pdf)

Incidence/Prevalence

* **estimated global breast cancer incidence 2,088,849 cases in 2018**

Population-based Surveillance[CA Cancer J Clin 2018 Nov;68(6):394](http://pubmed.ncbi.nlm.nih.gov/30207593?dopt=Abstract)

studySummary

* + based on population-based cancer registries, vital registration data, and mortality data from 185 countries or territories with total population > 150,000 during 2018Population-based Surveillance
  + incidence data regarding basal cell carcinoma excluded from analysis
  + breast cancer incidence
    - estimated new breast cancer cases 2,088,849 (11.6% of all new cancer cases)
    - cumulative global lifetime risk (ages 0-74 years) 5.03%
    - age-standardized rates (ASRs) per 100,000 women
      * overall, ASR 46.3
      * in more developed regions, ASR 54.4
      * in less developed regions, ASR 31.3

| Estimated Global Breast Cancer Incidence by Global Region, 2018 | |
| --- | --- |
| **Region** | **ASRs per 100,000** |
| **Americas** | |
| North America | 84.8 |
| Central America | 38.3 |
| Caribbean | 50.2 |
| South America | 56.8 |
| **Africa** | |
| Northern Africa | 48.9 |
| Western Africa | 37.3 |
| Middle Africa | 27.9 |
| Eastern Africa | 29.9 |
| Southern Africa | 46.2 |
| **Europe** | |
| Western Europe | 92.6 |
| Northern Europe | 90.1 |
| Southern Europe | 80.3 |
| Eastern Europe | 54.5 |
| **Asia** | |
| Western Asia | 45.3 |
| South Central Asia | 25.9 |
| Eastern Asia | 39.2 |
| South-Eastern Asia | 38.1 |
| **Oceana** |  |
| Australia/New Zealand | 94.2 |
| Melanesia | 49.7 |
| Micronesia/Polynesia | 58.2 |
| Abbreviations: ASR, age-standardized rates. | |

* + CA: a cancer journal for clinicians20181101CA Cancer J Clin686394394 Reference - GLOBOCAN 2018 ([CA Cancer J Clin 2018 Nov;68(6):394](http://pubmed.ncbi.nlm.nih.gov/30207593?dopt=Abstract))
* INCIDENCE\_PREVALENCE\_\_LI\_SVY\_L1R\_DVBEU10112210/11/2022 03:20:57 PMevidenceUpdatestandardOncologic\_Disease 5-year age-adjusted breast cancer incidence 128.3 per 100,000 persons in United States during 2015-2019 (SEER Cancer Statistics Review [accessed 2022 Oct 11])

**5-year age-adjusted breast cancer incidence 128.3 per 100,000 person-years for female persons in United States during 2015-2019**

Population-based Surveillance[SEER Cancer Statistics Review](https://seer.cancer.gov/statistics-network/explorer/application.html?site=55&data_type=1&graph_type=10&compareBy=sex&chk_sex_3=3&series=9&race=1&age_range=1&stage=101&advopt_precision=1&advopt_show_ci=on&hdn_view=1)

studySummary

* + Population-based Surveillance based on population-based surveillance
  + annual population-based surveillance information on incidence (during 2015-2019) and mortality (during 2016-2020) of breast cancer in female persons in the United States from Surveillance, Epidemiology, and End Results (SEER) database was evaluated
  + incidence was age-adjusted to standard population of United States in 2000
  + 5-year age-adjusted incidence of breast cancer 128.3 per 100,000 person-years
  + 5-year age-adjusted incidence of breast cancer by race and ethnicity
    - 111.3 per 100,000 person-years for American Indians and Alaska Natives (non-Hispanic)
    - 106.9 per 100,000 person-years for Asians and Pacific Islanders (non-Hispanic)
    - 129.6 per 100,000 person-years for Black persons (non-Hispanic)
    - 99.9 per 100,000 person-years for Hispanic persons
    - 137.6 per 100,000 person-years for White persons (non-Hispanic)
  + 5-year age-adjusted incidence of breast cancer by age
    - 22.9 per 100,000 person-years for ages 15-39 years
    - 217.1 per 100,000 person-years for ages 40-64 years
    - 447.7 per 100,000 person-years for ages 65-74 years
    - 408.4 per 100,000 person-years for ages ≥ 75 years
  + PubMed36190501CA: a cancer journal for cliniciansCA Cancer J Clin20221003Reference - [SEER Cancer Statistics Review](https://seer.cancer.gov/statistics-network/explorer/application.html?site=55&data_type=1&graph_type=10&compareBy=sex&chk_sex_3=3&series=9&race=1&age_range=1&stage=101&advopt_precision=1&advopt_show_ci=on&hdn_view=1) (accessed 2022 Oct 11) on 5-year age-adjusted incidence stratified by race, 5-year age-adjusted incidence stratified by age
* age-standardized incidence of breast cancer in women in Italy 120 per 100,000 person-years in 2015 ([24158072Tumori 2013 May-Jun;99(3):416](http://pubmed.ncbi.nlm.nih.gov/24158072?dopt=Abstract)[PDF](http://www.tumorijournal.com/article/estimates-of-cancer-burden-in-italy))
* age-standardized incidence 114.5 per 100,000 person-years for breast cancer in women in Australia in 2014 ([a9h108929809t pcxh108929809t pmdc26264473pAsia Pac J Clin Oncol 2015 Sep;11(3):208](http://pubmed.ncbi.nlm.nih.gov/26264473?dopt=Abstract) [full-text](http://onlinelibrary.wiley.com/doi/10.1111/ajco.12407/full))
* **compared to White women in the United States, Black, Asian-Pacific Islander, and Hispanic women may have higher risk of triple negative or human epidermal growth factor receptor type 2 (HER2)-positive breast cancer**

Cohort Study[24777111J Natl Cancer Inst 2014 Apr 28;106(5):](http://pubmed.ncbi.nlm.nih.gov/24777111?dopt=Abstract)[Full Text](http://jnci.oxfordjournals.org/content/106/5/dju055.long)

studySummary

* + based on retrospective cohort analysis of Surveillance, Epidemiology, and End Results (SEER) database from 2010, including 57,483 women with breast cancer Cohort Study
  + 50,571 women had known hormone receptor (combination of estrogen receptor and progesterone receptor) (HR) and/or HER2 status
  + overall in women with known status
    - 72.7% were HR positive and HER2 negative
    - 12.2% were HR negative and HER2 negative (triple negative)
    - 10.3% were HR positive and HER2 positive
    - 4.6% were HR negative and HER2 positive
  + HR status and HER2 status by race or ethnicity, stage, and age at diagnosis

| Breast Cancer HR and HER2 Status by Race or Ethnicity, Stage, and Age at Diagnosis | | | | |
| --- | --- | --- | --- | --- |
|  | **HR Positive /HER2 Negative** | **HR Negative /HER2Negative (Triple Negative)** | **HR Positive /HER2 Positive** | **HR Negative /HER2 Positive** |
| **Age Range at Diagnosis** | | | | |
| < 50 years | 64.8% | 15.2% | 14.4% | 5.6% |
| 50-64 years | 70.7% | 13.2% | 10.7% | 5.4% |
| 65-74 years | 77.8% | 10.4% | 8.5% | 3.4% |
| ≥ 75 years | 80.1% | 9.3% | 7.4% | 3.3% |
| **Race or Ethnicity** | | | | |
| White | 75.5% | 10.7% | 9.8% | 4% |
| Black | 60.2% | 22.5% | 11.4% | 6% |
| Asian-Pacific Islander | 71.1% | 9.7% | 12.3% | 6.9% |
| Hispanic | 68.2% | 14.7% | 11.4% | 5.7% |
| **AJCC Stage at Diagnosis** | | | | |
| I | 79.5% | 9% | 8.4% | 3.1% |
| II | 69.3% | 14.9% | 11% | 4.8% |
| III | 62.6% | 16.1% | 13.6% | 7.8% |
| IV | 61.2% | 15.1% | 14.8% | 8.9% |
| Unknown | 66.2% | 13.5% | 13.7% | 6.6% |
| Abbreviations: AJCC, American Joint Committee on Cancer; HER2, human epidermal receptor 2; HR, hormone receptor. | | | | |

* + compared to White women
    - Black women had increased likelihood of
      * triple negative breast cancer (adjusted odds ratio [OR] 2, 95% CI 1.8-2.2)
      * HR negative and HER2 positive breast cancer (adjusted OR 1.4, 95% CI 1.2-1.6)
      * HR positive and HER2 positive breast cancer (adjusted OR 1.2, 95% CI 1-1.3)
    - Asian-Pacific Islander women had
      * decreased likelihood of triple negative breast cancer (adjusted OR 0.8, 95% CI 0.7-0.9)
      * increased likelihood of HR negative and HER2 positive breast cancer (adjusted OR 1.8, 95% CI 1.5-2.1)
      * increased likelihood of HR positive and HER2 positive breast cancer (adjusted OR 1.2, 95% CI 1.1-1.4)
    - Hispanic women had increased likelihood of
      * triple negative breast cancer (adjusted OR 1.3, 95% CI 1.2-1.5)
      * HR negative and HER2 positive breast cancer (adjusted OR 1.4, 95% CI 1.2-1.6)
      * HR positive and HER2 positive breast cancer (adjusted OR 1.1, 95% CI 1-1.2)
  + PubMed24777111Journal of the National Cancer Institute20140428J Natl Cancer Inst1065 Reference - [24777111J Natl Cancer Inst 2014 Apr 28;106(5):](http://pubmed.ncbi.nlm.nih.gov/24777111?dopt=Abstract)[full-text](http://jnci.oxfordjournals.org/content/106/5/dju055.long), editorial can be found in [24777110J Natl Cancer Inst 2014 Apr 28;106(5)](http://pubmed.ncbi.nlm.nih.gov/24777110?dopt=Abstract)
* stage distribution of breast cancer by race in United States from 2008 to 2014

| Table 1: Incidence of Breast Cancer by Stage and Race | | | |
| --- | --- | --- | --- |
|  | **Localized Disease\*** | **Regional Disease\*\*** | **Distant Disease\*\*\*** |
| All women | 62% | 31% | 6% |
| White women | 63% | 30% | 6% |
| Black women | 54% | 36% | 9% |
| \* Localized disease is stage I and II if negative lymph node(s).  \*\* Regional disease is stage II and III if positive lymph node(s).  \*\*\* Distant disease is metastatic, stage IV.  Reference - [CA Cancer J Clin 2019 Jan;69(1);7](http://pubmed.ncbi.nlm.nih.gov/30620402?dopt=Abstract)[full-text](https://onlinelibrary.wiley.com/doi/full/10.3322/caac.21551). | | | |

* **likelihood of breast cancer diagnosis at stage 1 appears to vary with race and ethnicity in United States**

Population-based Surveillance[cxh100436460pmdc25585328pJAMA 2015 Jan 13;313(2):165](http://pubmed.ncbi.nlm.nih.gov/25585328?dopt=Abstract)

studySummary

* + based on analysis of 373,563 women with invasive breast cancer diagnosed from 2004 to 2011 in SEER database in United States Population-based Surveillance
  + breast cancer diagnosis at stage 1 in 50.8% of cases in non-Hispanic White women
  + compared to non-Hispanic White women diagnosed with stage 1 breast cancer, likelihood of diagnosis at stage 1 significantly lower in
    - Black women (odds ratio [OR] 0.65, 95% CI 0.64-0.67)
    - Hispanic women (OR, 0.71, 95% CI 0.7-0.73)
    - South Asian women (OR 0.73, 95% CI 0.67-0.79)
  + no significant difference in rates of stage 1 diagnosis comparing women of Chinese descent to non-Hispanic White women
  + rates of stage 1 diagnosis significantly higher in women of Japanese descent than non-Hispanic White women
  + PubMed25585328JAMA20150113JAMA3132165165 Reference - [cxh100436460pmdc25585328pJAMA 2015 Jan 13;313(2):165](http://pubmed.ncbi.nlm.nih.gov/25585328?dopt=Abstract) , correction can be found in [mdc26057299pJAMA 2015 Jun 9;313(22):2287](http://pubmed.ncbi.nlm.nih.gov/26057299?dopt=Abstract) , editorial can be found in [cxh100436455pmdc25585323pJAMA 2015 Jan 13;313(2):141](http://pubmed.ncbi.nlm.nih.gov/25585323?dopt=Abstract) ,(correction can be found in JAMA 2015 Feb 17;313(7):729)
* **incidence of breast cancer with remote metastasis at diagnosis 2.9 per 100,000 women aged 25-39 years in 2009 in United States**

Cohort Study[mdc23443443pJAMA 2013 Feb 27;309(8):800](http://pubmed.ncbi.nlm.nih.gov/23443443?dopt=Abstract)

studySummary

* + based on retrospective cohort analysis of SEER database from 1976 to 2009 Cohort Study
  + SEER database included 28% of United States population in 2009
  + incidence of breast cancer with remote metastasis at diagnosis significantly increased from 1976 to 2009 in women aged 25-39 years
    - 2.9 (95% CI 2.31-3.59) per 100,000 women in 2009
    - 1.53 (95% CI 1.01-2.21) per 100,000 women in 1976
  + PubMed23443443JAMA20130227JAMA3098800800 Reference - [mdc23443443pJAMA 2013 Feb 27;309(8):800](http://pubmed.ncbi.nlm.nih.gov/23443443?dopt=Abstract) , correction can be found in JAMA 2013 Mar 27;309(12):1229
* pregnancy-associated breast cancer
  + PubMed31776799Current treatment options in oncologyCurr Treat Options Oncol2019112720128686prevalence of pregnancy-associated breast cancer may be increasing as women are becoming pregnant at later age when incidence of breast cancer is more common ([Curr Treat Options Oncol 2019 Nov 27;20(12):86](http://pubmed.ncbi.nlm.nih.gov/31776799))
  + reported to occur in 1 in 3,000 to 1 in 10,000 pregnancies and up to 3% of breast cancer diagnosis ([J Am Coll Radiol 2018 Nov;15(11S):S263](http://pubmed.ncbi.nlm.nih.gov/30392595)[PDF](https://acsearch.acr.org/docs/3102382/Narrative/))
  + PubMed24485752Diagnostic and interventional imagingDiagn Interv Imaging20140401954435-414350.7% incidence of pregnancy-associated breast cancer reported in cohort of 16,555 women 20-43 years old in France between 1993 and 2009 ([Diagn Interv Imaging 2014 Apr;95(4):435](http://pubmed.ncbi.nlm.nih.gov/24485752)[full-text](https://www.sciencedirect.com/science/article/pii/S2211568413004294?via%3Dihub))
  + **increasing incidence of pregnancy-associated cancer in Denmark from 1977 to 2006**

Cohort Study[23921869Obstet Gynecol 2013 Sep;122(3):608](http://pubmed.ncbi.nlm.nih.gov/23921869)

studySummary

* + - based on cohort from Danish Cancer Registry 1977-2006Cohort Study
    - 2,426 women with pregnancy-associated cancer (diagnosed during pregnancy and up to 1 year after pregnancy has ended) evaluated
    - 3 most common cancers were melanoma, cervical cancer, and breast cancer
    - overall crude incidence rate of all pregnancy-associated cancer 89.6 per 100,000 pregnancies
    - total number of all pregnancy-associated cancers increased from 572 cases during 1977-1986 to 1,052 cases during 1997-2006
    - proportion of all pregnancy-associated cancers among all cancers increased from 5.4% during 1997-1986 to 8.3% during 1997-2006
    - mean annual increase in pregnancy-associated cancer 2.9%
    - PubMed23921869Obstetrics and gynecology20130901Obstet Gynecol1223608608Reference - [23921869Obstet Gynecol 2013 Sep;122(3):608](http://pubmed.ncbi.nlm.nih.gov/23921869)
  + **incidence of pregnancy-associated breast cancer 37.4 per 100,000 deliveries in Sweden**

Cohort Study[19701036Obstet Gynecol 2009 Sep;114(3):568](http://pubmed.ncbi.nlm.nih.gov/19701036?dopt=Abstract)

studySummary

* + - based on population-based cohort from Swedish registers of women aged 15-44 years Cohort Study
    - 1,161 (7%) cases of pregnancy-associated breast cancer among total of 16,620 breast cancer cases from 1963 to 2002
    - increase in pregnancy-associated breast cancer from 16 per 100,000 deliveries in 1963 to 37.4 per 100,000 deliveries in 2002
    - PubMed19701036Obstetrics and gynecology20090901Obstet Gynecol1143568568 Reference - [19701036Obstet Gynecol 2009 Sep;114(3):568](http://pubmed.ncbi.nlm.nih.gov/19701036?dopt=Abstract)

Risk Factors

Family History and Genetic Predispositions

* family history of breast cancer in a blood relative increases risk of breast cancer ([29209143Int J Biol Sci 2017;13(11):1387](http://pubmed.ncbi.nlm.nih.gov/29209143?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5715522/))
* greater genetic breast cancer risk associated with number of relatives diagnosed, genetic proximty to affected relatives (first- or second-degree) and diagnosis at a younger age ([NCCN 2022 Oct from NCCN website (free registration required)](https://www.nccn.org/guidelines/category_2))
* genetic predispositions and risk of breast cancer

| Table 2: Genetic Predispositions and Risk of Breast Cancer | |
| --- | --- |
| **Gene** | **Breast Cancer Risk and/or Prevalence** |
| BRCA1 or BRCA2 (Hereditary breast and ovarian cancer) | * + 41%-90% lifetime risk |
| CDH1 (Hereditary diffuse gastric cancer) | * + 39%-52% lifetime risk |
| PALB2 (Fanconi anemia; partner and localizer of BRCA2) | * + 41%-60% lifetime risk |
| STK11 (Peutz-Jeghers syndrome) | * + 8% risk in patients 40 years old   + 13% risk in patients 50 years old   + 31% risk in patients 60 years old   + 45% risk in patients 70 years old |
| TP53 (Li-Fraumeni syndrome) | * + at least 54% |
| PTEN (Cowden syndrome) | * + 40%-60% lifetime risk for PTEN, but some studies have reported lifetime risk up to 85%   + Diagnosis of PTEN genetic predisposition may be underestimated due to difficulty to diagnose |
| ATM (Ataxia-telangiectasia mutated) | * + 20%-30% lifetime risk |
| BARD1 (BRCA1-associated RING domain 1) | Prevalence 0.1%-0.51% of breast cancer cases |
| BRIP1 (BRCA1 interaction protein C-terminal helicase 1 gene) | * + Prevalence 1% of breast cancer cases |
| CHEK2 (cell cycle checkpoint kinase 2) | * + Estimated 20%-40% lifetime risk |
| Lynch Syndrome genes (MSH2, MSH6, MLH1, PMS2, EPCAM) | * + N/A |
| NF1 (Neurofibromatosis type 1) | * + Estimated lifetime risk 59.6% |
| RAD51C | * + Prevalence 0.23%-0.45% of triple-negative breast cancer cases |
| RAD51D | * + Prevalence 0.29%- 0.38% of triple-negative breast cancer cases |
| Abbreviation: N/A, not available  Reference - [NCCN 2022 Oct from NCCN website (free registration required)](https://www.nccn.org/guidelines/category_2), [ACI 2021 Dec 16](https://www.cancer.org/cancer/types/breast-cancer/risk-and-prevention/breast-cancer-risk-factors-you-cannot-change.html)[PDF](https://www.cancer.org/content/dam/CRC/PDF/Public/8578.00.pdf). | |

* for details on risk assessment see Risk Assessment for Screening in [Breast Cancer Screening](https://dpa-pde-oxford.shinyapps.io/prevention/breast-cancer-screening#GUID-D1970D67-E4C1-44E2-8114-27BA63C555D7)
* see also [Hereditary Breast and Ovarian Cancer (HBOC) Syndromes](https://dpa-pde-oxford.shinyapps.io/condition/hereditary-breast-and-ovarian-cancer-hboc-syndromes)

Medical and Reproductive History

* patient history of breast cancer (especially at younger age) increases risk of new breast cancer in the same or opposing breast ([Centers for Disease Control and Prevention Breast Cancer 2023 Jul 25](https://www.cdc.gov/cancer/breast/basic_info/risk_factors.htm))
* history of other breast conditions associated with increased risk of breast cancer
  + history of lobular carcinoma in situ, atypical ductal hyperplasia and/or lobular hyperplasia; see [Lobular Carcinoma In Situ](https://dpa-pde-oxford.shinyapps.io/condition/lobular-carcinoma-in-situ) and [Ductal Carcinoma in Situ (DCIS)](https://dpa-pde-oxford.shinyapps.io/condition/ductal-carcinoma-in-situ-dcis) for details
  + prior breast biopsies to diagnose cancer; multiple biopsies of the same lesion scored as a single biopsy
  + heterogenously and/or extremely dense breasts as evidenced on mammography
  + Reference - [NCCN 2022 Oct from NCCN website (free registration required)](https://www.nccn.org/guidelines/category_2)
* history of thoracic radiation therapy at < 30 years old ([NCCN 2022 Oct from NCCN website (free registration required)](https://www.nccn.org/guidelines/category_2))
* reproductive history associated with increased risk of breast cancer
  + reproductive factors associated with increased risk of breast cancer
    - younger age at menarche
    - nulliparity/ lower parity
    - older age at first live birth
    - older age at menopause
    - References - [NCCN 2022 Oct from NCCN website (free registration required)](https://www.nccn.org/guidelines/category_2), [29209143Int J Biol Sci 2017;13(11):1387](http://pubmed.ncbi.nlm.nih.gov/29209143?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5715522/))
  + current use or history of hormonal (estrogen and progesterone) agents
    - perinatal exposure to diethylstilbestrol (DES) associated with increased risk of breast cancer; children of women exposed to DES during pregnancy may also have increased risk ([Centers for Disease Control and Prevention Breast Cancer 2023 Jul 25](https://www.cdc.gov/cancer/breast/basic_info/risk_factors.htm))
    - combined oral contraceptives may be associated with small increased risk for breast cancer which decreases after method cessation; see Oral Contraceptives and Cancer in [Oral Contraceptives](https://dpa-pde-oxford.shinyapps.io/drug-review/oral-contraceptives#GUID-46CD586F-BD2F-422F-9EA5-0709F7F237B3) for details
    - hormonal intrauterine devices reported with very low systemic absorption and risk of breast cancer ([NCCN 2022 Oct from NCCN website (free registration required)](https://www.nccn.org/guidelines/category_2))
    - hormone replacement therapy
      * combined estrogen and progestin (hormone replacement therapy [HRT]) associated with increased risk for breast cancer, but evidence for ongoing risk after stopping treatment is conflicting
        + hormone replacement therapy associated with increased risk for invasive breast cancer ([level 1 [likely reliable] evidence](https://www.dynamed.com/home/editorial/editorial-process))
        + current use of HRT associated with increased risk of breast cancer incidence and mortality ([level 2 [mid-level] evidence](https://www.dynamed.com/home/editorial/editorial-process))
        + conflicting evidence for ongoing risk of breast cancer after stopping HRT
      * long-term use of estrogen alone may increase risk for breast cancer
        + estrogen alone does not appear to increase risk for invasive breast cancer but may increase risk for abnormalities on follow-up mammograms ([level 2 [mid-level] evidence](https://www.dynamed.com/home/editorial/editorial-process))
        + estradiol alone for > 5 years associated with increased risk for breast cancer ([level 2 [mid-level] evidence](https://www.dynamed.com/home/editorial/editorial-process))
        + use of unopposed estrogen for > 20 years might be associated with increased risk of invasive breast cancer ([level 2 [mid-level] evidence](https://www.dynamed.com/home/editorial/editorial-process))
      * HRT may increase risk for recurrent breast cancer in breast cancer survivors, but evidence is conflicting
        + HRT appears to increase risk of recurrent breast cancer ([level 2 [mid-level] evidence](https://www.dynamed.com/home/editorial/editorial-process)) in 2 randomized trials
        + HRT does not appear to increase risk for recurrent breast cancer based on systematic review of observational studies
        + HRT associated with nonsignificant increase in risk of new breast cancer event and contralateral breast cancer after 10 years ([level 2 [mid-level] evidence](https://www.dynamed.com/home/editorial/editorial-process))
        + among women with breast cancer, prediagnostic use of hormone therapy may be associated with decreased breast cancer mortality ([level 2 [mid-level] evidence](https://www.dynamed.com/home/editorial/editorial-process))
    - see [Hormonal Replacement Therapy (HRT) and Breast Cancer](https://dpa-pde-oxford.shinyapps.io/drug-review/hormonal-replacement-therapy-hrt-and-breast-cancer)for details
  + risk of breast cancer in transgender patients receiving gender-affirming hormone treatment
    - **transgender women and men who received gender-affirming hormone treatment may each have increased risk of invasive breast cancer compared to cisgender men and reduced risk compared to cisgender women**

Cohort Study[BMJ 2019 May 14;365:l1652](http://pubmed.ncbi.nlm.nih.gov/31088823?dopt=Abstract)[Full Text](https://www.bmj.com/content/365/bmj.l1652.long)

studySummarytransgender women and men who received gender-affirming hormone treatment may each have increased risk of invasive breast cancer compared to cisgender men and reduced risk compared to cisgender women (BMJ 2019 May 14)05/22/2019 09:23:25 AMOncologic\_DiseaseOncologic\_Diseasetransgender women and men who received gender-affirming hormone treatment may each have increased risk of invasive breast cancer compared to cisgender men and reduced risk compared to cisgender women (BMJ 2019 May 14)05/22/2019 09:23:25 AM

* + - * based on retrospective population-based cohort studyCohort Study
      * 2,260 adult transgender women (median age 51 years) and 1,229 adult transgender men (median age 39 years) in Netherlands who received gender-affirming hormone treatment were assessed
      * median duration of hormone treatment was 18 years in transgender women and 15 years in transgender men
      * median person time (calculated as number of years from start of hormone treatment to breast cancer diagnosis, death, or end of study) was 13 years for transgender women and 8 years for transgender men
      * overall, 15 cases of invasive breast cancer in transgender women and 4 cases of invasive breast cancer in transgender men were diagnosed
      * risk of invasive breast cancer in transgender women was
        + higher when compared to cisgender men (standardized incidence ratio [SIR] 46.7, 95% CI 27.2-75.4)
        + lower when compared to cisgender women (SIR 0.3, 95% CI 0.2-0.4)
      * risk of invasive breast cancer in transgender men was
        + higher when compared to cisgender men (SIR 58.9, 95% CI 18.7-142.2)
        + lower when compared to cisgender women (SIR 0.2, 95% CI 0.1-0.5)
      * BMJ (Clinical research ed.)20190514BMJ365l1652l1652Reference - [BMJ 2019 May 14;365:l1652](http://pubmed.ncbi.nlm.nih.gov/31088823?dopt=Abstract)[full-text](https://www.bmj.com/content/365/bmj.l1652.long), editorial can be found in [BMJ 2019 May 15;365:l2221](http://pubmed.ncbi.nlm.nih.gov/31092391?dopt=Abstract)
  + high levels of endogenous hormones (mainly estrogen) may contribute to risk of breast cancer in postmenopausal women, possibly through increased mitotic activity in breast tissue ([8405212Epidemiol Rev 1993;15(1):48](http://pubmed.ncbi.nlm.nih.gov/8405212?dopt=Abstract))
    - elevated levels of other hormones (androgens) may also contribute to breast cancer risk but relationship is not well established ([8405212Epidemiol Rev 1993;15(1):48](http://pubmed.ncbi.nlm.nih.gov/8405212?dopt=Abstract))
    - **in postmenopausal women, insulin-like growth factor-1 (IGF-1) and testosterone levels are associated with increased risk of breast cancer while sex hormone binding globulin (SHBG) is associated with a reduced risk; in premenopausal women IGF-1 levels seem (but not SHBG or testotesterone) s associated with increased risk of breast cancer**

Cohort Study[33864017Br J Cancer 2021 Jul;125(1):126](http://pubmed.ncbi.nlm.nih.gov/33864017?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8257641/)

studySummary

* + - * Cohort Studybased on population-based prospective cohort study
      * 163,859 women (mean age 52 years, 81% postmenopausal) from the UK Biobank study who had serum hormone levels measured
      * hormone concentrations from premenopausal women were standardized based on menstrual cycle
      * median follow-up 7.1 years
      * diagnosis of invasive breast cancer
        + 527 (0.3%) in premenopausal women
        + 2,997 (1.8%) in postmenopausal women
      * hormonal concentrations and breast cancer risk in 30,565 premenopausal women
        + IGF-1 per 5 nmol/L increment (hazard ratio [HR] 1.18, 95% CI 1.02-1.35)
        + testosterone, sex hormone binding globulin, oestradiol not associated with breast cancer risk
      * hormonal concentrations and breast cancer risk in 133,294 postmenopausal women
        + total testosterone per 0.5 nmol/L increment (HR 1.18, 95% CI 1.14-1.23)
        + free testosterone per 10 pmol/L increment (HR 1.31, 95% CI 1.23-1.4)
        + IGF-1 per 5 nmol/L increment (HR 1.07, 95% CI 1.01-1.12)
        + sex hormone binding globulin per 30 nmol/L increment (HR 0.89, 95% CI 0.84-0.94)
      * Reference - [33864017Br J Cancer 2021 Jul;125(1):126](http://pubmed.ncbi.nlm.nih.gov/33864017?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8257641/)

Patient Characteristics and Lifestyle Factors

* patient factors associated with risk of breast cancer include
  + age; risk for breast cancer among women increases with age
    - based on invasive female breast cancer incidence in United States 2015-2017
    - probability of developing invasive breast cancer during selected ages
      * 0.49% (1 in 204) in women from birth to age 39 years
      * 1.55% (1 in 65) in women aged 40-49 years
      * 2.4% (1 in 42) in women aged 50-59 years
      * 3.54% (1 in 28) in women aged 60-69 years
      * 4.1% (1 in 24) in women aged ≥ 70 years old
      * 12.4% (1 in 8) lifetime risk
      * Reference - [National Cancer Institute Breast Cancer Risk in American Women 2020 Dec 16](https://www.cancer.gov/types/breast/risk-fact-sheet)
    - TOPIC\_ILK\_KGL\_PYB\_\_LI\_IL1\_RC4\_QXBEU05312305/31/2023 03:20:58 PMevidenceUpdatestandardFamily\_Medicine Obstetric\_and\_Gynecologic\_Conditions Oncologic\_Disease Primary\_Carerisk of breast cancer death varies across different racial and ethnic populations, with non-Hispanic Black female adults having higher risk at younger ages compared to general female population in the United States (JAMA Netw Open 2023 Apr 3)

**risk of breast cancer death varies across different racial and ethnic populations, with non-Hispanic Black female adults having higher risk at younger ages compared to general female population in the United States**

Cross-Sectional Study[JAMA Netw Open 2023 Apr 3;6(4):e238893](https://pubmed.ncbi.nlm.nih.gov/37074714)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10116360/)

studySummary

* + - * Cross-Sectional Study based on population-based cross-sectional study
      * 415,277 female persons who died from invasive breast cancer of any stage in 2011-2020 from United States nationwide database were assessed
      * 27.7% died before age 60 years
      * 6 categories for race and ethnicity reported by funeral director on death certificate
        + 74.6% non-Hispanic White
        + 15.1% non-Hispanic Black
        + 6.9% Hispanic
        + 2.9% non-Hispanic Asian or Pacific Islander
        + 0.5% non-Hispanic American Indian or Alaska Native
        + 0.2% had unknown Hispanic origin and excluded from analysis
      * mean 10-year cumulative risk of death due to breast cancer in general female population
        + 0.329% at age 50 years
        + 0.235% at age 45 years
        + 0.154% at age 40 years
      * breast cancer deaths per 100,000 person-years by race or ethnicity in female adults aged 40-49 years
        + 27 for non-Hispanic Black female adults
        + 15 for non-Hispanic White female adults
        + 11 for Hispanic female adults
        + 11 for non-Hispanic Asian or Pacific Islander female adults
        + 11 for non-Hispanic American Indian or Alaska Native female adults
      * age at which different populations reach 10-year cumulative risk of death due to breast cancer that corresponds to age 50 years in general female population
        + 42 years for non-Hispanic Black female adults
        + 51 years for non-Hispanic White female adults
        + 57 years for Hispanic female adults
        + 57 years for non-Hispanic American Indian and Alaska Native female adults
        + 61 years for non-Hispanic Asian and Pacific Islander female adults
      * age at which different populations reach 10-year cumulative risk of death due to breast cancer that corresponds to age 45 years in general female population
        + 38 years for non-Hispanic Black female adults
        + 46 years for non-Hispanic White female adults
        + 49 years for Hispanic female adults
        + 50 years for non-Hispanic Asian and Pacific Islander female adults
        + 51 years for non-Hispanic American Indian or Alaska Native female adults
      * age at which different populations reach 10-year cumulative risk of death due to breast cancer that corresponds to age 40 years in general female population
        + 34 years for non-Hispanic Black female adults
        + 41 years for non-Hispanic White female adults
        + 43 years for Hispanic female adults
        + 43 years for non-Hispanic American Indian or Alaska Native female adults
        + 43 years for non-Hispanic Asian or Pacific Islander female adults
      * PubMed37074714JAMA network openJAMA Netw Open2023040364e238893e238893Reference - [JAMA Netw Open 2023 Apr 3;6(4):e238893](https://pubmed.ncbi.nlm.nih.gov/37074714)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10116360/)
* lifestyle factors associated with risk of breast cancer
  + higher body mass index (BMI) and adult weight gain associated with increased risk of breast cancer in postmenopausal patients
    - risk may be attributed to increased circulating endogenous estrogen levels due to more fatty tissue
    - potentially associated with greater risk for triple negative breast cancer
    - References - [NCCN 2022 Oct from NCCN website (free registration required)](https://www.nccn.org/guidelines/category_2), [33475289Cancer J 2021 Jan-Feb;27(1):17](http://pubmed.ncbi.nlm.nih.gov/33475289?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8422792/)
    - review on obesity and cancer can be found in [36672434Cancers (Basel) 2023 Jan 12;15(2)](http://pubmed.ncbi.nlm.nih.gov/36672434?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9857053/)
    - see also Cancer in Obesity in [Complications of Obesity](https://dpa-pde-oxford.shinyapps.io/condition/complications-of-obesity)
  + alcohol consumption ([National Cancer Institute Alcohol and Cancer Risk 2021 Jul 14](https://www.cancer.gov/about-cancer/causes-prevention/risk/alcohol/alcohol-fact-sheet#how-does-alcohol-affect-the-risk-of-cancer) )
  + smoking, although not as strong of a risk factor compared to weight status and alcohol intake ([NCCN 2022 Oct from NCCN website (free registration required)](https://www.nccn.org/guidelines/category_2))

Potential Risk Factors

* many studies have explored the relationship between various dietary components and risk of breast cancer, however, all studies are observational and therefore subject to confounding bias; further investigation may be needed to define specific associations with breast cancer risk
  + **> 36.3 g of red-meat consumption per day associated with increased risk of breast cancer in women with family history of breast cancer**

Cohort Study[31389007Int J Cancer 2020 Apr 15;146(8):2156](http://pubmed.ncbi.nlm.nih.gov/31389007?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7002279/#SD1)

studySummary

* + - Cohort Study based on prospective population-based cohort study
    - 42,012 women aged 35-74 years (mean age 55 years) in the United States with no history of breast cancer but have a sister or half-sister diagnosed with breast cancer were assessed
      * dietary data assessed with 110 item Food Frequency Questionnaire which then was used to create food groups
        + red meat defined as beef, veal, pork, lamb, game meat
        + white meat poultry defined as chicken, turkey, Cornish hen, duck, goose, quail, pheasant/game birds
        + cured/processed meats defined as hot dogs, sausages, corned beef, cured ham, cold cuts
        + seafood classified as high in omega-3 fatty acids or low in omega-3 fatty acids
      * diagnosis of breast cancer based of self-report during follow-up
    - 1,536 cases of breast cancer (3%) diagnosed during follow-up; mean follow-up 7.6 years
    - patients were divided into quartiles based on their amount of red meat consumption, median consumption of the highest quartile 52.7g (range 36.3- 415.5 g) red meat per day
    - > 36.3g of red meat consumption associated with increased risk of
      * invasive breast cancer (adjusted hazard ratio [HR] 1.32, 95% CI 1.02-1.48)
      * estrogen receptor positive invasive breast cancer (adjusted HR 1.27, 95% CI 1.03-1.57)
      * postmenopausal invasive breast cancer (adjusted HR 1.28, 95% CI 1.04-1.56)
      * effect of red meat consumption stronger among women with relative diagnosed with breast cancer < 50 years old
    - >34g of white meat poultry consumption associated with decreased risk of postmenopausal invasive breast cancer (adjusted HR 0.8, 95% CI 0.66-0.96)
    - cured meat, white meat, seafood intake, or cooking method were not associated with risk of invasive breast cancer
    - Reference - Sister Study ([31389007Int J Cancer 2020 Apr 15;146(8):2156](http://pubmed.ncbi.nlm.nih.gov/31389007?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7002279/#SD1)
  + **regular dairy consumption (≥1 time per week) associated with increased risk of female breast cancer among adults in China**

Cohort Study[35513801BMC Med 2022 May 6;20(1):134](http://pubmed.ncbi.nlm.nih.gov/35513801?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9074208/#MOESM1)

studySummary

* + - Cohort Study based on prospective population-based cohort study
    - 510,146 adults aged 35-74 years (mean age 52 years, 59% women) in China without history of cancer were assessed
      * dietary data collected from interviewer-lead questionnaires to obtain frequency of types of foods consumed
      * follow-up survey of 25,000 adults obtained information to quantify daily portions of foods consumed and was used to estimate mean total amounts consumed in analyses
      * diagnosis of breast cancer based on disease surveillance in registries, insurance claims, or clinical follow-up for patients without insurance
    - 0.8 cases of female breast cancer per 1,000 person years diagnosed during follow-up; mean follow-up 10.8 years
    - 20.4% of adults defined as regular dairy consumers (consume dairy at least once per week); mean dairy intake 80.8g/day
    - 68.5% of adults defined as nondairy consumers (never or rarely consume dairy); mean dairy intake 24g/day
    - compared to nondairy consumers, regular dairy consumption associated with increased risk of female breast cancer (adjusted hazard ratio [HR] 1.22, 95% CI 1.12-1.32)
    - risk of breast cancer for each 50g/day higher consumption of dairy (adjusted HR 1.17, 95% CI 1.07-1.29)
    - Reference - [35513801BMC Med 2022 May 6;20(1):134](http://pubmed.ncbi.nlm.nih.gov/35513801?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9074208/#MOESM1)
    - While frequency of dairy consumption and mean daily intake may seem low, average dairy consumption in China is reported lower than in other Western countries and is not as commonly consumed.
  + **increased consumption of ultra-processed foods associated with increased risk of breast cancer and cancer overall**

Cohort Study[29444771BMJ 2018 Feb 14;360:k322](http://pubmed.ncbi.nlm.nih.gov/29444771?dopt=Abstract)[Full Text](http://www.bmj.com/content/360/bmj.k322.long)

studySummaryincreased consumption of ultra-processed foods associated with increased risk of breast cancer and cancer overall (BMJ 2018 Feb 14)03/08/2018 03:48:00 PMObstetric\_and\_Gynecologic\_ConditionsOncologic\_DiseaseObstetric\_and\_Gynecologic\_Conditions Oncologic\_Diseaseincreased consumption of ultra-processed foods associated with increased risk of breast cancer and cancer overall (BMJ 2018 Feb 14)03/08/2018 03:48:00 PM29444771

* + - based on prospective population-based cohort study Cohort Study
    - 104,980 adults (mean age 42 years, 78% women) in France completed 3 web-based 24-hour dietary records every 6 months to assess processed food consumption
    - food was categorized based on degree of processing by NOVA classification
      * minimally or unprocessed food includes fruits, vegetables, pulses, rice, pasta, eggs, meat, fish, or milk
      * ultra-processed food includes mass-produced breads and desserts, packaged snacks, sweetened drinks, frozen or shelf-stable ready meals, reconstituted meat products, and food products made mostly from sugar, oils and fats, as well as hydrogenated oils, modified starches, flavoring agents, artificial sweeteners, and other cosmetic additives
    - ultra-processed food intake consisted mainly of sugary products (26%) and drinks (20%), starchy foods and breakfast cereals (16%), and ultra-processed fruits and vegetables (15%)
    - hazard ratios were adjusted for other dietary characteristics such as lipid, sodium, and carbohydrate intakes, as well as other biological factors
    - 2,228 adults developed cancer during median follow-up of 5 years (33% breast cancer, 13% prostate cancer, 7% colorectal cancer)
    - every 10% increase in proportion of ultra-processed foods in diet associated with
      * increased risk of breast cancer (adjusted hazard ratio [HR] 1.11, 95% CI 1.01-1.21)
      * increased risk of cancer overall (adjusted HR 1.13, 95% CI 1.07-1.18)
    - PubMed29444771BMJ (Clinical research ed.)20180214BMJ360k322k322 Reference - [29444771BMJ 2018 Feb 14;360:k322](http://pubmed.ncbi.nlm.nih.gov/29444771?dopt=Abstract)[full-text](http://www.bmj.com/content/360/bmj.k322.long)
  + **increased consumption of sugary drinks associated with increased risk of breast cancer and cancer overall**

Cohort Study[BMJ 2019 Jul 10;366:l2408](http://pubmed.ncbi.nlm.nih.gov/31292122?dopt=Abstract)

studySummaryincreased consumption of sugary drinks associated with increased risk of breast cancer and cancer overall (BMJ 2019 Jul 10)07/24/2019 09:51:43 AMOncologic\_DiseaseOncologic\_Diseaseincreased consumption of sugary drinks associated with increased risk of breast cancer and cancer overall (BMJ 2019 Jul 10)07/24/2019 09:51:43 AM

* + - based on population-based prospective cohort studyCohort Study
    - 101,257 adults (mean age 42 years, 79% women) in France were assessed for consumption of sugary drinks and artificially sweetened beverages using ≥ 2 repeated 24-hour dietary records
    - mean number of dietary records 5.6
    - mean sugary drink intake 92.9 mL/day, mean artificially sweetened beverage intake 24.2 mL/day, and mean 100% fruit intake 55.8 mL/day
    - median follow-up of 5.1 years
    - incident overall cancer in 2,193 adults (0.44 per 100 person-years) and incident breast cancer in 693 adults
    - increased risk of breast cancer associated with increased consumption of
      * sugary drinks overall (adjusted hazard ratio [HR] 1.22 per 100 mL/day, 95% CI 1.07-1.39)
      * sugary drinks except 100% fruit juice (adjusted HR 1.23 per 100 mL/day, 95% CI 1.03-1.48)
    - no significant differences in risk of breast cancer associated with increased consumption of 100% fruit juice or artificially sweetened beverages
    - increased risk of overall cancer associated with increased consumption of
      * sugary drinks overall (adjusted HR 1.18 per 100 mL/day, 95% CI 1.1-1.27)
      * 100% fruit juice (adjusted HR 1.12 per 100 mL/day, 95% CI 1.03-1.23)
    - no significant difference in risk of overall cancer associated with increased consumption of artificially sweetened beverages
    - BMJ (Clinical research ed.)20190710BMJ366l2408l2408Reference - [BMJ 2019 Jul 10;366:l2408](http://pubmed.ncbi.nlm.nih.gov/31292122?dopt=Abstract), [full-text](https://www.bmj.com/content/366/bmj.l2408.long)
  + review comparing risk of breast cancer between Western and Mediterranean dietary patterns can be found in [37432206Nutrients 2023 Apr 25;15(9)](http://pubmed.ncbi.nlm.nih.gov/37432206?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10181478/)
  + review on impact of dietary fat on breast cancer incidence can be found in [36381753Cureus 2022 Oct;14(10):e30003](http://pubmed.ncbi.nlm.nih.gov/36381753?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9637429/#:~:text=Elevated%20total%20and%20saturated%20fats,progesterone%20receptor%2Dpositive%20breast%20cancer.&text=Saturated%20fat%20consumption%20was%20linked%20to%20an%20increased%20risk%20of%20breast%20cancer.)
* exposure to organochlorine compounds are thought to contribute to breast cancer risk due to their ability to mimic hormones (particularly estrogen) and disrupt the endocrine system but evidence is inconclusive ([12363327CA Cancer J Clin 2002 Sep-Oct;52(5):301](http://pubmed.ncbi.nlm.nih.gov/12363327?dopt=Abstract))
* nightshift work may increase risk of breast cancer after > 20 years of work or after shorter duration but more intense night shifts ([28770538Curr Environ Health Rep 2017 Sep;4(3):325](http://pubmed.ncbi.nlm.nih.gov/28770538?dopt=Abstract))

Factors Associated With Decreased Risk

* factors associated with decreased risk of breast cancer include
  + menopause prior to 45 years old
  + prior use of risk-reducing agent such as anastrozole, exemestane, tamoxifen, or raoloxifene,
  + exercise
  + history of breastfeeding
  + Reference - [NCCN 2022 Oct from NCCN website (free registration required)](https://www.nccn.org/guidelines/category_2)
* TOPIC\_Q1G\_G4L\_PYB\_\_LI\_TZJ\_Y22\_MBCEU05212405/21/2024 07:37:49 PMevidenceUpdatelowplusFamily\_Medicine Internal\_Medicine Oncologic\_Disease Prevention\_and\_Screening Primary\_Careincreasing cardiorespiratory fitness might be associated with reduced risk of colorectal cancer, but body mass index may play mediating role (Br J Cancer 2024 Jan)

**increasing cardiorespiratory fitness might be associated with reduced risk of breast cancer, but body mass index may play mediating role**

Cohort Study[Br J Cancer 2024 Jan;130(1):114](http://doi.org/10.1038/s41416-023-02489-3)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10781786/)

studySummary

* + Cohort Studybased on population-based cohort study
  + 72,572 adults aged 40-46 years who had submaximal fitness test between 2009 and 2012 from the United Kingdom Biobank were assessed
  + 4,290 cancers were diagnosed over median follow-up 11 years
  + adjustment for confounding
    - model for colorectal cancer adjusted for age, sex, self-reported racial or ethnic group, Townsend index of deprivation, education, employment status, smoking status, alcohol consumption, red and processed meat consumption, fish consumption, fruit and vegetable consumption, salt consumption, diabetes, hypertension, medication use (beta-blockers, calcium channel blocker, angiotensin-converting enzyme inhibitor, diuretic, bronchodilator, lipid-lowering agent, iron deficiency agents, nonsteroidal anti-inflammatory drug, metformin)
    - model for female reproductive cancers additionally adjusted for age at menarche, age at menopause, parity, hormone replacement therapy, and oral contraceptive use
  + increasing cardiorespiratory fitness associated with reduced risk of
    - breast cancer (adjusted hazard ratio [HR] 0.96 per 3.5 mL O2/minute/kg total body mass increase in fitness (equivalent to 1 metabolic equivalent of task, 95% CI 0.92-0.99)
    - endometrial cancer (adjusted HR 0.81 per 3.5 mL O2/minute/kg total body mass increase in fitness, 95% CI 0.73-0.89)
    - colorectal cancer (adjusted HR 0.94 per 3.5 mL O2/minute/kg total body mass increase in fitness, 95% CI 0.9-0.99)
  + no significant difference in risk of cancers in model additionally adjusted for body mass index
  + in Mendelian randomization analysis, higher level of genetically predicted fitness associated with decreased risk of breast cancer (odds ratio 0.92 per 5 mL O2/minute/kg fat-free mass increase, 95% CI 0.86-0.98)
  + Reference - [Br J Cancer 2024 Jan;130(1):114](http://doi.org/10.1038/s41416-023-02489-3)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10781786/)
* no specific dietary components are clearly known to reduce risk of breast cancer, but as adult weight gain and obesity are known risk factors for breast cancer proper nutrition may help maintain an appropriate bodyweight and decrease cancer risk
  + some evidence suggests diets high in fruits and vegetables may decrease risk of breast cancer
  + vitamin D is theorized to play a role in cancer prevention but further evidence is needed; see also Vitamin D in [Vitamins for Disease Prevention](https://dpa-pde-oxford.shinyapps.io/prevention/vitamins-for-disease-prevention#GUID-AEA8EB97-8FC5-4DF8-8C70-325087DA31E2)
  + Reference - [NCCN 2022 Oct from NCCN website (free registration required)](https://www.nccn.org/guidelines/category_2)
  + TOPIC\_Q1G\_G4L\_PYB\_\_LI\_LVJ\_CWX\_WWBEU03222303/22/2023 11:19:47 AMevidenceUpdatestandardObstetric\_and\_Gynecologic\_Conditions Oncologic\_Diseasenondeficient circulating 25-hydroxyvitamin D level (> 20 ng/mL) associated with reduced risk of breast cancer among non-Black Hispanic or Latina persons but not among Black or African American persons (Cancer 2022 Jul 1)

**adequate 25-hydroxyvitamin D level (> 20 ng/mL) associated with reduced risk of breast cancer among non-Black Hispanic or Latina persons but not among Black or African American persons**

Case-cohort study[Cancer 2022 Jul 1;128(13):2463](https://pubmed.ncbi.nlm.nih.gov/35466399)

studySummary

* + - Case-cohort study based on case-cohort study
    - 50,884 female adults aged 35-74 years without history of breast cancer who had a sister previously diagnosed with breast cancer from Sister Study cohort were assessed
    - 1,862 persons who self-identified as Black or African American or non-Black Hispanic or Latina with baseline serum and/or plasma 25-hydroxyvitamin D data were included in analysis
      * 290 Black or African American persons who developed breast cancer (invasive breast cancer or ductal carcinoma in situ) were compared to 1,084 Black or African American persons (6.8% with breast cancer) randomly selected from Sister Study cohort
      * 125 Hispanic or Latina persons who developed breast cancer were compared to 461 Hispanic or Latina persons (5.2% with breast cancer) randomly selected from Sister Study cohort
    - mean follow-up of 9.2 years
    - nondeficient 25-hydroxyvitamin D level (> 20 ng/mL) associated with reduced risk of breast cancer among non-Black Hispanic or Latina persons (adjusted hazard ratio 0.52, 95% CI 0.29-0.93)
    - no significant association between nondeficient 25-hydroxyvitamin D level and risk of breast cancer among Black or African American persons (adjusted hazard ratio 0.89, 95% CI 0.68-1.18)
    - PubMed35466399CancerCancer20220701128132463-24732463Reference - [Cancer 2022 Jul 1;128(13):2463](https://pubmed.ncbi.nlm.nih.gov/35466399)

Associated Conditions

* **thyroid disease associated with breast cancer**

Case-Control Study[J Clin Endocrinol Metab 1996 Mar;81(3):990](http://pubmed.ncbi.nlm.nih.gov/8772562/)

studySummary

* + Case-Control Study based on study of 102 breast cancer patients and 100 age-matched controls
  + comparing breast cancer patients vs. controls
    - 46% vs. 14% had evidence for thyroid disease
    - 23.5% vs. 8% had thyroperoxidase antibody
  + PubMed8772562The Journal of clinical endocrinology and metabolismJ Clin Endocrinol Metab19960301813990-4990Reference - [J Clin Endocrinol Metab 1996 Mar;81(3):990](http://pubmed.ncbi.nlm.nih.gov/8772562/) in J Watch Women's Health 1996 Apr;1(1):7

Etiology and Pathogenesis

Causes

* etiology mostly unknown, but family history is a strong determinant of risk, indicating hereditary factors play a role, such as
  + high penetrance cancer susceptibility genes, such as *BRCA1*, *BRCA2*, and *TP53*
  + single nucleotide polymorphisms (SNPs) in *FGFR2*, *TNRC9*, *MAP3K1*, *LSP1*, *CASP8*, and *TGFB1*
  + Reference - [mnh17975657pcxh27477499pmdc17975657pJ Clin Invest 2007 Nov;117(11):3155](http://pubmed.ncbi.nlm.nih.gov/17975657?dopt=Abstract) [full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2045618/)
* somatic genetic mutational profiles by intrinsic molecular subtype
  + luminal A and B tumors have distinct mutational profiles with mutations in regulators of luminal differentiation in normal mammary gland, such as *PI3K*, *MAP3K1*, *GATA3*, *FOXA1*, and *TBX3*
  + basal-like tumors
    - generally have higher number of somatic mutations and genomic instability than luminal A and B tumors but have lower number of frequently mutated genes
    - very high rate of *TP53* mutations (the only frequently mutated gene in this subtype)
  + Reference - [mnh25703331paph110398578pa9h110398578pbyh110398578pcxh110398578pmdc25703331pOncogene 2015 Oct 16;34(42):5309](http://pubmed.ncbi.nlm.nih.gov/25703331?dopt=Abstract) [full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4734640/)

Pathogenesis

Normal breast development and morphology

* prenatal breast development
  + the formation of primary mammary bud and development of rudimentary mammary gland occur during prenatal period
  + development process does not differ between males and females
  + during first trimester
    - proliferation of paired areas of epithelial cells in epidermis of thoracic region occurs around day 35 and extends in a line between fetal axilla and inguinal region, forming 2 ridges known as mammary crests or milk lines
    - these mammary crests atrophy, other than the solid epithelial masses in pectoral region which form paired primary mammary buds
    - near end of first trimester, in response to mesenchymal signalling, primary mammary buds grow inward into mesenchyme and become larger; indentations appear along basolateral margins and become sites for eventual secondary mammary outgrowths
    - by end of first trimester, well-defined paired mammary buds penetrating upper dermis are present with surrounding mesenchymal cells differentiating to form fibroblasts, smooth muscle cells, capillary endothelial cells, and adipocytes
  + during second trimester
    - secondary epithelial buds appear from indentations on main mammary bud and develop vertically reaching into surrounding mesenchyme
    - secondary epithelial sprouts canalize and form secondary buds that eventually become lactiferous ducts
    - epithelial cells lining lactiferous ducts organize into 2 layers: the luminal layer gains secretory functions and the other differentiates into myoepithelial cells
    - during 5th month of gestation, ectoderm forms the areola
    - by end of second trimester, a tubular architecture within dense fibroconnective tissue stroma is present
  + during third trimester
    - secondary epithelial buds continue to branch, canalize and develop into ducts
    - epidermis becomes depressed and forms mammary pit in the region of the future nipple; lactiferous ducts drain into retroareolar ampullae that connect to mammary pit on overlying skin
    - longitudinal and circular smooth muscle fibers align to form the nipple
    - in last several weeks of gestation, vascularity of loose fibroconnective tissue stroma increases and some limited secretory activity may occur
    - by full term, about 15-20 lobes of glandular tissue (each with a lactiferous duct that opens onto breast surface through mammary pit) are present
    - surrounding skin and fibrous suspensory ligaments of Cooper anchor breast to pectoralis major fascia and provide support
  + PubMed24872732Seminars in plastic surgerySemin Plast Surg201302012715-125Reference - [Semin Plast Surg 2013 Feb;27(1):5](http://pubmed.ncbi.nlm.nih.gov/24872732)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3706056/)
* infant breast development
  + neonatal pituitary glands is stimulated to produce prolactin due to falling maternal estrogen levels; this can reportedly lead to unilateral or bilateral breast enlargement and/or transient secretion of milk in as many as 70% of newborns
  + after birth, nipples turn outward from proliferation of underlying mesoderm and the areolae darken
  + morphological changes
    - type 1 - branching ductal system containing ≤ 2 dichotomous branchings
    - type 2 - branching ductal system containing > 2 dichotomous branchings; terminal lobular units absent
    - type 3- branching ductal system containing multiple branchings; lobular system well-developed
  + stages of functional maturation
    - type 1- all ducts and ductules lined with secretory type of epithelium
    - type 2- mixture of ducts lined with secretory and apocrine type of epithelium
    - type 3- nearly all ducts lined by apocrine type of epithelium
    - type 4 - mixture of ducts lined by apocrine type of epithelium and involuting ducts lined by multiple layers of epithelium
  + by 2 years old, the breast consists of small ductal structures in fibroblastic stroma; additional changes do not typically occur until puberty
  + PubMed24872732Seminars in plastic surgerySemin Plast Surg201302012715-125Reference - [Semin Plast Surg 2013 Feb;27(1):5](http://pubmed.ncbi.nlm.nih.gov/24872732)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3706056/)
* breast development during puberty
  + breast development begins to differ between males and female during puberty
  + development at this stage is largely influenced by levels of sex hormones, particularly estrogen
  + anatomic changes in adolescent girls vary based on pubertal maturity, ethnicity, and hormone levels
  + Tanner stages describe outward appearance of breasts on examination, typical ages reported from British cohort and reportedly occur earlier in United States
    - in stage 1 (preadolescence), the papilla become elevated; this typically occurs in girls between 8.5 and 13.5 years old
    - in stage 2, small mound of breast tissue develops with elevation of the nipple forming the breast bud; areola diameter increases; this typically occurs at about 11 years old
    - in stage 3, the breast and areola continue to increase in size; this typically occurs at about 12.5 years old
    - in stage 4, the nipple and areola increase in size and result in formation of secondary mound on breast; this typically occurs in girls between 13 and 14 years old
    - in stage 5, the secondary mound disappears as the areola recedes onto the breast forming a single contour; this typically occurs at about 15 years old
  + cellular changes during puberty
    - stroma with increases in fatty and fibrous tissue
    - epithelium forms into a branching, bilayered ductal structure including an outer layer of basal myoepithelial cells and an inner layer of luminal cells; luminal cell layer further separated into ductal luminal cells which line insides of ducts and alveolar luminal cells that secrete milk during lactation
    - ductal elongation and branching starts at the mammary stem cells in the terminal end bud
    - primary ducts that reach nipple form a network of subsidiary ducts with branching into segmental and subsegmental ducts
    - subsegmental ducts lead to terminal duct formation and subdivide into several terminal ductules or acini
    - group of acini from 1 terminal duct and the surrounding intralobular stroma make up a terminal duct lobular unit, which is the functional unit of breast
    - adipose tissue, immune cells, blood vessels, and fibroblasts make up the remaining breast space
    - lobular development consists of 4 types
      * type 1 consists of short terminal duct ending in collection of secretory cells (alveoli)
      * types 2-4 consist of terminal duct that branches into several ductules and increasing number of alveoli; type 4 lobules occur in adult women who have gone through both pregnancy and lactation
    - PubMed24872732Seminars in plastic surgerySemin Plast Surg201302012715-125Reference - [Semin Plast Surg 2013 Feb;27(1):5](http://pubmed.ncbi.nlm.nih.gov/24872732)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3706056/)

Breast cancer development

* 2 possible models for origin of breast tumor subtypes
  + in cell-of-origin model, each tumor subtype originates in different stem or progenitor cell
  + in tumor subtype-specific event model, cell of origin may be same for different tumor subtypes, with differences in tumor phenotype determined by acquired genetic and epigenetic events
  + Reference - [mnh17975657pcxh27477499pmdc17975657pJ Clin Invest 2007 Nov;117(11):3155](http://pubmed.ncbi.nlm.nih.gov/17975657?dopt=Abstract) [full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2045618/)
* progression thought to occur through defined pathological and clinical stages, beginning with ductal hyperproliferation through in situ and invasive carcinomas and finally into metastatic disease
  + no specific genetic events have yet been identified that indicate progression from in situ to invasive or metastatic disease
  + tumor progression may be driven by accumulation of additional genetic changes combined with clonal expansion and selection
  + epithelial-mesenchymal interactions, cells within the microenvironment (such as myoepithelial and endothelial cells, fibroblasts, myofibroblasts, leukocytes, and other cell types) and extracellular matrix molecules are important for both normal development and breast tumorigenesis
  + abnormal autocrine/paracrine signaling also plays role in breast tumor progression; chemokines upregulated in tumor myoepithelial cells and myofibroblasts enhance tumor cell proliferation, migration, and invasion, and promote angiogenesis and metastatic spread
  + some microenvironmental changes in tumors may be permanent, suggesting these may be due to heritable epigenetic modifications that reflect abnormal differentiation in tumor cells
  + African American women and women in Africa develop basal-like tumors (with higher risk of metastases) more often than women of European descent, suggesting microenvironment associated with specific genotypes influence risk of metastases
  + Reference - [mnh17975657pcxh27477499pmdc17975657pJ Clin Invest 2007 Nov;117(11):3155](http://pubmed.ncbi.nlm.nih.gov/17975657?dopt=Abstract) [full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2045618/)
* possible mechanisms for estrogen in the tumorigenesis of breast cancer
  + metabolism of estradiol by a cytochrome P-450 isoform expressed in breast tissue gives rise to oxidative metabolites
    - one metabolite, 3,4-quinone, may form unstable adducts with adenine and guanine in DNA, leading to depurination and mutation of DNA in breast tissue
    - PubMed31170150PLoS computational biologyPLoS Comput Biol20190606156e1007071e1007071 reduction of quinones back to hydroquinones and catechols may produce reactive oxygen molecules, leading to oxidative damage of DNA in breast tissue
  + increasing levels of estrogen bind to estrogen receptors in breast tissue, altering gene expression and ultimately leading to increased cell proliferation and decreased apoptosis
  + Reference - [16421368N Engl J Med 2006 Jan 19;354(3):270](http://pubmed.ncbi.nlm.nih.gov/16421368?dopt=Abstract), commentary can be found in [16611962N Engl J Med 2006 Apr 13;354(15):1647](http://pubmed.ncbi.nlm.nih.gov/16611962?dopt=Abstract)

History and Physical

History and Physical

Clinical presentation

* some women present with breast abnormalities detected during screening, without any other signs or symptoms[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
* common presenting signs and symptoms include[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + palpable breast mass
  + nipple discharge
  + skin changes on breast or nipple
  + asymmetric thickening or nodularity
  + focal breast pain
  + axillary mass
* pregnancy-associated breast cancer commonly presents as a palpable mass; other signs/symptoms include focal pain, diffuse breast enlargement, nipple discharge (especially persistent unilateral bloody discharge), and rarely, unilateral milk rejection (infant rejects feeding from cancer-affected breast) [J Am Coll Radiol 2018 Nov;15(11S):S263](http://pubmed.ncbi.nlm.nih.gov/30392595)[PDF](https://acsearch.acr.org/docs/3102382/Narrative/)
* for workup by specific presentation, see [Diagnosis and staging](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-189F6A48-4A35-4F7F-8E7F-1A22CF3863B4)

History

Chief concern (CC)

* when present, breast-related symptoms may include[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + breast mass; see also [Palpable breast mass evaluation in women](https://dpa-pde-oxford.shinyapps.io/evaluation/palpable-breast-mass-evaluation-in-female-patients)
  + nipple discharge
  + asymmetric thickening or nodularity
  + skin changes, such as peau d'orange, erythema, ulcers, scaling, eczema, or nipple excoriation
  + focal breast pain
  + axillary mass

History of present illness (HPI)

* ask about[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + palpable breast mass including
    - duration of mass
    - changes in size of mass
    - changes related to menstrual cycle
  + asymmetric thickening or nodularity including
    - duration
    - changes in size
    - changes related to menstrual cycle
  + nipple discharge including
    - duration, color, and whether it has been bloody
    - whether spontaneous, unilateral, and or comes from a single duct
    - medication use associated with nipple discharge, such as prior or current use of oral contraceptives, estrogen, opiates, or antihypertensive or psychoactive drugs
  + breast pain including
    - type of pain
    - location
    - severity
    - duration
    - relationship to menstrual cycle or physical activity
    - what factors seem to make it better or worse
  + skin changes including
    - duration
    - changes over time
  + axillary mass
    - duration
    - changes over time
    - pain
* **breast pain without other symptoms not associated with increased risk of breast cancer**

Cohort Study[9831579BMJ 1998 Nov 28;317(7171):1492](http://pubmed.ncbi.nlm.nih.gov/9831579?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC28731/?tool=pubmed)

studySummary

* + based on cohort study Cohort Study
  + 987 women with mammography and/or ultrasonography for breast pain alone and 987 asymptomatic women with screening mammography
  + malignancy in 0.8% of cases (4 patients with cancer in painful breast, 4 with cancer in contralateral asymptomatic breast) vs. 0.7% of controls, all identified on imaging studies and confirmed surgically (no p value reported)
  + PubMed9831579BMJ (Clinical research ed.)19981128BMJ317717114921492 Reference - [9831579BMJ 1998 Nov 28;317(7171):1492](http://pubmed.ncbi.nlm.nih.gov/9831579?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC28731/?tool=pubmed), commentary can be found in [10336279BMJ 1999 Apr 10;318(7189):1009](http://pubmed.ncbi.nlm.nih.gov/10336279?dopt=Abstract)

Past medical history (PMH)

* ask about[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + prior history of breast cancer
  + prior thoracic radiation (especially received before aged 30 years)
  + use of postmenopausal hormone replacement therapy (HRT)
  + history of ovarian cancer
  + number of previous breast biopsies (if any)
  + history of atypical hyperplasia in a breast biopsy
  + history of breast carcinoma in situ
  + age at menarche
  + age at first live birth (if any)

Family history (FH)

* ask about family history[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + of known mutation in cancer susceptibility gene within the family
  + of cancer incidence in first- or second-degree relatives and age at presentation, especially if breast or ovarian cancer
* **patient-reported family cancer histories for first-degree relatives are accurate for breast and colon cancer**

Systematic Review[mdc15383520pJAMA 2004 Sep 22/29;292(12):1480](http://pubmed.ncbi.nlm.nih.gov/15383520?dopt=Abstract)

studySummary

* + based on systematic review Systematic Review
  + 14 studies comparing patient-reported family histories of cancer with review of relatives' medical records, death certificates, and cancer registries
  + patient-reported family history of breast cancer in first-degree relative had positive likelihood ratio 8.9 (95% CI 5.4-15) and negative likelihood ratio 0.2 (95% CI .08-0.49)
  + PubMed15383520JAMA20040922JAMA2921214801480 Reference - [mdc15383520pJAMA 2004 Sep 22/29;292(12):1480](http://pubmed.ncbi.nlm.nih.gov/15383520?dopt=Abstract)
* 13.6% of patients with breast cancer had family history of breast cancer in Swedish Family-Cancer Database ([17804474Ann Oncol 2008 Jan;19(1):163](http://pubmed.ncbi.nlm.nih.gov/17804474?dopt=Abstract))
* family history may detect patients with *BRCA1* or *BRCA2* (breast cancer susceptibility genes)
  + *BRCA1* and *BRCA2* mutations associated with increased risk for breast, ovarian, fallopian tube, and primary peritoneal carcinoma
  + *BRCA2* mutations may be associated with increased risks for prostate cancer, pancreatic cancer, gallbladder and bile duct cancer, stomach cancer, and malignant melanoma
  + see [Hereditary Breast and Ovarian Cancer (HBOC) Syndromes](https://dpa-pde-oxford.shinyapps.io/condition/hereditary-breast-and-ovarian-cancer-hboc-syndromes)
* brief review of family history of breast cancer can be found in [15626802BMJ 2005 Jan 1;330(7481):26](http://pubmed.ncbi.nlm.nih.gov/15626802?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC539848/), correction can be found in BMJ 2005 Feb 5;330(7486):307, commentary can be found in [15790649BMJ 2005 Mar 26;330(7493):730](http://pubmed.ncbi.nlm.nih.gov/15790649?dopt=Abstract)

Physical

Breast exam

* breast exam, including both inspection and palpation[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + inspection is performed in both upright and supine positions
  + patient positioning may be done to elicit subtle shape or contour changes
  + palpation for detection of mass, asymmetric thickening, or nodularity ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - inspect for skin changes suggestive of inflammatory breast cancer such as peau d'orange, skin thickening, edema, and erythema, nipple excoriation, scaling or eczema, or ulcers ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - inspect for other skin changes suggestive of breast cancer or Paget disease such as nipple excoriation, scaling, eczema, and skin ulceration ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + examine nipple for discharge, retraction, or nipple inversion ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + breast exam should include breast, axilla, and clavicular lymph nodes
* clinical breast exam (CBE)
  + helps detect early stage palpable cancers, particularly those that are mammographically occult such as lobular carcinoma
  + time spent on clinical breast exam is associated with increased detection of palpable mass
  + note location and distance of any abnormalities from nipple for comparison with imaging
  + CBE technique
    - suggested technique
      * value of inspection unproven as studies focus on palpation
      * patient position
        + supine
        + to flatten lateral part of breast (particularly useful if larger breasts), have patient roll onto contralateral hip, rotate shoulders into supine position, and place ipsilateral hand on forehead
        + to flatten medial part of breast, have patient lie flat on back and move elbow to shoulder level
      * thoroughness of search
        + cover area from clavicle to bra line
        + cover area from midsternum to midaxillary line
        + use systematic overlapping pattern; vertical strip pattern with overlapping vertical rows found to be more thorough than concentric circles or radial spoke pattern in 1 study
      * finger motion developed on studies using silicone breast models
        + 3 middle fingers held together
        + finger pads used for exam
        + palpation done with dime-sized circular motion
        + light, medium, and deep pressure used for each spot
      * longer duration of exam of silicone breast models associated with higher sensitivity in silicone models, article states at least 3 minutes necessary for careful exam of average-sized breast but no clear evidence
      * use of correct technique and examiner experience may improve detection of masses, but limited evidence
      * palpation of axillary and supraclavicular areas for adenopathy recommended, but not tested
      * palpation of nipple area recommended to be done similar to rest of breast, squeezing the nipple to assess for nonspontaneous nipple discharge on exam not shown to increase cancer detection rates
      * PubMed10517431JAMAJAMA19991006282131270-801270Reference - [JAMA 1999 Oct 6;282(13):1270](http://pubmed.ncbi.nlm.nih.gov/10517431), commentary can be found in [JAMA 2000 Apr 5;283(13):1687](http://pubmed.ncbi.nlm.nih.gov/10755490?dopt=Abstract), [J Am Geriatr Soc 2001 Jul;49(7):991](http://pubmed.ncbi.nlm.nih.gov/11527493?dopt=Abstract)
    - **formal training in vertical strip 3 pressure method (VS3PM) and longer duration of examination each may be associated with increased detection of breast masses in silicone models by first-year residents (**[**level 3 [lacking direct] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cohort Study[18058184J Gen Intern Med 2008 Feb;23(2):129](http://pubmed.ncbi.nlm.nih.gov/18058184?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2359163/)

studySummary3

* + - * based on cohort study without clinical outcomesCohort Study
      * 75 first-year residents were formally trained in VS3PM of breast examination while 93 second-year residents were not and both groups performed palpable breast exam on breast model containing 1 (3 mm sized) nodule
      * VS3PM entails consistent search pattern, deep palpitation, circling downward, and adequate overlap of coverage
      * factors significantly associated with detection of breast lump were
        + using components of VS3PM (p < 0.0001)
        + increased duration of examination (p < 0.0001)
      * residents formally trained in VS3PM performed better than more experienced residents without training (p < 0.0001)
      * PubMed18058184Journal of general internal medicine20080201J Gen Intern Med232129129 Reference - [18058184J Gen Intern Med 2008 Feb;23(2):129](http://pubmed.ncbi.nlm.nih.gov/18058184?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2359163/)

Performance status scales

* performance status evaluation to help characterize patient and inform management
  + Karnofsky Performance Status (KPS) scale
    - total score range 0% (dead) to 100% (normal)
  + Eastern Cooperative Oncology Group/World Health Organization (ECOG/WHO) Performance Status Scale
    - total score range 0 (fully active) to 5 (dead)

Diagnosis and Staging

Diagnosis\_and\_StagingDiagnosis\_and\_Staging

Making the Diagnosis

* suspect breast cancer in patients with any of the following signs or symptoms[1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF5142),[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__ANC_1607337114),[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + abnormal screening mammogram
  + palpable breast mass
  + nipple discharge
  + skin changes on breast or nipple
  + asymmetric thickening or nodularity
  + focal breast pain
  + axillary mass
* diagnosis based on clinical [breast exam](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#BREAST_EXAM) and lymph node assessment plus imaging and confirmed by pathological assessment of biopsy[1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF5142),[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__ANC_1607337114),[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + [imaging](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#IMAGING_STUDIES)
    - generally performed using [diagnostic mammogram](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#DIAGNOSTIC_MAMMOGRAPHY) and [ultrasound](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#ULTRASOUND) of breast and regional lymph nodes; recommendations for imaging vary based on presentation and age
    - [magnetic resonance imaging (MRI)](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#MRI_FOR_DETECTION_OF_RECURRENT_OR_METASTATIC_DISEASE_AT_PRESENTATION) of breast not routinely recommended for diagnosis, but may be considered in patients with hereditary breast cancer associated with *BRCA* mutations, breast implants, lobular cancers, suspicion of multifocality or multicentricity, or in case of discrepancies between conventional imaging and clinical examination ([ESMO Grade B, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
  + pathological assessment of [biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#BIOPSY_AND_PATHOLOGY)
    - generally performed using core needle biopsy, preferably with ultrasound or stereotactic guidance
    - also assess suspicious lymph nodes using ultrasound-guided fine needle aspiration or core needle biopsy ([ESMO Grade A, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
* blood tests and radiologic studies to assess for metastases after diagnosis; staging only indicated for symptomatic patients or those at high risk of relapse[1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF5142),[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF6778),[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__ANC_1607337114),[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + [blood tests](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#BLOOD_TESTS) generally not performed except for patients with signs and symptoms suggesting metastases ([ESMO Grade D, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
  + chest computed tomography (CT), abdominal ultrasound, and/or bone scan may be considered for patients with clinically positive axillary nodes, primary tumors ≥ 5 cm, aggressive biology, or clinical signs, symptoms, or laboratory values suggesting metastases ([ESMO Grade B, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
  + fluorodeoxyglucose positron emission tomography (PET)/CT may be useful for patients with suspected locally advanced and/or inflammatory disease ([ESMO Grade B, Level V](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE)), or if conventional imaging findings inconclusive ([ESMO Grade A, Level V](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))

Differential Diagnosis

* for pain
  + fibrocystic changes
  + dorsal radiculitis
  + [Tietze syndrome](https://dpa-pde-oxford.shinyapps.io/condition/costochondritis) (inflammation in costochondral junction)
  + [mastitis](https://dpa-pde-oxford.shinyapps.io/condition/lactational-mastitis)
  + see also [Mastalgia](https://dpa-pde-oxford.shinyapps.io/condition/mastalgia) for additional information
* for palpable breast mass
  + fibroadenoma (most common)
  + lactating adenoma
  + benign phyllodes tumor
  + galactocele
  + [lipoma](https://dpa-pde-oxford.shinyapps.io/condition/common-benign-skin-lesions)
  + fat necrosis and scarring
  + simple cyst
  + intracystic papilloma
  + hematoma
  + [mastitis](https://dpa-pde-oxford.shinyapps.io/condition/lactational-mastitis)
  + abscess
  + [ductal carcinoma in situ](https://dpa-pde-oxford.shinyapps.io/condition/ductal-carcinoma-in-situ-dcis) (DCIS)
  + [lymphoma](https://dpa-pde-oxford.shinyapps.io/condition/non-hodgkin-lymphoma-nhl)
  + melanoma
  + see [Palpable breast mass evaluation in women](https://dpa-pde-oxford.shinyapps.io/evaluation/palpable-breast-mass-evaluation-in-female-patients) for additional causes and information
* for nipple discharge
  + endocrine abnormalities, such as pituitary adenoma, primary hypothyroidism, ectopic production of prolactin, or hypothalamic disorders
  + pregnancy
  + drug use, such as psychoactive drugs, antihypertensive medications, gastrointestinal medications, opiates, oral contraceptives, or estrogen replacement therapy
  + intraductal papilloma
  + duct ectasia
  + trauma
  + proliferative breast disease
  + Reference - [17914335Cancer Control 2007 Oct;14(4):350](http://pubmed.ncbi.nlm.nih.gov/17914335?dopt=Abstract)
* for abnormal mammogram findings[1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF5142),[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF6778),[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__ANC_1607337114),[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + [ductal carcinoma in situ](https://dpa-pde-oxford.shinyapps.io/condition/ductal-carcinoma-in-situ-dcis)
  + [lobular carcinoma in situ](https://dpa-pde-oxford.shinyapps.io/condition/lobular-carcinoma-in-situ)
  + radial scar (benign sclerosing lesion)
  + cyst
  + lymph node
  + fibroadenoma and other benign fibroepithelial tumors

Testing Overview

* prior to diagnosis, assure [history](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#HISTORY_OF_PRESENT_ILLNESS__HPI_) taken, [risk factors](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#PAST_MEDICAL_HISTORY__PMH_) updated, and [clinical exam](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#BREAST_EXAM) performed
* initial testing generally includes [imaging](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#IMAGING_FOR_DIAGNOSIS), usually performed using [diagnostic mammogram](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#DIAGNOSTIC_MAMMOGRAPHY) and [ultrasound](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#ULTRASOUND) of breast and regional lymph nodes
* additional work-up depends on initial presentation and results from initial mammogram or ultrasound, see follow-up imaging recommendations for
  + [palpable breast mass](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#RECOMMENDATIONS_FOR_PALPABLE_BREAST_MASS)
  + [nipple discharge](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#RECOMMENDATIONS_FOR_NIPPLE_DISCHARGE)
  + [asymmetric thickening or nodularity](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#RECOMMENDATIONS_FOR_ASYMMETRIC_THICKENING_OR_NODULARITY)
  + [skin changes](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#RECOMMENDATIONS_FOR_SKIN_CHANGES)
  + [breast pain](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#RECOMMENDATIONS_FOR_BREAST_PAIN)
  + [axillary mass](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#RECOMMENDATIONS_FOR_AXILLARY_MASS)
  + [abnormal screening mammogram](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#RECOMMENDATIONS_FOR_AN_ABNORMAL_SCREENING_MAMMOGRAM)
* malignancy is confirmed by pathologic assessment of [biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#BIOPSY_AND_PATHOLOGY)
  + generally by [core needle biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#CORE_NEEDLE_BIOPSY), preferably with imaging guidance
  + assess clinically suspicious [lymph nodes](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#AXILLARY_LYMPH_NODE_EVALUATION) using ultrasound-guided fine needle aspiration or core needle biopsy
* in case neoadjuvant systemic therapy is planned, determine tumor subtype before proceeding

Staging System(s)

* American Joint Committee on Cancer (AJCC) staging for breast cancer, 8th ed.

| Table 5: Clinical Staging | | | |
| --- | --- | --- | --- |
| **Stage** | **T** | **N** | **M** |
| 0 | Tis | N0 | M0 |
| IA | T1\* | N0 | M0 |
| IB | T0 | N1mi | M0 |
| T1\* | N1mi | M0 |
| IIA | T0 | N1\*\* | M0 |
| T1\* | N1\*\* | M0 |
| T2 | N0 | M0 |
| IIB | T2 | N1 | M0 |
| T3 | N0 | M0 |
| IIIA | T0 | N2 | M0 |
| T1\* | N2 | M0 |
| T2 | N2 | M0 |
| T3 | N1-N2 | M0 |
| IIIB | T4 | N0-N2 | M0 |
| IIIC | Any T | N3 | M0 |
| IV | Any T | Any N | M1 |
| \* T1 includes T1mi.  \*\* T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB. M0 includes M0(i+)If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered stage IV and remains stage IV regardless of response to neoadjuvant therapy. Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy. Postneoadjuvant therapy is designated with "yc" or "yp" prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0. | | | |

* definitions of staging abbreviations
  + primary tumor (T)
    - TX - primary tumor cannot be assessed
    - T0 - no evidence of primary tumor
    - Tis - carcinoma in situ
      * Tis (DCIS) - ductal carcinoma in situ (lobular carcinoma in situ [LCIS] is a benign entity and is removed TNM staging in the AJCC 8th ed.)
      * Tis (Paget) - Paget disease of nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS) in underlying breast parenchyma. Carcinomas in breast parenchyma associated with Paget disease are categorized based on size and characteristics of parenchymal disease, although the presence of Paget disease should still be noted.
    - T1 - tumor ≤ 20 mm in greatest dimension
      * T1mi - tumor ≤ 1 mm in greatest dimension
      * T1a - tumor > 1 mm but ≤ 5 mm in greatest dimension (round any measurement 1.0-1.9 mm to 2 mm)
      * T1b - tumor > 5 mm but ≤ 10 mm in greatest dimension
      * T1c - tumor > 10 mm but ≤ 20 mm in greatest dimension
    - T2 - tumor > 20 mm but ≤ 50 mm in greatest dimension
    - T3 - tumor > 50 mm in greatest dimension
    - T4 - tumor of any size with direct extension to chest wall and/or to skin (ulceration or macroscopic nodules); invasion of dermis alone does not qualify as T4
      * T4a - extension to chest wall; invasion or adherence to pectoralis muscle in absence of invasion of chest wall structures does not qualify as T4
      * T4b - ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of skin that does not meet criteria for inflammatory carcinoma
      * T4c - both T4a and T4b are present
      * T4d - inflammatory carcinoma
        + restricted to cases with typical skin changes of diffuse erythema and edema (peau d'orange) involving at least one-third of skin of breast
        + histologic presence of invasive carcinoma invading dermal lymphatics supportive of diagnosis, but not required
        + dermal lymphatic invasion without typical clinical findings not sufficient for diagnosis of inflammatory breast cancer
  + regional lymph nodes (N)
    - (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel mode biopsy or fine needle aspiration (FNA}/core needle biopsy respectively, with no further resection of nodes
    - clinical (cN)
      * cNX - regional lymph nodes cannot be assessed (for example, previously removed); used sparingly in cases where regional lymph nodes have previously been surgically removed or where there is no documentation of physical examination of axilla
      * cN0 - no regional lymph node metastases (by imaging or clinical examination)
      * cN1 - metastases to movable ipsilateral level I, II axillary lymph node(s)
        + cN1mi - micrometastases (approximately 200 cells, > 0.2 mm but < 2 mm); rarely used but may be appropriated in cases where sentinel node biopsy is performed before tumor resection, most likely to occur in cases treated with neoadjuvant therapy
      * cN2 - metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; *or* in ipsilateral internal mammary nodes in absence of axillary lymph node metastases
        + cN2a - metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
        + cN2b - metastases only in ipsilateral internal mammary nodes in absence of axillary lymph node metastases
      * cN3 - metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; *or* in ipsilateral internal mammary lymph node(s) with or without level I,II axillary lymph node metastases; *or* metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
        + cN3a - metastases in ipsilateral infraclavicular lymph node(s)
        + cN3b - metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
        + cN3c - metastases in ipsilateral supraclavicular lymph node(s)
    - pathological (pN)
      * pNX - regional lymph nodes cannot be assessed (for example, not removed for pathological study or previously removed)
      * pN0 - no regional lymph node metastasis identified or isolated tumor cell clusters (ITCs) only
        + pN0(i+) - ITCs only (malignant cell clusters ≤ 0.2 mm in regional lymph node(s)
        + pN0(mol+) - positive molecular findings by reverse transcriptase polymerase chain reaction (RT-PCR); no ITCs detected
      * pN1 - micrometastases; or metastases in 1-3 axillary lymph nodes; and/or clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy
        + pN1mi - micrometastases (approximately 200 cells, > 0.2 mm but ≤ 2.0 mm)
        + pN1a - metastases in 1-3 axillary lymph nodes, at least 1 metastasis > 2.0 mm
        + pN1b - metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
        + pN1c - pN1a and pN1b combined
      * pN2 - metastases in 4-9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
        + pN2a - metastases in 4-9 axillary lymph nodes (at least 1 tumor deposit > 2.0 mm)
        + pN2b - metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes
      * pN3 - metastases in ≥ 10 axillary lymph nodes; *or* in infraclavicular (level III axillary) lymph nodes; *or* positive ipsilateral internal mammary lymph nodes by imaging in the presence of ≥ 1 positive level I, II axillary lymph nodes; *or* in > 3 axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes; *or* in ipsilateral supraclavicular lymph nodes
        + pN3a - metastases > 10 axillary lymph nodes (at least 1 tumor deposit > 2.0 mm); *or* metastases to the infraclavicular (level III axillary lymph) nodes
        + pN3b - pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging); *or* pN2a in the presence of pN1b
        + pN3c - metastases in ipsilateral supraclavicular lymph nodes
  + distant metastasis (M)
    - M0 - no clinical or radiographic evidence of distant metastases (imaging studies are not required to assign the cM0 category)
      * cM0(i+) - no clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits ≤ 0.2 mm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other nonregional nodal tissue in a patient without symptoms or signs of metastases
    - cM1 - distant metastases detected by clinical and radiographic means
    - pM1 - any histologically proven metastases in distant organs; or if in non-regional lymph nodes, metastases > 0.2 mm
* *Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.*

Blood Tests

* recommended blood tests in early and locally advanced breast cancer include[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF6778),[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__ANC_1607337114),[4](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF4502)
  + for stage I-IIB disease and signs and symptoms suggesting metastases, perform blood tests such as complete blood count (CBC) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)) and comprehensive metabolic panel, including liver function tests, renal function tests, and alkaline phosphatase and calcium levels ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade B, Level V](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
  + for stage IIIA disease, strongly consider additional workup including CBC and comprehensive metabolic panel, including liver function tests and alkaline phosphatase level ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESO/ESMO Grade 1B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOGRADE) for full staging workup including lab tests)
  + for patients with inoperable locally advanced breast cancer and in symptomatic patients with operable breast cancer, consider testing to assess for distant metastatic disease including CBC and comprehensive metabolic panel, including liver function tests and alkaline phosphatase ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESO/ESMO Grade 1B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOGRADE) for full staging workup including lab tests)
  + asymptomatic distant metastases are uncommon in early and locally advanced disease, so most women do not benefit from comprehensive laboratory staging, including tumor markers ([ESMO Grade D, Level II](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
* recommended blood tests in metastatic or recurrent breast cancer include[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF6778),[4](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF4502)
  + CBC ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESO/ESMO Grade 2C](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOGRADE) for including hematology and biochemistry tests as part of staging)
  + comprehensive metabolic panel, including liver function tests and alkaline phosphatase ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

Imaging Studies

Imaging for diagnosis

Recommendations for palpable breast mass

American College of Radiology (ACR)

* for evaluation of pregnant or lactating women, ultrasound is preferred initial test; diagnostic mammography should be added if clinical exam suspicious ([ACR 2018 PDF](https://acsearch.acr.org/docs/3102382/Narrative/)); see [Considerations Specific to Diagnostic Evaluation During Pregnancy or Lactation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#TOPIC_GCS_MSQ_2PB)
* evaluation of nonpregnant women varies by age
  + for patients < 30 years old
    - ultrasound is recommended for initial imaging ([ACR Rating 9](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE)); diagnostic mammography and diagnostic digital breast tomosynthesis (DBT) usually not appropriate ([ACR Rating 3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE)), but may consider adding in patients with a suspicious clinical exam ([ACR Ungraded](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE))
    - if ultrasound findings suspicious for malignancy ([BIRADS 4 or 5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#DIAGNOSTIC_MAMMOGRAPHY__SNIPPET-POINTER_2050577235))
      * bilateral diagnostic mammography or DBT recommended prior to biopsy as biopsy can obscure more subtle findings ([ACR Rating 8](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE))
      * perform [core needle biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#CORE_NEEDLE_BIOPSY) ([ACR Rating 9](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE))
    - if ultrasound findings likely benign ([BIRADS 3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#DIAGNOSTIC_MAMMOGRAPHY__SNIPPET-POINTER_2050577235))
      * short-interval (every 6-12 months) follow-up with ultrasound for 1-2 years recommended if low clinical suspicion ([ACR Rating 9](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE))
      * diagnostic mammography and DBT usually not indicated ([ACR Rating 3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE))
      * routine fine needle aspiration or core needle biopsy usually not indicated, but may be used in select circumstances such as planned pregnancy, high risk patient, or to alleviate anxiety ([ACR Rating 2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE) for fine needle aspiration; [ACR Rating 3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE) for core needle biopsy)
    - if ultrasound findings benign ([BIRADS 2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#DIAGNOSTIC_MAMMOGRAPHY__SNIPPET-POINTER_2050577235)) (such as simple cyst or lymph node), additional testing (mammography, ultrasound with short-interval follow-up, or image-guided fine needle aspiration) usually not indicated ([ACR Rating 2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE))
    - if ultrasound findings negative ([BIRADS 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#DIAGNOSTIC_MAMMOGRAPHY__SNIPPET-POINTER_2050577235)), diagnostic mammography, DBT and breast magnetic resonance imaging (MRI) without and with contrast usually not indicated ([ACR Rating 3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE) for diagnostic mammography and DBT, [ACR Rating 2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE) for breast MRI) but DBT may be performed if mass is clinically suspicious and breast is dense, with follow-up based on findings
  + for patients aged 30-39 years
    - observation without radiologic evaluation not suggested
    - initial evaluation includes diagnostic mammography/diagnostic DBT or targeted ultrasound ([ACR Rating 8](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE))
      * targeted ultrasound considerations
        + most benign lesions in young patients not visible on mammography
        + ultrasound appears to be more sensitive than mammography in patients ages 30-39
        + consider adding diagnostic mammography if other risk factors or suspicious clinical exam
        + if ultrasound findings are suspicious, bilateral diagnostic mammography recommended
      * diagnostic mammography/diagnostic DBT considerations
        + if mammography detects a definite benign lesion, ultrasound not necessary if benign mass correlates with the clinical exam findings
        + if mammography detects a probable benign lesion, ultrasound usually suggested to help clarify the findings
      * further evaluation based on results of initial test used (mammography or ultrasound)
        + see [patients aged ≥ 40 years](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#TOPIC_NDC_LDP_FTB__ANC_1872996795) for further evaluation based on mammography as initial test
        + see [patients aged < 30 years](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#TOPIC_NDC_LDP_FTB__ANC_211578440) for further evaluation based on ultrasound as initial test
  + for patients ≥ 40 years old
    - observation without radiologic evaluation not suggested
    - ultrasound may be considered for initial evaluation instead of diagnostic mammography if mammogram completed in previous 6 months ([ACR Rating 4](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE))
    - if mammographic findings suspicious for malignancy ([BIRADS 4 or 5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#DIAGNOSTIC_MAMMOGRAPHY__SNIPPET-POINTER_2050577235))
      * targeted ultrasound recommended (if not already performed) to assess if biopsy can be performed under ultrasound guidance ([ACR Rating 9](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE))
      * perform [core needle biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#CORE_NEEDLE_BIOPSY) ([ACR Rating 2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE))
    - if mammographic findings likely benign ([BIRADS 3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#DIAGNOSTIC_MAMMOGRAPHY__SNIPPET-POINTER_2050577235)) and targeted ultrasound
      * characteristics are suspicious, [core needle biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#CORE_NEEDLE_BIOPSY) is indicated ([ACR Rating 8](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE))
      * confirms probably benign findings
        + short-interval follow-up (every 6-12 months) for 1-2 years with diagnostic mammogram or diagnostic DBT is recommended if low clinical suspicion on exam ([ACR Rating 8](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE))
        + tissue sampling usually not indicated ([ACR Rating 2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE))
    - if mammographic findings benign ([BIRADS 2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#DIAGNOSTIC_MAMMOGRAPHY__SNIPPET-POINTER_2050577235)) (like lipoma or lymph node in palpable area), ultrasound is not recommended unless inconsistency between clinical findings and mammography ([ACR Rating 2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE))
    - if mammographic findings negative ([BIRADS 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#DIAGNOSTIC_MAMMOGRAPHY__SNIPPET-POINTER_2050577235)), targeted ultrasound recommended to correlate with clinical exam findings ([ACR Rating 9](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE)); if ultrasound negative but clinically suspicious, perform [core needle biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#CORE_NEEDLE_BIOPSY) ([ACR ungraded](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE))
* see [Palpable breast mass evaluation in women](https://dpa-pde-oxford.shinyapps.io/evaluation/palpable-breast-mass-evaluation-in-female-patients) for additional information

National Comprehensive Cancer Network (NCCN)

* TOPIC\_ANV\_LDP\_FTB\_\_LI\_J3H\_TJJ\_GTBGSU04182204/18/2022 09:22:53 AMguidelineSummaryUpdatelowplusOncologic\_DiseaseNational Comprehensive Cancer Network (NCCN) recommendations for screening and diagnosis of breast cancer (NCCN 2021 May) for patients < 30 years old[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + may observe for 1-2 menstrual cycles without radiological evaluation if low clinical suspicion for malignancy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if mass resolves spontaneously, resume routine screening ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if mass persists, proceed with evaluation ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + ultrasound is preferred for initial imaging ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); if high suspicion for malignancy, perform mammogram ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if ultrasound findings benign (BIRADS 2, such as simple cyst) and there is concordance between clinical exam and findings on imaging, resume routine screening ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)) and consider therapeutic aspiration if symptoms continue
    - if ultrasound findings indicate solid mass
      * if BIRADS 3, perform core needle biopsy for clinically suspicious masses ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)) , otherwise may proceed with observation at regular follow-up exam with imaging for 2 years (at 6, 12, and 24 months) to evaluate for changes ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)) ; interval between follow-up based on level of clinical suspicion
        + if mass remains stable or decreases in size on follow-up exam, resume routine screening ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + if increased clinical suspicion or significant change in size on follow-up exam, consider core needle biopsy (preferred) or aspiration ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * if BIRADS 4 or 5, perform core needle biopsy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if ultrasound findings indicate complex (cystic and solid) mass, manage as BIRADS 4 or 5 and perform core needle biopsy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if ultrasound findings indicate complicated cyst
      * if complicated cyst confirmed by ultrasound (contents visually mobile), further work-up or short interval follow-up unnecessary; resume routine screening ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * if BIRADS 3, consider follow-up physical exam with imaging (same imaging modality as completed at baseline) for 2 years to evaluate for changes ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)) ; interval between follow-up based on level of clinical suspicion
        + if mass remains stable or decreases in size on follow-up exam, resume routine screening ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + if increased clinical suspicion or significant change in size on follow-up exam, consider core needle biopsy (preferred) or aspiration ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * may consider [aspiration](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#FINE_NEEDLE_ASPIRATION__FNA_) with further evaluation based on findings ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if no abnormalities are detected on ultrasound (BIRADS 1)
      * for clinically suspicious mass, consider diagnostic mammography ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)) and proceed based on [BIRADS](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#DIAGNOSTIC_MAMMOGRAPHY__SNIPPET-POINTER_2050577235) category
        + if mass remains clinically suspicious after diagnostic mammography, [core needle biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#CORE_NEEDLE_BIOPSY) recommended ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + if BIRADS 1-2 and imaging alleviates clinical suspicion, consider follow-up physical exam in 3-6 months to evaluate for changes ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)) ; interval before physical exam based on level of clinical suspicion
        + if BIRADS 3 and imaging relieves clinical suspicion, consider follow-up physical exam with imaging (same imaging modality as completed at baseline) for 2 years to evaluate for changes ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)) ; interval between follow-up based on level of clinical suspicion
        + if BIRADS 4 or 5, perform [core needle biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#CORE_NEEDLE_BIOPSY) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); if there is not concordance between clinical exam and findings on imaging, proceed with workup of palpable mass same as BIRADS 1-2
      * for mass with low clinical suspicion, consider follow-up physical exam in 3-6 months to evaluate for changes ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)) ; interval before physical exam based on level of clinical suspicion
      * additional testing based on findings at follow-up exam
        + if mass remains stable on follow-up, resume routine screening ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + if increased clinical suspicion or significant change in size, consider additional ultrasound with or without diagnostic mammogram followed by core needle biopsy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); if no abnormality noted on imaging, may consider palpation-guided tissue sampling
* for patients ≥ 30 years old[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + perform diagnostic mammogram with ultrasound as part of initial evaluation ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if mammogram findings are definitively benign (such as calcified fat necrosis), complementary ultrasound may not be necessary
    - in individuals 30-39 years old, with either suspected simple cyst or other palpable mass with low suspicion for malignancy, ultrasound is preferred as initial imaging modality
  + additional testing is based on mammogram and ultrasound findings
    - if mammographic and ultrasound findings are negative, benign, or probably benign (BIRADS 1,2,or 3)
      * for BIRADS 1
        + if mass remains clinically suspicious after diagnostic mammography, perform [core needle biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#CORE_NEEDLE_BIOPSY) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); if no abnormality noted on imaging, may consider palpation-guided tissue sampling
        + if low clinical suspicion, consider follow-up physical exam in 6-12 months for 1-2 years to evaluate for changes, then return to age-appropriate screening ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

if mass remains stable, continue with regular screening ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

if increased suspicion for malignancy returns or significant change in size, consider additional mammogram and ultrasound followed by core needle biopsy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); if no abnormality noted on imaging, may consider palpation-guided tissue sampling

* + - * for BIRADS 2 and there is concordance between clinical exam and finding on imaging, return to age-appropriate screening ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); if clinical symptoms persist, may consider therapeutic aspiration
      * for BIRADS 3, either provide observation through regular follow-up (if low clinical suspicion) or perform core needle biopsy then regular follow-up (if clinically suspicious) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + consider follow-up physical exam with imaging for 2 years (typically at 6, 12, and 24 months) to evaluate for changes ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); interval between follow-up based on level of clinical suspicion
        + additional testing is based on findings at follow-up exam

if mass remains stable or decreases in size, resume routine screening ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

if increased clinical suspicion or significant change in size, perform core needle biopsy (preferred, though aspiration may be acceptable in some situations) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

* + - if mammographic findings are negative, benign, or probably benign (BIRADS 1,2,or 3) and ultrasound detects [solid mass](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#TOPIC_ANV_LDP_FTB__LI_UYC_BZ3_GTB), [complex mass](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#TOPIC_ANV_LDP_FTB__LI_R2B_CZ3_GTB), or suspected [complicated cyst](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#TOPIC_ANV_LDP_FTB__LI_UR3_CZ3_GTB), follow same workup as for < 30 years old ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if mammographic and/or ultrasound findings are suspicious or highly suggestive (BIRADS 4 or 5), perform [core needle biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#CORE_NEEDLE_BIOPSY) (preferred, though aspiration may be acceptable in some situations) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
* see also [Palpable breast mass evaluation in women](https://dpa-pde-oxford.shinyapps.io/evaluation/palpable-breast-mass-evaluation-in-female-patients)

Recommendations for nipple discharge

American College of Radiology (ACR)

* TOPIC\_KGC\_FWG\_FTB\_\_LI\_D4S\_PHJ\_GTBGSU04182204/18/2022 09:08:02 AMguidelineSummaryUpdatelowplusOncologic\_DiseaseAmerican College of Radiology guidelines for evaluation of nipple discharge (ACR 2022 PDF)ACR does not recommend initial imaging in adults presenting with physiologic nipple discharge ([ACR Rating 1-3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE)); characteristics of physiologic discharge include
  + bilateral in nature
  + colored white, green, or yellow
  + origination from multiple duct orifices
  + presentation associated with stimulation
  + Reference - [ACR 2022 PDF](https://acsearch.acr.org/docs/3099312/Narrative/)
* ACR recommendations for initial imaging in adults with pathologic discharge
  + for any individuals ≥ 30 years old, breast ultrasound, diagnostic digital breast tomosynthesis, and diagnostic mammogram are generally recommended ([ACR Rating 7-9](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE))
  + for individuals < 30 years old
    - if assigned male sex at birth, breast ultrasound, diagnostic digital breast tomosynthesis, and diagnostic mammogram are generally recommended ([ACR Rating 7-9](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE))
    - if assigned female sex at birth, breast ultrasound is generally recommended ([ACR Rating 7-9](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE))
  + Reference - [ACR 2022 PDF](https://acsearch.acr.org/docs/3099312/Narrative/)

National Comprehensive Cancer Network

* if discharge multiduct or nonspontaneous ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + for individuals < 40 years old, observe and/or educate to stop breast compression and report spontaneous discharge ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + for individuals ≥ 40 years old, perform mammogram if not done within last year and educate to stop breast compression and report spontaneous discharge; provide follow-up based on [mammography findings](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#RECOMMENDATIONS_FOR_AN_ABNORMAL_SCREENING_MAMMOGRAM) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
* if discharge persistent and reproducible on exam, spontaneous, unilateral, from a single duct, and/or bloody or clear[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + for individuals < 30 years old, perform [ultrasound](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#ULTRASOUND) with or without [diagnostic mammogram](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#DIAGNOSTIC_MAMMOGRAPHY) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + for individuals ≥ 30 years old, perform diagnostic mammogram plus ultrasound ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + proceed based on mammogram and/or ultrasound findings ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - for [BI-RADS](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#DIAGNOSTIC_MAMMOGRAPHY__SNIPPET-POINTER_2050577235) 1-3, optional breast MRI (preferred) or ductogram ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * if remains BI-RADS 1-3, options include ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + endocrine workup, if discharge is bilateral and milky
        + duct excision

if benign, proceed with normal age-appropriate screening protocol

if malignant, manage according to breast cancer stage and subtype

* + - * + surveillance with physical exam and diagnostic mammogram with or without ultrasound every 6 months for 1-2 years

if suspicious progression, perform core needle [biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#BIOPSY_AND_PATHOLOGY) or surgical excision

if remains stable or resolves, proceed with normal age-appropriate screening protocol

* + - * + if BI-RADS 3 finding is unrelated to nipple discharge, follow-up according to [mammography findings](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#RECOMMENDATIONS_FOR_AN_ABNORMAL_SCREENING_MAMMOGRAM)
      * if BI-RADS 4-5, perform tissue biopsy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + if biopsy results are benign, perform clinical correlation to assess need for duct excision ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + if biopsy result is malignant, manage according to breast cancer stage and subtype ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - for BI-RADS 4-5, perform tissue biopsy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * if biopsy results are benign, perform clinical correlation to assess need for duct excision ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * if biopsy result is malignant, manage according to breast cancer stage and subtype ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
* certain medications are associated with nipple discharge, such as prior or current use of oral contraceptives, estrogen, opiates, antihypertensives, or psychoactive drugs[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)

Recommendations for asymmetric thickening or nodularity

* in women < 30 years old, perform [ultrasound](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#ULTRASOUND) with or without [diagnostic mammography](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#DIAGNOSTIC_MAMMOGRAPHY) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
* in women ≥ 30 years old, perform diagnostic mammogram plus ultrasound ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); for women aged 30-39 years in whom there is low suspicion of malignancy, ultrasound may be preferred over mammogram[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
* for BI-RADS 1-2, negative or benign findings[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + with ultrasound findings indicating simple cyst, proceed with normal age-appropriate [screening](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#SCREENING) protocol ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + with low clinical suspicion, perform physical exam for 2 years to assess for changes ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); timing of follow-up may vary based on level of suspicion
    - if remains stable, proceed with normal age-appropriate screening protocol ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if becomes suspicious or significant change in size, perform diagnostic imaging (with consideration of MRI if mass is suspicious) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * if findings indicate simple cyst, proceed with [recommendations for palpable breast mass](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#RECOMMENDATIONS_FOR_PALPABLE_BREAST_MASS) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * for all others, consider [biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#BIOPSY_AND_PATHOLOGY) (core needle biopsy, palpation-guided fine-needle aspiration, or surgical biopsy) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + with clinically suspicious lesion, consider [biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#BIOPSY_AND_PATHOLOGY) (core needle biopsy, palpation-guided fine-needle aspiration, or surgical biopsy) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
* for BI-RADS 3 probably benign findings[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + with low clinical suspicion, perform physical exam for 2 years to assess for changes ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); timing of follow-up may vary based on level of suspicion
    - if remains stable, proceed with normal age-appropriate screening protocol ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if becomes suspicious or significant change in size, perform diagnostic imaging (with consideration of MRI if mass is suspicious) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * if findings indicate simple cyst, proceed with [recommendations for palpable breast mass](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#RECOMMENDATIONS_FOR_PALPABLE_BREAST_MASS) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * for all others, consider [biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#BIOPSY_AND_PATHOLOGY) (core needle biopsy, palpation-guided fine-needle aspiration, or surgical biopsy) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + with clinically suspicious lesion, consider [biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#BIOPSY_AND_PATHOLOGY) (core-needle biopsy, palpation-guided fine-needle aspiration, or surgical biopsy) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + if location of the abnormality on mammogram or ultrasound does not agree with the location on clinical exam, proceed with [workup as for BI-RADS 1-2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#RECOMMENDATIONS_FOR_ASYMMETRIC_THICKENING_OR_NODULARITY__ANC_406790604) to further workup the palpable finding ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
* for BI-RADS 4-5, suspicious or suggestive of malignancy[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + perform core needle biopsy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + if location of the abnormality on mammogram or ultrasound does not agree with the location on clinical exam, proceed with [workup as for BI-RADS 1-2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#RECOMMENDATIONS_FOR_ASYMMETRIC_THICKENING_OR_NODULARITY__ANC_406790604) to further workup the palpable finding ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

Recommendations for skin changes

* assess skin changes to the breast including[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + for suspicion of inflammatory breast cancer
    - signs and symptoms include pitted or dimpled skin appearance also known as peau d'orange, skin thickening, edema, and erythema
    - if low suspicion for breast cancer or high suspicion for infection, may consider 7-10 days of antibiotics for mastitis
  + for suspicion of [Paget disease](https://dpa-pde-oxford.shinyapps.io/condition/paget-disease-of-the-breast) or other manifestation of breast cancer
    - signs and symptoms include nipple excoriation, scaling, and skin ulceration
    - if low suspicion for Paget disease or high suspicion for eczema, may consider short course of topical corticosteroids
* perform diagnostic mammogram plus ultrasound ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); if there is low suspicion of malignancy, ultrasound alone may be adequate[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778),)
* proceed based on mammogram and/or ultrasound findings ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + for BI-RADS 1-3, negative, benign, or likely benign findings, options include
    - consider MRI ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * if findings are abnormal, core needle biopsy is preferred ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * if findings are normal, may perform punch biopsy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - perform punch [biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#BIOPSY_AND_PATHOLOGY) of skin or nipple biopsy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * diagnosis of inflammatory breast cancer is based on clinical exam and any biopsy of breast or lymph nodes revealing breast cancer, it does not require positive skin punch biopsy
      * if biopsy results are benign ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + perform clinical pathological correlation
        + consider breast magnetic resonance imaging
        + consider repeat biopsy
        + consider referral to breast specialist, if not already done
        + if clinical suspicion for inflammatory breast cancer and skin punch biopsy is benign, diagnosis is not ruled out and should proceed with further evaluation
      * if biopsy result is malignant, manage according to breast cancer stage and subtype ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + for BI-RADS 4-5, suspicious or suggestive of malignancy, perform core needle biopsy (preferred) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if biopsy results are benign ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * perform clinical pathological correlation
      * consider breast magnetic resonance imaging
      * consider repeat biopsy
      * consider referral to breast specialist, if not already done
      * if clinical suspicion for inflammatory breast cancer and skin punch biopsy is benign, diagnosis is not ruled out and should proceed with further evaluation
    - if biopsy result is malignant, manage according to breast cancer stage and subtype ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

Recommendations for breast pain

* persistent or severe breast pain is defined as pain lasting at least 4-6 weeks despite symptomatic management[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
* for women with persistent or severe breast pain, perform history and physical exam ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + exam should include inspection in upright and supine positions, and palpation of all breast components including axillary and clavicular lymph node basins
  + time spent on exam is associated with increased detection of palpable abnormalities
  + compare location and distance from nipple with findings from imaging
* base imaging decisions on additional signs and symptoms, including[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + [breast mass](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#RECOMMENDATIONS_FOR_PALPABLE_BREAST_MASS) or [asymmetric thickening and nodularity](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#RECOMMENDATIONS_FOR_ASYMMETRIC_THICKENING_OR_NODULARITY)
  + [nipple discharge](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#RECOMMENDATIONS_FOR_SKIN_CHANGES)
  + [skin changes](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#RECOMMENDATIONS_FOR_SKIN_CHANGES)
  + for no physical findings
    - further evaluation is based on pain characteristics
      * if pain is cyclic, diffuse, and nonfocal (larger than quadrant) and if breast imaging screening is current, reassure patient (as long as breast imaging is current) and offer treatment for pain if patient needs or desires it ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * if pain is focal
        + in individuals < 30 years old, perform [ultrasound](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#ULTRASOUND) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + in individuals ≥ 30 years old perform diagnostic mammogram and ultrasound, especially if mammogram does not explain pain ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

for women aged 30-39 years in whom there is low suspicion of malignancy, ultrasound is preferred over mammogram as first imaging modality

mammogram may not be necessary in individuals 30-39 years old or in those with mammogram with negative findings within previous 6 months

* + - proceed based on mammogram and/or ultrasound findings ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * for BI-RADS 1, provide symptomatic management, if desired ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * for BI-RADS 2, and simple cyst on ultrasound, consider drainage for symptom relief; for complicated cyst, consider aspiration ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * for BI-RADS 3, perform physical exam and diagnostic mammogram and/or ultrasound for 2 years to assess for changes ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); timing of follow-up may vary based on level of suspicion
        + if remains stable, proceed with normal age-appropriate screening protocol ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + if becomes suspicious or significant change in size, perform core needle biopsy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * for BI-RADS 4-5, perform core needle [biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#BIOPSY_AND_PATHOLOGY) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

Recommendations for axillary mass

* for axillary mass localized to axilla without signs of lymphoma[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + for bilateral axillary masses, evaluate for systemic disease
    - if systemic disease
      * and malignant, manage according to breast cancer stage ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * and benign, manage as clinically appropriate ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if no systemic disease
      * in individuals < 30 years old, perform ultrasound ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); mammogram is optional unless ultrasound findings are suspicious
      * in individuals ≥ 30 years old, perform ultrasound and diagnostic mammogram ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); mammogram strongly recommended if not completed within last 6 months, but may be considered optional in those with negative findings on recent mammogram ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + for unilateral axillary mass and no systemic disease, perform ultrasound and diagnostic mammogram ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); in individuals < 30 years old, mammogram is optional unless ultrasound findings are suspicious
  + if either bilateral or unilateral axillary mass and ultrasound or diagnostic mammogram is suspicious, perform biopsy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); if lymphoma suspected, may need specialized pathologic processing and/or surgical excision
    - if no malignancy, manage as clinically appropriate ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if malignancy is found
      * in axillary node alone with breast origin but without breast mass, perform magnetic resonance imaging and manage according to breast cancer stage ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * in axillary node alone with nonbreast origin, manage according to guidelines for appropriate malignancy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * in axillary node and breast, manage according to breast cancer stage ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

Recommendations for an abnormal screening mammogram

* BI-RADS 1-2 are not abnormal; for women with BIRADS 1-2, normal or benign findings, proceed with normal age-appropriate [screening](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#SCREENING) protocol ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
* for women with an abnormal screening mammogram[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + for BI-RADS 0, perform diagnostic workup including comparison to prior films and diagnostic mammogram and/or ultrasound as indicated, and follow protocol for final assessment category ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + for BI-RADS 3, likely benign finding, perform follow-up with repeat diagnostic mammogram for 2 years (at 6, 12, and 24 months) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if lesion remains stable, or resolves, proceed with normal age-appropriate screening protocol ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if, in any interval mammogram, there is increased suspicion, perform core needle [biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#BIOPSY_AND_PATHOLOGY) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if return visit uncertain, or if patient prefers, perform [biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#BIOPSY_AND_PATHOLOGY) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + BI-RADS 4 or 5, findings are suspicious or suggestive of malignancy
    - complete imaging evaluation ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - sample tissue by image-guided core needle biopsy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + BI-RADS 6, known malignancy - manage according to breast cancer stage ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + see also [Mammography for breast cancer screening](https://dpa-pde-oxford.shinyapps.io/topic/an:dmp2:T115728)

Diagnostic mammography

* in screening mammography, 2 standard x-ray views are taken of each breast; diagnostic mammography differs from screening mammography in that additional views are taken to evaluate suspicious findings (such as spot compression or magnification)[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
* Breast Imaging Reporting and Data System (BI-RADS) classification for mammography assessment
  + BI-RADS 0 assessment incomplete, need additional imaging evaluation and/or prior mammograms for comparison
    - mostly used for screening, but may occasionally be used in diagnostic mammogram
    - additional imaging may include use of spot compression (with or without magnification), special mammogram views, and ultrasound
    - not used for diagnostic breast imaging findings that warrant further evaluation with magnetic resonance imaging (MRI)
  + BI-RADS 1 negative - normal examination with no characteristics on which to comment
  + BI-RADS 2 benign finding(s) - normal examination with description of benign findings such as benign-appearing calcifications, metallic foreign bodies, and fat-containing lesions
  + BI-RADS 3 probably benign finding(s)
    - typically includes noncalcified, circumscribed, solid mass, focal asymmetry, or solitary group of punctate calcifications
    - estimated risk of malignancy > 0% and ≤ 2%
  + BI-RADS 4 suspicious abnormality
    - BI-RADS 4A - estimated risk of malignancy > 2% and ≤ 10%
    - BI-RADS 4B - estimated risk of malignancy > 10% and ≤ 50%
    - BI-RADS 4C - estimated risk of malignancy > 50% and < 95%
  + BI-RADS 5 highly suggestive of malignancy
    - a benign biopsy requires additional core needle biopsy or excision
    - estimated risk of malignancy ≥ 95%
  + BI-RADS 6 known biopsy-proven malignancy, treatment pending
  + Reference - Breast Cancer Screening and Diagnosis. Version 2.2018. In: National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines). NCCN 2018 May from [NCCN website](http://www.nccn.org/professionals/physician_gls/f_guidelines.asp) (free registration required)
* **diagnostic mammogram has modest positive predictive value and high negative predictive value for breast cancer in women with palpable mass or other breast symptoms (**[**level 1 [likely reliable] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Diagnostic Cohort Study[12165640J Natl Cancer Inst 2002 Aug 7;94(15):1151](http://pubmed.ncbi.nlm.nih.gov/12165640?dopt=Abstract)

studySummary1

* + based on diagnostic cohort studyDiagnostic Cohort Study
  + 41,427 diagnostic mammograms performed on symptomatic women aged 25-89 years with no history of breast cancer
  + reference standard was histologically confirmed breast cancer (invasive and ductal carcinoma in situ)

| Performance of Diagnostic Mammography | | | |
| --- | --- | --- | --- |
| **Diagnostic Accuracy Parameter** | **Entire Cohort** | **Women With Self-Reported Lump** | **Women Without Self-Reported Lump** |
| Number evaluated | 41,427 | 15,853 | 16,895 |
| Prevalence of breast cancer | 3.9% | 6.1% | 2.2% |
| Sensitivity | 85.8% | 87.3% | 82.3% |
| Specificity | 87.7% | 84.5% | 91.2% |
| Positive predictive value | 21.8% | 26.8% | 17.5% |
| Negative predictive value | 99.4% | 99% | 99.6% |

* + PubMed12165640Journal of the National Cancer Institute20020807J Natl Cancer Inst941511511151Reference - [12165640J Natl Cancer Inst 2002 Aug 7;94(15):1151](http://pubmed.ncbi.nlm.nih.gov/12165640?dopt=Abstract)

Ultrasound

* ultrasound of regional lymph nodes recommended for initial diagnosis of breast cancer, and any suspicious lymph nodes should be assessed using ultrasound-guided fine needle aspiration or core needle [biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#BIOPSY_AND_PATHOLOGY) ([ESMO Grade A, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__ANC_1607337114)
* Breast Imaging Reporting and Data System (BI-RADS) classification for ultrasound findings[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + BI-RADS 0 - assessment incomplete; need additional imaging evaluation and/or prior ultrasound for comparison
    - mostly used for screening, but may occasionally be used in diagnostic mammography report
    - not used for diagnostic breast imaging findings that warrant further evaluation with magnetic resonance imaging (MRI)
  + BI-RADS 1 - negative; normal exam with no characteristics on which to comment
  + BI-RADS 2 - benign finding(s); normal exam with description of benign findings such as simple cysts, intramammary lymph nodes, postsurgical fluid collections, breast implants, or unchanged complicated cysts/probable fibroadenomas
  + BI-RADS 3 - probably benign finding(s)
    - typically includes probable fibroadenomas, isolated complicated cysts, or clustered microcysts
    - estimated risk of malignancy > 0% and ≤ 2%
  + BI-RADS 4 - suspicious abnormality
    - BI-RADS 4A - estimated risk of malignancy > 2% and ≤ 10%
    - BI-RADS 4B - estimated risk of malignancy > 10% and ≤ 50%
    - BI-RADS 4C - estimated risk of malignancy > 50% and < 95%
  + BI-RADS 5 - highly suggestive of malignancy
    - includes lesions that may be considered nonmalignant based on percutaneous tissue diagnosis however ultrasound results disagree, therefore repeat vacuum-assisted or surgical biopsy is recommended
    - estimated risk of malignancy ≥ 95%
  + BI-RADS 6 - known biopsy-proven malignancy, treatment pending
* **addition of ultrasound to clinical examination and mammogram may help diagnose or rule out breast cancer in patients with palpable breast masses or abnormal screening mammography (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Diagnostic Cohort Study[12767956Arch Intern Med 2003 May 26;163(10):1194](http://pubmed.ncbi.nlm.nih.gov/12767956?dopt=Abstract)

studySummary2

* + based on diagnostic cohort study with unclear blinding of reference standard or test under investigationDiagnostic Cohort Study
  + 2,020 consecutive patients (3,835 breasts) had mammogram plus clinical examination followed by ultrasound
  + indication for examination included
    - referral for clinical or mammographic abnormalities in 2,812 breasts
    - screening contralateral side or patient reassurance in 1,023 breasts
  + reference standard was pathologic results of core needle biopsies, open biopsies, and other surgical interventions within 12-month follow-up
  + prevalence of breast cancer was 6.3% by reference standard in total cohort
  + diagnostic performance for detection of breast cancer comparing ultrasound plus clinical examination and mammogram vs. clinical examination and mammogram alone
    - sensitivity 96.9% vs. 91.5% (with ultrasound detecting 8 additional malignancies)
    - specificity 94.8% vs. 87% (with ultrasound appropriately downgrading 332 cases from suggested malignancy to no malignancy, but providing false-positive results for 46 additional cases)
    - positive predictive value 39.2% vs. 19.7%
    - negative predictive value 99.9% vs. 99.7%
  + ultrasound increased diagnostic yield in patients with palpable breast masses (p = 0.004) and patients referred for abnormal screening mammogram results (p = 0.05)
  + PubMed12767956Archives of internal medicine20030526Arch Intern Med1631011941194Reference - [12767956Arch Intern Med 2003 May 26;163(10):1194](http://pubmed.ncbi.nlm.nih.gov/12767956?dopt=Abstract)
* ultrasound had 99.8% negative predictive value (1 false-negative) in retrospective study of 448 women with nonpalpable solid masses with benign morphologic features ([17581897Radiology 2007 Jul;244(1):87](http://pubmed.ncbi.nlm.nih.gov/17581897?dopt=Abstract)[full-text](http://radiology.rsna.org/content/244/1/87.long))
* sonoelastography
  + sonoelastography is imaging technique using in conjunction with B-mode ultrasound to better characterize breast lesions ([23619293Diagn Interv Imaging 2013 May;94(5):503](http://pubmed.ncbi.nlm.nih.gov/23619293?dopt=Abstract))
  + **addition of sonoelastography to B-mode ultrasound may increase sensitivity but decrease specificity for detection of breast cancer in patients with palpable or nonpalpable masses (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Diagnostic Cohort Study[20614414Ultraschall Med 2010 Dec;31(6):596](http://pubmed.ncbi.nlm.nih.gov/20614414?dopt=Abstract)

studySummary2

* + - based on diagnostic cohort studyDiagnostic Cohort Study
    - 97 palpable or nonpalpable breast lesions were evaluated by sonoelastography, B-mode ultrasound, and mammography
    - 32% breast lesions were malignant by biopsy with histopathologic examination (reference standard)

| Diagnostic Performance | | | | |
| --- | --- | --- | --- | --- |
|  | **Mammography** | **B-mode Ultrasound** | **Sonoelastography** | **B-mode Ultrasound plus Sonoelastography** |
| Sensitivity | 84% | 97% | 71% | 100% |
| Specificity | 89% | 82% | 48% | 38% |
| Positive predictive value | 79% | 71% | 39% | 43% |
| Negative predictive value | 92% | 98% | 78% | 100% |

* + - diagnostic performance results were similar for palpable and nonpalpable masses
    - PubMed20614414Ultraschall in der Medizin (Stuttgart, Germany : 1980)20101201Ultraschall Med316596596Reference - [20614414Ultraschall Med 2010 Dec;31(6):596](http://pubmed.ncbi.nlm.nih.gov/20614414?dopt=Abstract)
  + **sonoelastography alone may have higher specificity and lower sensitivity than B-mode ultrasound in evaluation of breast lesions (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Case-Control Study[17138118Acad Radiol 2006 Dec;13(12):1496](http://pubmed.ncbi.nlm.nih.gov/17138118?dopt=Abstract)

studySummary2

* + - based on diagnostic case-control studyCase-Control Study
    - 132 patients with malignant breast lesions and 168 patients with benign breast lesions had sonoelastography, B-mode ultrasound, and mammography
    - diagnostic performance for differentiation of breast lesions
      * sonoelastography had 82% sensitivity and 87% specificity
      * B-mode ultrasound had 94% sensitivity and 83% specificity
      * mammography had 87% sensitivity and 85% specificity
    - PubMed17138118Academic radiology20061201Acad Radiol131214961496Reference - [17138118Acad Radiol 2006 Dec;13(12):1496](http://pubmed.ncbi.nlm.nih.gov/17138118?dopt=Abstract)

Breast magnetic resonance imaging (MRI)

* criteria for performance and interpretation of high-quality breast MRI include[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + dedicated breast coil
  + radiologists experienced with breast MRI
  + ability to perform MRI-guided biopsy
* For women with inconclusive conventional imaging findings, a palpable breast mass and negative imaging findings, or noncalcified equivocal breast lesions, breast MRI may help rule out breast cancer. However, the positive predictive value may be too low to diagnose malignancy.
  + **MRI rules out breast cancer but positive predictive value too low to diagnose cancer in women with inconclusive conventional imaging findings (**[**level 1 [likely reliable] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Diagnostic Cohort Study[25454098Eur J Radiol 2015 Jan;84(1):61](http://pubmed.ncbi.nlm.nih.gov/25454098?dopt=Abstract)

studySummary1

* + - based on diagnostic cohort study Diagnostic Cohort Study
    - 111 consecutive women (mean age 51 years) who were referred for MRI due to inconclusive findings on digital mammography and/ultrasound in 2012
    - reference standard was histopathology or imaging follow-up of ≥ 1 year
    - MRI category BI-RADS 4 or 5 in 26 of 111 (23.4%); 15 of 26 (57.7%) were malignant on histopathology
    - of the 15 diagnosed malignancies, 12 (80%) were lesions with mammographic mass
    - performance of MRI for detecting cancer
      * overall
        + sensitivity 100%
        + specificity 88.5%
        + positive predictive value 57.7%
        + negative predictive value 100%
      * with mammographic mass
        + sensitivity 100%
        + specificity 74.1%
        + positive predictive value 22.2%
        + negative predictive value 100%
    - PubMed25454098European journal of radiology20150101Eur J Radiol8416161 Reference - [25454098Eur J Radiol 2015 Jan;84(1):61](http://pubmed.ncbi.nlm.nih.gov/25454098?dopt=Abstract)
  + **MRI may help rule out breast cancer, but positive predictive value may be too low to diagnose cancer in women with palpable breast mass and negative conventional imaging findings (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Diagnostic Cohort Study[aph83230057pa9h83230057pbyh83230057pafh83230057pbeh83230057przh104434687pc8h104434687phch83230057pnyh83230057pnxh83230057ppbh83230057psih83230057pcxh83230057pJ Womens Health (Larchmt) 2012 Nov;21(11):1149](http://pubmed.ncbi.nlm.nih.gov/23046046?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3698622/)

studySummary2

* + - based on diagnostic cohort study with reference test not applied to all patients Diagnostic Cohort Study
    - 77 women (mean age 52 years) with palpable breast mass and negative diagnostic mammogram or ultrasound findings ≤ 90 days before testing had MRI to detect cancer
    - high risk for breast cancer due to personal or strong family history of breast cancer in 48%; no patients had known *BRCA* gene mutations
    - reference standard was biopsy or clinical follow-up
    - positive or suspicious MRI findings in anatomic location corresponding to palpated mass in 8 of 77 women (10.4%), and all had biopsy (core needle biopsy in all but 1)
    - biopsy positive for malignancy in 2 of 8 (25%)
    - negative MRI in 69 women; 14 of 69 (20.3%) had biopsy
    - of women who were negative on MRI and did not have biopsy, 26 of 55 (47%) were lost to follow up
    - in the 37 women with palpable breast mass and biopsy or follow-up outcomes available, performance of MRI for detecting cancer
      * sensitivity 100%
      * specificity 82.9%
      * positive predictive value 25%
      * negative predictive value 100%
    - PubMed23046046Journal of women's health (2002)20121101J Womens Health (Larchmt)211111491149 Reference - [aph83230057pa9h83230057pbyh83230057pafh83230057pbeh83230057przh104434687pc8h104434687phch83230057pnyh83230057pnxh83230057ppbh83230057psih83230057pcxh83230057pJ Womens Health (Larchmt) 2012 Nov;21(11):1149](http://pubmed.ncbi.nlm.nih.gov/23046046?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3698622/)
  + **negative result on dynamic contrast-enhanced MRI appears to help rule out malignancy in patients with noncalcified equivocal breast lesions (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[aph117146226pa9h117146226pafh117146226pcxh117146226pmdc27482715pPLoS One 2016;11(8):e0160346](http://pubmed.ncbi.nlm.nih.gov/27482715?dopt=Abstract)[Full Text](http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0160346)

studySummary2

* + - based on systematic review limited by heterogeneity Systematic Review
    - systematic review of 14 diagnostic studies evaluating performance of dynamic contrast-enhanced MRI for diagnosis of breast cancer in 2,295 patients with noncalcified equivocal breast lesions (2,316 lesions)
      * most patients had BI-RADS 0 or 3 lesions, but some studies included patients with BI-RADS 4
      * subgroups were used for analysis in some studies
    - reference standard was histopathologic findings and/or imaging at ≥ 12-month follow-up
    - prevalence of malignancy ranged from 2% to 56% across studies (pooled prevalence 14.3%) by reference standard
    - pooled performance of dynamic contrast-enhanced MRI for diagnosis of breast cancer in analysis of all studies
      * sensitivity 99% (95% CI 93%-100%), results limited by significant heterogeneity
      * specificity 89% (95% CI 85%-92%), results limited by significant heterogeneity
      * positive likelihood ratio 9
      * negative likelihood ratio 0.01
      * negative predictive value
        + 99.8% assuming 14% prevalence
        + < 1% assuming < 40% prevalence (pretest probability < 40%)
    - PubMed27482715PloS one201601PLoS One118e0160346e0160346 Reference - [aph117146226pa9h117146226pafh117146226pcxh117146226pmdc27482715pPLoS One 2016;11(8):e0160346](http://pubmed.ncbi.nlm.nih.gov/27482715?dopt=Abstract) [full-text](http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0160346)
* **preoperative MRI may not reduce risk of recurrence in women with breast cancer having breast-conserving surgery (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[cxh94302542pmdc24395846pJ Clin Oncol 2014 Feb 10;32(5):392](http://pubmed.ncbi.nlm.nih.gov/24395846?dopt=Abstract)

studySummary2

* + based on systematic review without assessment of study quality Systematic Review
  + systematic review of 1 randomized trial and 3 cohort studies comparing preoperative assessment with conventional imaging plus MRI vs. conventional imaging alone in 3,169 women with breast cancer
    - analyses based on pooled individual patient data obtained from study authors
    - median length of follow-up was 2.9 years
  + 3,180 breasts involved (11 women had bilateral breast cancer); 2,888 breast tumors (90.8%) were invasive and 292 breast tumors (9.2%) were ductal carcinoma in situ
  + all women had breast-conserving surgery or attempted breast-conserving surgery
  + no significant difference in 8-year local recurrence-free survival or 8-year distant recurrence-free survival
  + consistent results in analyses adjusted for baseline characteristics and in analysis excluding women having mastectomy or not receiving radiation therapy
  + PubMed24395846Journal of clinical oncology : official journal of the American Society of Clinical Oncology20140210J Clin Oncol325392392 Reference - [cxh94302542pmdc24395846pJ Clin Oncol 2014 Feb 10;32(5):392](http://pubmed.ncbi.nlm.nih.gov/24395846?dopt=Abstract) , editorial can be found in [cxh94302537pmdc24395864pJ Clin Oncol 2014 Feb 10;32(5):370](http://pubmed.ncbi.nlm.nih.gov/24395864?dopt=Abstract)
* **preoperative MRI may result in more women converted to mastectomy from planned breast-conserving surgery, but fewer women require reoperation in women ≤ 56 years old (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Randomized Trial[mnh24817517pcxh97193872pmdc24817517pWorld J Surg 2014 Jul;38(7):1685](http://pubmed.ncbi.nlm.nih.gov/24817517?dopt=Abstract)

studySummary2

* + based on randomized trial without blinding Randomized Trial
  + 440 women ≤ 56 years old (median age 46 years) with newly diagnosed invasive or noninvasive breast cancer were randomized to preoperative breast MRI vs. no MRI
  + 56 years chosen as age cutoff because younger women more often have dense breast tissue and breast cancer in younger women has an increased risk for multifocal and bilateral disease
  + among 220 women who had preoperative MRI, 83 women (38%) had additional findings on MRI and 40 women (18%) had altered treatment due to these findings
  + in the 40 women with altered treatment due to MRI findings, treatment included
    - conversion to mastectomy form breast-conserving surgery in 55%
    - conversion to axillary dissection from sentinel lymph node biopsy in 37.5%
    - conversion from mastectomy to breast-conserving surgery in 2.5%
    - addition of neoadjuvant chemotherapy in 7.5%
    - replacement of neoadjuvant chemotherapy with mastectomy in 2.5%
  + comparing preoperative MRI vs. no MRI
    - total number of definitive mastectomies 42.7% vs. 40.5% (no p value reported)
    - conversion to mastectomy from planned breast-conserving surgery in 20% vs. 10% (p = 0.02)
    - reoperation after breast-conserving surgery in 5% vs. 22% (p < 0.0001)
    - ipsilateral breast reoperation rate 5% vs. 15% (p < 0.0001)
  + PubMed24817517World journal of surgery20140701World J Surg38716851685 Reference - POMB trial ([mnh24817517pcxh97193872pmdc24817517pWorld J Surg 2014 Jul;38(7):1685](http://pubmed.ncbi.nlm.nih.gov/24817517?dopt=Abstract) )
* **preoperative MRI may increase reexcision rate in women with breast cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Randomized Trial[21195605Eur J Cancer 2011 Apr;47(6):879](http://pubmed.ncbi.nlm.nih.gov/21195605?dopt=Abstract)

studySummary2

* + based on randomized trial without intention-to-treat analysis Randomized Trial
  + 463 women (mean age 56 years) with nonpalpable breast lesions (BI-RADS 3-5) receiving mammography, ultrasound, and large core needle biopsy were randomized to preoperative MRI (56.8% with invasive breast cancer) vs. no preoperative MRI (52% with invasive breast cancer) and followed for mean 41 months
  + 45 patients excluded after randomization, 418 patients (90%) analyzed
  + comparing preoperative MRI vs. no MRI
    - reexcision in 34% vs. 12% (p = 0.008, NNH 5)
    - primary breast-conserving surgery in 68% vs. 66% (no p value reported)
    - conversion to mastectomy after primary breast-conserving surgery in 11% vs. 14% (not significant)
    - additional surgical intervention after primary breast-conserving surgery in 45% vs. 28% (p = 0.07)
  + PubMed21195605European journal of cancer20110401Eur J Cancer476879879 Reference - MONET trial ([21195605Eur J Cancer 2011 Apr;47(6):879](http://pubmed.ncbi.nlm.nih.gov/21195605?dopt=Abstract))

Other imaging techniques

* Tc99m scintimammography
  + **mean overall sensitivity and specificity ≤ 85% may limit diagnostic utility of scintimammography for suspected primary breast cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[16794520Nucl Med Commun 2006 Jul;27(7):589](http://pubmed.ncbi.nlm.nih.gov/16794520?dopt=Abstract)

studySummary2

* + - based on systematic review with inadequate assessment of trial quality Systematic Review
    - systematic review of 17 studies evaluating scintimammography for detecting primary breast cancer since 1997 in 5,473 patients
    - 12 single-center trials (2,424 patients) and 5 multicenter trials (3,049 patients) were analyzed separately
    - reference standard was histopathologic exam
    - sensitivities
      * 85% overall in both single-center and multicenter trials
      * 71%-93% in multicenter trials
      * 69%-90% in single-center trials
    - specificities
      * 83% in multicenter trials (range 69%-90%)
      * 84% in single-center trials (range 71%-94%)
    - in 3 multicenter trials with 1,307 patients
      * sensitivity ranged from 76% to 94% for palpable tumors, and from 30% to 75% for nonpalpable tumors
      * specificity ranged from 61% to 85% for palpable tumors, and from 50% to 93% for nonpalpable tumors
    - PubMed16794520Nuclear medicine communications20060701Nucl Med Commun277589589 Reference - [16794520Nucl Med Commun 2006 Jul;27(7):589](http://pubmed.ncbi.nlm.nih.gov/16794520?dopt=Abstract)
  + **breast-specific gamma imaging might have higher specificity than MRI for detection of breast cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Diagnostic Cohort Study[mdc24791629pAm J Surg 2014 May;207(5):698](http://pubmed.ncbi.nlm.nih.gov/24791629?dopt=Abstract)

studySummary2

* + - based on retrospective diagnostic cohort study with unclear blinding Diagnostic Cohort Study
    - 75 women had breast-specific gamma imaging and MRI within 2 months of each other for diagnosis of breast cancer
    - 51% had breast cancer
    - diagnostic performance for breast cancer comparing breast-specific gamma irradiation vs. MRI (no p values reported)
      * sensitivity 92% vs. 89%
      * specificity 73% vs. 54%
      * positive predictive value 78% vs. 67%
      * negative predictive value 90% vs. 83%
    - PubMed24791629American journal of surgery20140501Am J Surg2075698698 Reference - [mdc24791629pAm J Surg 2014 May;207(5):698](http://pubmed.ncbi.nlm.nih.gov/24791629?dopt=Abstract)

Imaging to assess for metastatic disease

Recommendations

* in the absence of signs or symptoms of metastatic disease, most patients will not benefit from radiologic staging studies ([ESMO Grade D, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__ANC_1607337114)
* consider additional radiologic staging for patients with clinically positive axillary nodes, primary tumors ≥ 5 cm, aggressive biology, or clinical signs, symptoms, or laboratory values suggesting metastatic disease ([ESMO Grade B, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__ANC_1607337114)
* consider testing to assess for distant metastatic disease in patients with inoperable breast cancer and in symptomatic or [high-risk](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#RECOMMENDATIONS_IMAGING_METASTATIC__ANC_441764537) patients with operable breast cancer including[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF6778),[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__ANC_1607337114),[4](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF4502)
  + chest computed tomography (CT) scan with contrast ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade B, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE); [ESO/ESMO Grade 1B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOGRADE) for full staging workup before systemic therapy including imaging of chest, CT preferred)
  + abdominal with or without pelvic CT scan with contrast or magnetic resonance imaging (MRI) with contrast if ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade B, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE); [ESO/ESMO Grade 1B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOGRADE))
    - abdominal symptoms
    - abnormal physical examination of abdomen or pelvis
    - abnormal liver function tests
    - elevated alkaline phosphatase levels
  + bone scan or sodium fluoride positron emission tomography (PET)/CT ([NCCN Category 2B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade B, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE) for bone scan; [ESO/ESMO Grade 1B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOGRADE) for full staging workup before systemic therapy including imaging of bone)
  + fluorodeoxyglucose (FDG)-PET/CT (optional) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade B, Level V](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE); [ESMO Grade A, Level V](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE) if conventional imaging findings inconclusive; [ESO/ESMO Grade 2B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOGRADE) for PET/CT if available in place of CT and bone scan)

Bone scan

* indications[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF6778),[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__ANC_1607337114)
  + consider if clinical signs, symptoms or laboratory values suspicious for bone metastasis ([ESMO Grade B, Level V](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE); [NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE) for clinical stage I, IIA or IIB if localized bone pain or elevated alkaline phosphatase)
  + consider if clinically positive axillary lymph nodes, tumor size ≥ 5 cm or aggressive biology ([ESMO Grade B, Level V](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
  + consider for clinical stage IIA or IIB if neoadjuvant systemic therapy planned ([NCCN Category 2B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + consider for clinical stages III through IV ([NCCN Category 2B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

Computerized tomography (CT)

* indications[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF6778),[4](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF4502)
  + consider chest CT with contrast in women with early breast cancer only if signs or symptoms of pulmonary metastasis ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade D, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
  + consider abdominal (with or without pelvis) CT with contrast in women with early breast cancer only if any of the following is present ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade D, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
    - signs or symptoms of abdominal metastasis
    - abnormal liver function tests
    - elevated alkaline phosphatase
  + consider chest, abdominal (with or without pelvis) CT with contrast in women with locally advanced breast cancer ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

MRI for detection of metastatic cancer at presentation

* for evaluation of suspected metastatic disease at presentation, use MRI to assess for
  + presence and extent of visceral metastases, in combination with x-ray, ultrasound, and CT
  + presence and extent of metastases in bones of axial skeleton
    - as option along with bone windows on a CT scan, or bone scintigraphy
    - if other imaging is equivocal
    - if more information is needed (for example, if lytic metastases are encroaching on spinal canal)
  + Reference - National Institute for Health and Clinical Excellence (NICE) guideline on advanced breast cancer: diagnosis and treatment ([NICE 2009 Feb CG81](https://www.nice.org.uk/guidance/CG81/chapter/1-Recommendations#diagnosis-and-assessment-2)[PDF](https://www.nice.org.uk/guidance/cg81/resources/advanced-breast-cancer-diagnosis-and-treatment-pdf-975683850181))
* For women with breast cancer, MRI appears to be more effective than ultrasound, CT, scintimammography (SMM), or PET for identifying recurrent or metastatic breast cancer. For detecting bone metastases, breast MRI may be more useful than bone scintigraphy or PET.
  + **MRI appears to identify recurrent or metastatic breast cancer better than ultrasound, CT, SMM, or PET (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[mnh20091186pmdc20091186pJ Cancer Res Clin Oncol 2010 Jul;136(7):1007](http://pubmed.ncbi.nlm.nih.gov/20091186?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2874488/?tool=pubmed)

studySummary2

* + - based on systematic review limited by heterogeneity Systematic Review
    - systematic review of 42 prospective and retrospective cohort studies evaluating various imaging modalities for diagnosing breast cancer recurrence and/or metastasis in 5,421 patients
    - imaging included ultrasound, CT, MRI, SMM, and PET
    - reference standard included histopathologic analysis and/or close clinical and imaging follow-up ≥ 6 months
    - recurrence or metastasis in 1,647 patients or lesions

| Summary Estimates of Diagnostic Performance | | | | | |
| --- | --- | --- | --- | --- | --- |
|  | **Ultrasound** | **CT** | **MRI** | **SMM** | **PET** |
| Sensitivity | 85.7% | 84.8% | 95% | 90% | 95.3% |
| Specificity | 96.2% | 73.5% | 92.9% | 79.8% | 86.3% |
| Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; SMM, scintimammography. | | | | | |

* + - no significant differences in sensitivity between MRI and PET; both had significantly greater sensitivity than ultrasound, CT, and SMM
    - no significant differences in specificity between MRI and ultrasound; both had significantly greater specificity than PET, CT, and SMM
    - PubMed20091186Journal of cancer research and clinical oncology20100701J Cancer Res Clin Oncol136710071007 Reference - [mnh20091186pmdc20091186pJ Cancer Res Clin Oncol 2010 Jul;136(7):1007](http://pubmed.ncbi.nlm.nih.gov/20091186?dopt=Abstract) [full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2874488/?tool=pubmed)
  + **MRI may be more useful than PET or bone scintigraphy for detecting bone metastases in patients with breast cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[mdc20495798pSkeletal Radiol 2011 May;40(5):523](http://pubmed.ncbi.nlm.nih.gov/20495798?dopt=Abstract)

studySummary2

* + - based on systematic review with wide confidence intervals Systematic Review
    - systematic review of 13 articles consisting of 23 studies evaluating MRI, FDG-PET, or technitium-99m-methylene diphosphonate (99mTc-MDP) bone scintigraphy for detecting bone metastases in 2,115 patients with breast cancer aged 29-90 years
    - studies using PET combined with CT were excluded
    - reference standard was histopathologic exam and/or close clinical and imaging follow-up for ≥ 6 months

| Diagnostic Performance Comparing MRI vs. PET vs. Bone Scan (Pooled Per-patient Estimates) | | | |
| --- | --- | --- | --- |
| **Diagnostic Performance** | **MRI(3 Studies with 136 Patients)** | **PET(3 Studies with 184 Patients)** | **BS(10 Studies with 678 Patients)** |
| Sensitivity | 97.1% | 83.3% (p < 0.05 vs. MRI) | 87% (p < 0.05 vs. MRI, no significant difference vs. PET) |
| Specificity | 97% | 94.5% (p < 0.05 vs. bone scan, no significant difference vs. MRI) | 88.1% (p < 0.05 vs. MRI and PET) |
| Diagnostic odds ratio | 298.5 (95% CI 48.5-1,836.9) | 82.1 (95% CI 17.4-387.5, p < 0.05 vs. MRI) | 49.3 (95% CI 17.2-141.5, p < 0.05 vs. MRI, no significant difference vs. PET) |
| Abbreviations: BS, bone scintigraphy; MRI, magnetic resonance imaging; PET, positron emission tomography. | | | |

* + - pooled per-lesion analysis comparing PET (3 studies with 99 patients and 1,214 lesions) vs. bone scan (4 studies with 133 patients and 1,303 lesions)
      * sensitivity 52.7% vs. 87.8% (p < 0.05)
      * specificity 99.6% vs. 96.1% (p < 0.05)
      * diagnostic odds ratio 283.3 (95% CI 96-835.5) vs. 66.8 (95% CI 4.9-903.6) (p < 0.05)
    - insufficient data to evaluate per-lesion performance of MRI
    - PubMed20495798Skeletal radiology20110501Skeletal Radiol405523523 Reference - [mdc20495798pSkeletal Radiol 2011 May;40(5):523](http://pubmed.ncbi.nlm.nih.gov/20495798?dopt=Abstract)

Positron Emission Tomography (PET) and PET/CT

* indications[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF6778),[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__ANC_1607337114)
  + sodium fluoride PET/CT (or alternative of bone scan)
    - consider for clinical stage IIA or IIB, if neoadjuvant systemic therapy planned ([NCCN Category 2B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - consider for clinical stage III through IV ([NCCN Category 2B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + fluorodeoxyglucose (FDG) PET/CT
    - not indicated in stage I-II, IIA, IIB, or operable IIIA
    - consider for stage IIIA (if N2), IIIB, IIIC, and IV ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * may be useful in identifying regional nodal disease or distant metastasis when used in addition to standard imaging
      * most useful when standard imaging is equivocal or suspicious ([ESMO Grade A, Level V](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
    - PET/CT may replace traditional imaging if neoadjuvant chemotherapy planned and high-risk breast cancer ([ESMO Grade B, Level V](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
* FDG-PET may not rule out axillary lymph node involvement in women with breast cancer, and appears insufficient for diagnosing primary breast cancer, recurrence, and metastasis.
  + **FDG-PET does not appear sufficient for primary tumor diagnosis or to rule out axillary lymph node involvement, cancer recurrence, or metastases (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[19277913Med Oncol 2010 Mar;27(1):114](http://pubmed.ncbi.nlm.nih.gov/19277913?dopt=Abstract)

studySummary2

* + - based on systematic review of low-quality trials Systematic Review
    - systematic review of 73 studies evaluating FDG-PET for diagnosis, staging, detecting recurrent/metastatic disease, or assessing response to treatment
    - for detecting primary tumors
      * FDG-PET had 48%-95.7% sensitivity (16 studies) and 73.3%-100% specificity (8 studies that reported specificity)
      * sensitivity decreases with small tumors (< 10 mm) or with reduced uptake of FDG
      * FDG-PET associated with better diagnostic efficacy compared to conventional techniques such as mammography, physical exam, or ultrasound
    - for axillary lymph node staging
      * FDG-PET had 20%-90.9% sensitivity (22 studies) and 74%-100% specificity (17 studies that reported specificity)
      * diagnostic efficacy related to size of metastases and number of lymph nodes involved
      * FDG-PET associated with better diagnostic efficacy compared to physical exam, but less effective than sentinel lymph node biopsy
    - for detecting recurrent or metastatic disease, FDG-PET had 17%-100% sensitivity and 20%-100% specificity in 23 studies
    - PubMed19277913Medical oncology (Northwood, London, England)20100301Med Oncol271114114 Reference - [19277913Med Oncol 2010 Mar;27(1):114](http://pubmed.ncbi.nlm.nih.gov/19277913?dopt=Abstract)
  + **negative FDG-PET not sufficient to rule out axillary lymph node involvement in patients with breast cancer (**[**level 1 [likely reliable] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[mnh20140703pcxh52169463pmdc20140703pBreast Cancer Res Treat 2010 Aug;123(1):281](http://pubmed.ncbi.nlm.nih.gov/20140703?dopt=Abstract)

studySummary1

* + - based on systematic review Systematic Review
    - systematic review of 25 studies evaluating FDG-PET for axillary lymph node staging in 2,460 patients with breast cancer
    - reference standard was axillary or sentinel lymph node histology
    - nodes positive in 1,042 patients (42%)
    - FDG-PET had 67% sensitivity (range 20%-100%) and 91% specificity (range 65%-100%)
    - PubMed20140703Breast cancer research and treatment20100801Breast Cancer Res Treat1231281281 Reference - [mnh20140703pcxh52169463pmdc20140703pBreast Cancer Res Treat 2010 Aug;123(1):281](http://pubmed.ncbi.nlm.nih.gov/20140703?dopt=Abstract)
  + **PET with or without CT may have limited sensitivity for identifying axillary lymph node metastasis in patients newly diagnosed with early stage invasive primary breast cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[21276372Health Technol Assess 2011 Jan;15(4):iii](http://pubmed.ncbi.nlm.nih.gov/21276372?dopt=Abstract)

studySummary2

* + - based on systematic review of studies with methodologic limitations Systematic Review
    - systematic review of 35 prospective and retrospective cohort studies evaluating accuracy of PET (with and without CT), or MRI for detection of axillary lymph node metastasis in patients newly diagnosed with early stage invasive primary breast cancer
    - most common limitations to studies were unclear blinding of reference results and relevant clinical information not available to interpreting radiologist
    - most common reference standards were axillary lymph node dissection or sentinel lymph node biopsy
    - prevalence of axillary node metastasis ranged from 26% to 59%
    - PET/CT in 7 studies with 862 patients
      * mean sensitivity 56% (95% CI 44%-67%)
      * mean specificity 96% (95% CI 90%-99%)
    - PET only in 19 studies with 1,729 patients
      * mean sensitivity 66% (95% CI 50%-79%)
      * mean specificity 93% (95% CI 89%-96%)
    - PubMed21276372Health technology assessment (Winchester, England)20110101Health Technol Assess154iiiiii Reference - [21276372Health Technol Assess 2011 Jan;15(4):iii](http://pubmed.ncbi.nlm.nih.gov/21276372?dopt=Abstract)

Biopsy and Pathology

Core needle biopsy (CNB)

* diagnosis of malignancy is based on CNB, preferably obtained by [ultrasound](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#ULTRASOUND) or stereotactic ([mammogram](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#DIAGNOSTIC_MAMMOGRAPHY)) guidance ([ESMO Grade A, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))[1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF5142),[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778),[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__ANC_1607337114)
* advantages of core biopsy compared to [fine needle aspiration](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#FINE_NEEDLE_ASPIRATION__FNA_) (FNA)[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + provides tissue sample size that can be used for pathologic assessment without need for follow-up biopsy if malignancy found
  + may result in better accuracy compared to FNA when no mass palpable
  + allows placement of a marker clip for later identification of site should lesion be no longer palpable or visible on imaging due to
    - removal with CNB
    - disappearance with neoadjuvant systemic therapy
* recommendations for follow-up after CNB ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + for benign histology and agreement with imaging results, consider either
    - return to regular, age and risk-appropriate [screening](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#SCREENING) protocol ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - physical exam, with or without ultrasound and/or mammogram, every 6-12 months for 1 year, as needed, to assess for stability on imaging; if remains stable, return to regular, age and risk-appropriate screening protocol ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if increased suspicion or change in size, perform surgical excision ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + for indeterminate histology, benign histology but disagreement with imaging results, atypical ductal hyperplasia (ADH), pleomorphic lobular carcinoma in situ (LCIS), or other histologies that may require more tissue for diagnosis (such as mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scar, or other histologies of concern to pathologist)
    - perform [surgical excisional biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#SURGICAL_EXCISIONAL_BIOPSY) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - for some patients with ADH, flat epithelial atypia (FEA), papillomas, fibroepithelial lesions, and radial scar, consider monitoring rather than surgical excision ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + for LCIS or atypical lobular hyperplasia (ALH)
    - with disagreement between histology and imaging results, perform surgical excisional biopsy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - with agreement between histology and imaging results, consider either
      * physical exam with or without ultrasound and/or mammogram every 6-12 months for 1 year and counseling for risk reduction ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * surgical excision ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); multifocal/extensive LCIS involving > 4 terminal ductal lobular units may be associated with increased risk of invasive cancer on surgical excision
  + for malignant findings, proceed with breast cancer treatment ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
* For women with palpable or nonpalpable lesions, both stereotactic and ultrasound-guided core needle biopsy (CNB) methods may have similar diagnostic accuracy. However, CNB may miss the diagnosis of breast cancer in women diagnosed with columnar cell lesions with atypia or atypical ductal hyperplasia.
  + **stereotactic and ultrasound-guided core needle biopsy methods appear to have high sensitivity and specificity for diagnosing breast lesions in women with palpable or nonpalpable breast abnormalities (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[AHRQ Comparative Effectiveness Review 2014 Sep:139](https://effectivehealthcare.ahrq.gov/topics/breast-biopsy-update/research)[PDF](https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/breast-biopsy-update_research.pdf)

studySummary2

* + - based on systematic review with study-specific quality measures not reportedSystematic Review
    - systematic review of randomized trials or cohort studies comparing core needle vs. open surgical biopsy for diagnosing breast lesions in women with palpable or nonpalpable breast abnormalities not previously diagnosed with breast cancer
    - 161 prospective or retrospective cohort studies evaluated diagnostic accuracy of core needle biopsy methods for detection of breast lesions
    - reference standards included open surgical biopsy or follow-up by clinical examination and/or mammography at ≥ 6 months
    - median prevalence of malignant disease (invasive carcinoma or ductal carcinoma in situ) 34% (range 1%-94%)
    - pooled diagnostic performance for detecting breast lesions in women at average risk of cancer
      * stereotactically guided, automated core needle biopsy in analysis of 37 studies
        + sensitivity 97% (95% credible interval [CrI] 95%-98%)
        + specificity 97% (95% CrI 96%-98%)
        + positive likelihood ratio 33.6 (95% CrI 22.6-50.9)
        + negative likelihood ratio 0.03 (95% CrI 0.02-0.05)
      * stereotactically guided, vacuum-assisted core needle biopsy in analysis of 43 studies
        + sensitivity 99% (95% CrI 98%-99%)
        + specificity 92% (95% CrI 89%-94%)
        + positive likelihood ratio 12.8 (95% CrI 9.4-17.9)
        + negative likelihood ratio 0.01 (95% CrI 0.01-0.02)
      * ultrasound-guided, automated core needle biopsy in analysis of 27 studies
        + sensitivity 99% (95% CrI 98%-99%)
        + specificity 97% (95% CrI 95%-98%)
        + positive likelihood ratio 33.5 (95% CrI 20.7-56.9)
        + negative likelihood ratio 0.01 (95% CrI 0.01-0.02)
      * ultrasound-guided, vacuum-assisted core needle biopsy in analysis of 12 studies
        + sensitivity 97% (95% CrI 92%-99%)
        + specificity 98% (95% CrI 96%-99%)
        + positive likelihood ratio 57.7 (95% CrI 25.8-138.7)
        + negative likelihood ratio 0.03 (95% CrI 0.01-0.08)
      * freehand, automated core needle biopsy in analysis of 10 studies
        + sensitivity 91% (95% CrI 80%-96%)
        + specificity 98% (95% CrI 95%-100%)
        + positive likelihood ratio 58.4 (95% CrI 19-226.9)
        + negative likelihood ratio 0.09 (95% CrI 0.04-0.2)
      * magnetic resonance imaging (MRI)-guided, automated core needle biopsy in analysis of 2 studies
        + sensitivity 90% (95% CrI 57%-99%)
        + specificity 99% (95% CrI 91%-100%)
        + positive likelihood ratio 62.3 (95% CrI 9.4-726.3)
        + negative likelihood ratio 0.1 (95% CrI 0.01-0.44)
    - core needle biopsy methods associated with decreased risk for multiple surgical procedures compared to open surgical biopsy
    - Reference - [AHRQ Comparative Effectiveness Review 2014 Sep:139](https://effectivehealthcare.ahrq.gov/topics/breast-biopsy-update/research)[PDF](https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/breast-biopsy-update_research.pdf)
  + **stereotactic vacuum-assisted biopsy and CNB may have similar diagnostic accuracy in women referred for breast biopsy with nonpalpable lesions (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Randomized Trial[mnh26654214pcxh113169576pmdc26654214pBr J Radiol 2016;89(1058):20150504](http://pubmed.ncbi.nlm.nih.gov/26654214?dopt=Abstract)[Full Text](http://www.birpublications.org/doi/full/10.1259/bjr.20150504)

studySummary2

* + - based on randomized trial with early termination and without blinding Randomized Trial
    - 129 women aged 18-90 years referred for biopsy after routine screening mammography but without palpable lesion were randomized to stereotactic 11-gauge vacuum-assisted biopsy (VAB) vs. 14-gauge CNB and followed for 12 months
    - both biopsy procedures used full-field digital mammography
    - reference standard was final surgical pathology in patients having surgery, and multidisciplinary review in patients not having surgery
    - surgery indicated in 24.6% VAB group and 38% in CNB group
    - trial enrollment stopped early (at 21% of planned enrollment) for futility without predefined stopping rule
    - 3 women in VAB group had bleeding during procedure, and crossed over to CNB
    - comparing stereotactic VAB vs. CNB
      * diagnostic accuracy 83% vs. 87% (not significant)
      * upgrade from ductal carcinoma in situ to invasive at surgery in 14.3% vs. 15.8% (no p value reported)
      * repeat biopsy in 12% vs. 8% (not significant)
      * repeat surgery in 44% vs. 29% (not significant)
    - no significant differences in quality of life
    - PubMed26654214The British journal of radiology201601Br J Radiol8910582015050420150504 Reference - [mnh26654214pcxh113169576pmdc26654214pBr J Radiol 2016;89(1058):20150504](http://pubmed.ncbi.nlm.nih.gov/26654214?dopt=Abstract) [full-text](http://www.birpublications.org/doi/full/10.1259/bjr.20150504)
  + **CNB may miss the diagnosis of breast cancer in women diagnosed with columnar cell lesions with atypia or atypical ductal hyperplasia (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[21989373Ann Surg 2012 Feb;255(2):259](http://pubmed.ncbi.nlm.nih.gov/21989373?dopt=Abstract)

studySummary2

* + - based on systematic review limited by clinical heterogeneity Systematic Review
    - systematic review of 24 cohort studies evaluating risk of ductal carcinoma in situ or invasive carcinoma in women diagnosed with columnar cell lesions with CNB
    - reference standard was direct surgical excision or clinical follow-up
    - analyses limited by heterogeneity in size of tumors, presence of mammographic abnormalities, size and number of needle biopsies, and experience of operators
    - pooled underestimation risks for progression to ductal carcinoma in situ or invasive carcinoma
      * 1.5% (95% CI 0.6%-4%) for columnar cell lesions without atypia in analysis of 6 studies with 630 patients
      * 9% (95% CI 5%-14%) for columnar cell lesions with atypia in analysis of 22 studies with 668 patients
      * 20% (95% CI 13%-28%) for atypical ductal hyperplasia associated with columnar cell lesions in analysis of 8 studies with 384 patients
    - PubMed21989373Annals of surgery20120201Ann Surg2552259259 Reference - [21989373Ann Surg 2012 Feb;255(2):259](http://pubmed.ncbi.nlm.nih.gov/21989373?dopt=Abstract)
* **CNB associated with higher diagnostic accuracy for detection of breast cancer than FNA cytology in patients with palpable breast masses (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Randomized Trial[Saudi Med J 2005 Jan;26(1):42](https://pubmed.ncbi.nlm.nih.gov/15756351)Diagnostic Cohort Study[Acta Radiol 2008 Oct;49(8):863](https://pubmed.ncbi.nlm.nih.gov/18618302)Diagnostic Cohort Study[Eur J Surg Oncol 2003 May;29(4):374](https://pubmed.ncbi.nlm.nih.gov/12711292)Diagnostic Cohort Study[Ann R Coll Surg Engl 2001 Mar;83(2):110](https://pubmed.ncbi.nlm.nih.gov/11320918)[PDF](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2503348/pdf/annrcse01630-0044.pdf)

studySummary

* + Randomized TrialDiagnostic Cohort StudyDiagnostic Cohort StudyDiagnostic Cohort Study based on 1 randomized trial with indirect comparisons and 3 diagnostic cohort studies without blinding of reference standard
  + 296 women aged 15-74 years with palpable breast masses randomized to CNB vs. FNA cytology
    - results compared to final diagnosis by histopathology
    - comparing CNB vs. FNA cytology (p < 0.05 for overall diagnostic accuracy)
      * sensitivity 92.3% vs. 66.7%
      * specificity 94.8% vs. 81.8%
      * positive predictive value 100% vs. 100%
      * negative predictive value 100% vs. 90%
    - PubMed15756351Saudi medical journalSaudi Med J2005010126142-642Reference - [Saudi Med J 2005 Jan;26(1):42](https://pubmed.ncbi.nlm.nih.gov/15756351)
  + diagnostic cohort of 688 patients aged 14-93 years with solid breast lump had FNA (590 lesions) and/or CNB (98 lesions)
    - reference standard was pathology report in surgically treated patients and cancer diagnosis in biopsied breast during 2-year follow-up in conservatively treated patients
    - patients who had both FNA and CNB were analyzed according to whichever test was done first
    - comparing CNB biopsy vs. FNA
      * false-positive rate 1% vs. 9% (no p value reported)
      * false-negative rate 11% vs. 19% (no p value reported)
    - PubMed18618302Acta radiologica (Stockholm, Sweden : 1987)Acta Radiol20081001498863-9863 Reference - [Acta Radiol 2008 Oct;49(8):863](https://pubmed.ncbi.nlm.nih.gov/18618302)
  + diagnostic cohort of 330 consecutive patients with 344 palpable breast masses evaluated by physical exam, ultrasound, and (if > 35 years old or solid mass) mammogram
    - patients with solid mass had CNB and FNA cytology (with or without ultrasound guidance) with histology
    - malignant lesions in 25.6% based on results of all tests
    - comparing CNB vs. FNA
      * malignancy in 25.3% vs. 19.8% (no p value reported)
      * inadequate epithelial cells for diagnosis in 16.3% vs. 31.7% (no p value reported)
    - CNB diagnosed malignancy in 19 specimens (21.8%) not diagnosed by FNA
    - PubMed12711292European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical OncologyEur J Surg Oncol20030501294374-8374 Reference - [Eur J Surg Oncol 2003 May;29(4):374](https://pubmed.ncbi.nlm.nih.gov/12711292)
  + diagnostic cohort of 52 patients with symptomatic breast masses and clinical or radiologic suspicion of breast cancer, had standard triple test (clinical exam, mammogram, and FNA) plus automated CNB
    - 31 (59.6%) had definitive diagnosis of breast cancer by FNA, and 50 (96.2%) by CNB
    - comparing sensitivity with automated CNB vs. FNA cytology
      * 97% vs. 61% when mammogram was diagnostic of cancer (p value not reported)
      * 95% vs. 53% when mammogram not diagnostic of cancer (p value not reported)
    - PubMed11320918Annals of the Royal College of Surgeons of EnglandAnn R Coll Surg Engl20010301832110-2110 Reference - [Ann R Coll Surg Engl 2001 Mar;83(2):110](https://pubmed.ncbi.nlm.nih.gov/11320918)[PDF](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2503348/pdf/annrcse01630-0044.pdf), commentary can be found in [11995763Ann R Coll Surg Engl 2002 Mar;84(2):146](http://pubmed.ncbi.nlm.nih.gov/11995763?dopt=Abstract)
* CORE\_NEEDLE\_BIOPSY\_\_LI\_P4Y\_QZN\_FTBEU04012004/01/2020 10:49:26 AMevidenceUpdatelowOncologic\_Diseaseupgrade from pure atypical ductal hyperplasia diagnosed with percutaneous needle biopsy to ductal carcinoma in situ or invasive ductal carcinoma reported in 29% of surgically excised lesions and 5% of lesions managed with follow-up (Radiology 2020 Jan)

**upgrade from pure atypical ductal hyperplasia diagnosed with percutaneous needle biopsy to ductal carcinoma in situ or invasive ductal carcinoma reported in 29% of surgically excised lesions and 5% of lesions managed with follow-up (**[**level 3 [lacking direct] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[Radiology 2020 Jan;294(1):76](http://pubmed.ncbi.nlm.nih.gov/31660803)

studySummary

* + Systematic Review based on noncomparative data in systematic review of observational studies
  + systematic review of 93 diagnostic cohort studies evaluating upgrade rates of 7,601 percutaneously diagnosed pure atypical ductal hyperplasia (ADH) lesions
    - biopsy methods reported included core-needle biopsy (24 studies), vacuum-assisted biopsy (44 studies), both core-needle and vacuum-assisted biopsy (21 studies)
    - imaging guidance used for biopsy included stereotaxis (29 studies), ultrasound (9 studies), magnetic resonance imaging (MRI; 9 studies), and mixed stereotaxis and ultrasound (8 studies)
  + reference standards were histopathology after surgical excision or negative imaging findings of lesions without surgical excision at follow-up
  + among 6,458 ADH lesions with data on reference standard
    - 5,911 lesions were surgically excised
    - 547 lesions were managed with follow-up
  + pooled upgrade rates of ADH lesions
    - upgrade rate to invasive ductal carcinoma or ductal carcinoma in situ at surgery or follow-up
      * for surgically excised lesions, 29% (95% CI 26%-32%)
      * for lesions managed with follow-up, 5% (95% CI 4%-8%)
    - upgrade rate to invasive ductal carcinoma
      * for surgically excised lesions, 9% (95% CI 7%-11%)
      * for lesions managed with follow-up, 3.4% (95% CI 1.8%-6.4%)
    - upgrade to ductal carcinoma in situ
      * for surgically excised lesions, 20% (95% CI 18%-23%
      * for lesions managed with follow-up, 2.8% (95% CI 1.5%-5.1%)
  + PubMed31660803RadiologyRadiology20200101294176-8676Reference - [Radiology 2020 Jan;294(1):76](http://pubmed.ncbi.nlm.nih.gov/31660803), editorial can be found in [Radiology 2020 Jan;294(1):87](http://pubmed.ncbi.nlm.nih.gov/31661362)

Fine needle aspiration (FNA)

* FNA involves use of small-bore needle to obtain cytologic samples from breast mass[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + FNA of nonpalpable lesions may be performed using [ultrasound](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#ULTRASOUND)
  + may be less accurate than core needle or excisional biopsy in evaluation of nonpalpable breast lesions
* recommendations for follow-up after cyst aspiration ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + aspiration may be indicated in any of the following situations
    - confirmation of cystic lesion is needed
    - abscess is suspected
    - symptomatic relief is needed
  + for persistent mass, perform ultrasound and image-guided core needle biopsy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + for resolved mass and bloody aspirate not felt traumatic, send fluid for cytology ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if cytology is negative, return to regular age and risk-appropriate screening protocol ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if cytology is atypical or malignant, perform surgical excision ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + for resolved mass and normal (nonbloody) cyst fluid, return to regular age and risk-appropriate [screening](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#SCREENING) protocol; if mass recurs, provide clinical follow-up with age-appropriate imaging ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
* compared to [core needle biopsy](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#CORE_NEEDLE_BIOPSY), FNA biopsy for solid lesions offers[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + advantages
    - minimally invasive procedure
    - low cost
  + disadvantages
    - requires pathologists with expertise in breast cytology
    - requires follow-up CNB or surgical biopsy if atypia or malignant cells on cytology
* **ultrasound-guided FNA cytology may help diagnose breast cancer in patients with breast lesions (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cohort Study[12926154Anticancer Res 2003 May-Jun;23(3C):3009](http://pubmed.ncbi.nlm.nih.gov/12926154?dopt=Abstract)

studySummary2

* + based on cohort study Cohort Study
  + retrospective study of 354 breast masses (212 palpable) in patients with evaluation by physical exam, imaging, and ultrasound-guided FNA
  + reference standard was histologic results and clinical follow-up
  + 60 cases had histologic assessment, 18 were malignant
  + diagnostic performance of ultrasound-guided FNA cytology for detection of breast cancer
    - sensitivity 90%
    - specificity 100%
    - positive predictive value 100%
    - negative predictive value 90%
  + PubMed12926154Anticancer research20030501Anticancer Res233C30093009 Reference - [12926154Anticancer Res 2003 May-Jun;23(3C):3009](http://pubmed.ncbi.nlm.nih.gov/12926154?dopt=Abstract)
* **FNA biopsy may help diagnose breast cancer in patients with palpable breast masses in low resource areas (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Diagnostic Cohort Study[J Cytol 2011 Jul;28(3):111](http://pubmed.ncbi.nlm.nih.gov/21897544-clinical-effectiveness-of-fine-needle-aspiration-biopsy-in-patients-with-palpable-breast-lesions-seen-at-the-university-college-hospital-ibadan-nigeria-a-10-year-retrospective-study/?dopt=Abstract)[Full Text](http://www.jcytol.org/article.asp?issn=0970-9371;year=2011;volume=28;issue=3;spage=111;epage=113;aulast=Ukah)Diagnostic Cohort Study[Mymensingh Med J 2011 Oct;20(4):658](http://pubmed.ncbi.nlm.nih.gov/22081186-diagnosis-of-breast-lump-by-fine-needle-aspiration-cytology-and-mammography/?dopt=Abstract)

studySummary

* + Diagnostic Cohort StudyDiagnostic Cohort Study based on 2 diagnostic cohort studies with reference test not applied to all patients
  + retrospective diagnostic cohort of 1,401 patients with palpable breast lesions from 1996 to 2005 in Nigeria who had FNA biopsy with cytology
    - histological analysis from biopsy (reference standard) applied to 250 patients (17.8%)
    - of patients who had biopsy, 124 patients (49.6%) had malignancy
    - diagnostic performance of FNA biopsy for detection of breast cancer (in analysis limited to patients who had biopsy)
      * sensitivity 91.1%
      * specificity 93.7%
      * positive predictive value 93.4%
      * negative predictive value 91.5%
    - of 1,151 patients who did not have biopsy, cytology results on FNA were malignant in 351 and suspicious of malignancy in 82
    - PubMed21897544Journal of cytologyJ Cytol20110701283111-3111Reference - [J Cytol 2011 Jul;28(3):111](http://pubmed.ncbi.nlm.nih.gov/21897544-clinical-effectiveness-of-fine-needle-aspiration-biopsy-in-patients-with-palpable-breast-lesions-seen-at-the-university-college-hospital-ibadan-nigeria-a-10-year-retrospective-study/?dopt=Abstract)[full-text](http://www.jcytol.org/article.asp?issn=0970-9371;year=2011;volume=28;issue=3;spage=111;epage=113;aulast=Ukah)
  + diagnostic cohort of 222 women in Bangladesh with palpable breast mass who had FNA cytology
    - 112 patients also had mammography
    - 89 cases had histopathologic analysis (reference standard)
    - 36 cases (40%) were malignant by reference standard
    - diagnostic performance for detection of breast cancer comparing of FNA cytology vs. mammogram
      * sensitivity 97.2% vs. 82.8%
      * specificity 99.5% vs. 90.4%
      * positive predictive value 97.2% vs. 75%
      * negative predictive value 99.5% vs. 93.8%
    - PubMed22081186Mymensingh medical journal : MMJMymensingh Med J20111001204658-64658Reference - [Mymensingh Med J 2011 Oct;20(4):658](http://pubmed.ncbi.nlm.nih.gov/22081186-diagnosis-of-breast-lump-by-fine-needle-aspiration-cytology-and-mammography/?dopt=Abstract)
* **FNA may have high rate of inadequate specimen collection, lower sensitivity, but higher specificity than CNB (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Diagnostic Cohort Study[22464444Am J Surg 2012 Aug;204(2):193](http://pubmed.ncbi.nlm.nih.gov/22464444?dopt=Abstract)

studySummary2

* + based on retrospective diagnostic cohort study with unclear blinding of reference standard Diagnostic Cohort Study
  + 162 consecutive patients who had FNA (68 patients) or CNB (94 patients) for palpable breast lesions in 2005
  + reference standard was histologic confirmation with surgical biopsy or ≥ 1-year clinical follow-up with mammography and/or ultrasound
  + ultrasound guided biopsy performed in 25% of patients having FNA and 75% of patients having CNB (p < 0.0001)
  + inadequate specimen in 0% with CNB and 21% (14 patients) with FNA
  + comparing diagnostic performance of CNB vs. FNA for detection of malignancy
    - sensitivity 100% vs. 89%
    - specificity 90% vs. 98%
    - positive predictive value 93% vs. 94%
    - negative predictive value 100% vs. 96%
  + PubMed22464444American journal of surgery20120801Am J Surg2042193193 Reference - [22464444Am J Surg 2012 Aug;204(2):193](http://pubmed.ncbi.nlm.nih.gov/22464444?dopt=Abstract)

Surgical excisional biopsy

* involves removal of entire breast mass or suspicious area of breast[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + more invasive than CNB, but useful when larger tissue samples are required
  + nonpalpable abnormal findings identified on breast imaging require radiologic localization with needle, wire or radioactive seed prior to surgery
* surgical removal of entire lesion indicated when CNB[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778),)
  + not feasible
  + result is indeterminate or is a histology requiring larger tissue sample (such as ADH, pleomorphic LCIS, mucinous producing lesions, papillary lesions, radial scar, and possible phyllodes tumor)
  + discordant with clinical or radiologic findings
* recommendations for follow-up after surgical excisional biopsy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))[5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF2778)
  + for benign histology, return to regular age and risk appropriate [screening](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#SCREENING) protocol ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + for ALH and classic or pleomorphic LCIS, proceed with high-risk screening and counseling for risk reduction ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + for malignant histology, proceed with treatment for breast cancer ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
* **in adults who had mammogram with wire-guided lumpectomy, missing clip not associated with rate of positive margins, re-excision, or recurrence**

Case-Control Study[Ann Surg Oncol 2021 Sep;28(9):4974](https://pubmed.ncbi.nlm.nih.gov/33677760)

studySummary

* + Case-Control Studybased on case-control study
  + 43 adults (mean age 55 years, 100% female) having mammogram with wire-guided localization with specimen radiograph showing missing clip were matched to 196 adults having mammogram with wire-guided localization with successful removal of clip
  + successful removal of clip confirmed with specimen radiograph
  + missing clip not associated with rate of positive margins, re-excision, or local and/or distant recurrence
  + PubMed33677760Annals of surgical oncologyAnn Surg Oncol202109012894974-49804974Reference - [Ann Surg Oncol 2021 Sep;28(9):4974](https://pubmed.ncbi.nlm.nih.gov/33677760)

Nipple fluid cytology

* TOPIC\_HDC\_YN4\_FTB\_\_LI\_VXF\_D44\_FTBEU04152204/15/2022 12:40:05 PMevidenceUpdatelowplusOncologic\_Diseasenipple discharge fluid cytology may help detect breast cancer in patients with discharge, but with low sensitivity to rule out diagnosis (Ann Surg Oncol 2022 Mar)

**nipple discharge fluid cytology may help detect breast cancer in patients with discharge, but with low sensitivity to rule out diagnosis (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[Ann Surg Oncol 2022 Mar;29(3):1774](https://pubmed.ncbi.nlm.nih.gov/34839426)[Full Text](https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC8627297/)

studySummary

* + Systematic Review based on systematic review of diagnostic cohort studies limited by heterogeneity
  + systematic review of 45 diagnostic cohort studies evaluating nipple discharge fluid cytology in 8,648 cytology samples from female adults with complaint of nipple discharge
  + reference standard was ductal histology
  + all results limited by significant heterogeneity
  + diagnostic performance of nipple discharge fluid cytology for detection of malignancy
    - for cytology indicating malignant (Cn5) breast disease in analysis of 13 studies
      * sensitivity 35% (95% CI 26%-44%)
      * specificity 100% (95% CI 100%-100%)
    - for cytology indicating atypical/equivocal (Cn3), suspicious (Cn4). or malignant (Cn5) breast disease in analysis of all studies
      * sensitivity 62% (95% CI 53%-71%)
      * specificity 71% (95% CI 57%-81%)
    - for cytology indicating benign (Cn2) breast disease in analysis of 32 studies
      * sensitivity 75% (95% CI 74%-77%)
      * specificity 87% (95% CI 86%-87%)
  + PubMed34839426Annals of surgical oncologyAnn Surg Oncol202203012931774-17861774Reference - [Ann Surg Oncol 2022 Mar;29(3):1774](https://pubmed.ncbi.nlm.nih.gov/34839426)[full-text](https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC8627297/)

Biopsy interpretation

* **overall agreement for interpretation of breast biopsies 75% among experienced pathologists, with highest agreement for diagnosis of invasive carcinoma and lowest agreement for diagnosis of atypical hyperplasia**

Diagnostic Cohort Study[cxh101610251pmdc25781441pJAMA 2015 Mar 17;313(11):1122](http://pubmed.ncbi.nlm.nih.gov/25781441?dopt=Abstract)

studySummary

* + based on diagnostic cohort study Diagnostic Cohort Study
  + 126 pathologists with ≥ 1 year experience interpreting breast specimens plus plans to continue for ≥ 1 additional year were randomized to review 1 of 4 test sets of slides from excisional or core needle breast biopsies (60 slides per test set, 240 slides total)
    - test set slides were randomly selected from registry of 19,498 cases with stratification based on original pathologist diagnosis, women's age, breast density, and biopsy type (1 slide per case)
    - reference standard was consensus diagnosis by panel of 3 experienced pathologists, internationally recognized for research on diagnostic breast pathology
  + reference diagnoses including invasive breast cancer in 10%, ductal carcinoma in situ (DCIS) in 30%, atypical hyperplasia in 30%, and benign without atypia in 30%
  + pathologists were not provided with standard diagnostic definitions, but were given women's age and type of biopsy for each sample
  + 115 pathologists (91%) independently interpreted all 60 cases in assigned test set, and their assessments were included in analysis
  + overall agreement with expert panel consensus diagnosis was 75.3%
  + concordance of 6,900 total interpretations by reference diagnosis

| **Reference Diagnosis** | **Rate of Concordance** | **Rate of Underinterpretation** | **Rate of Overinterpretation** |
| --- | --- | --- | --- |
| Invasive carcinoma | 96% | 4% | NA |
| DCIS | 84% | 13% | 3% |
| Atypical hyperplasia | 48% | 35% | 17% |
| Benign without atypia | 87% | NA | 13% |
| Abbreviations: DCIS, ductal carcinoma in situ; NA, not applicable. | | | |

* + misinterpretation was distributed widely among pathologists and cases
  + decreased concordance with reference standard significantly associated with
    - patient with increasing breast density
    - pathologists with lower weekly case volumes, working in smaller practices, or working in nonacademic settings
  + PubMed25781441JAMA20150317JAMA3131111221122 Reference - [cxh101610251pmdc25781441pJAMA 2015 Mar 17;313(11):1122](http://pubmed.ncbi.nlm.nih.gov/25781441?dopt=Abstract) , editorial can be found in [cxh101610207pmdc25781438pJAMA 2015 Mar 17;313(11):1109](http://pubmed.ncbi.nlm.nih.gov/25781438?dopt=Abstract)
* **seeking second opinion for interpretation of breast biopsy reported to reduce misclassification rates (**[**level 3 [lacking direct] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Modeling study[27334105BMJ 2016 Jun 22;353:i3069](http://pubmed.ncbi.nlm.nih.gov/27334105?dopt=Abstract)

studySummary3

* + based on simulation study Modeling study
  + 240 breast biopsy specimens selected from database were interpreted by 115 pathologists and first opinion diagnoses were compared to diagnoses based on addition of second opinion (12 strategies for seeking second opinion were assessed)
    - reference standard was independent expert consensus
    - simulated second opinion strategies included seeking second opinion on all biopsies, seeking second opinion only if first opinion is atypia, DCIS, or invasive carcinoma; other selective strategies based on first opinion, and strategies based on pathologists' weekly volume of biopsies
  + misclassification rates
    - 24.7% with first opinion only
    - 18.1% with second opinion on all samples
    - 14.3% with both first and second opinion by pathologists with high volume (≥ 10 biopsy specimens weekly)
  + misclassification rates significantly reduced with all second opinion strategies vs. first opinion only except for strategy seeking second opinion only if first opinion is invasive carcinoma
  + PubMed27334105BMJ (Clinical research ed.)20160622BMJ353i3069i3069 Reference - [27334105BMJ 2016 Jun 22;353:i3069](http://pubmed.ncbi.nlm.nih.gov/27334105?dopt=Abstract)

Pathology reporting

* pathology examination includes[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF6778),[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__ANC_1607337114)
  + determination of histological type according to [WHO classification](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#PATHOLOGY_REPORTING__LI_M3Z_5BQ_2MB) ([ESMO Grade A, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
  + determination of grade ([ESMO Grade A, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
  + immunohistochemical (IHC) evaluation of hormone receptor (HR) status, both estrogen receptor (ER) and progesterone receptor (PR) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade A, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
  + IHC evaluation of human epidermal growth factor receptor 2 (HER2) status ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade A, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
  + HER2 amplification may be determined directly using fluorescent, chromogenic, or silver in situ hybridization for tumors with ambiguous (2+) IHC scores ([ESMO Grade B, Level II](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
  + Ki67 index (may supply useful additional information, especially if assay can be standardized) ([ESMO Grade A, Level V](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
* 2019 World Health Organization classification of malignant breast tumors, 5th edition
  + epithelial tumors
    - epithelial-myoepithelial tumors, such as adenomyoepithelioma
    - papillary neoplasms
      * papillary ductal carcinoma in situ
      * encapsulated papillary carcinoma
      * solid papillary carcinoma (in situ and invasion)
      * invasive papillary carcinoma
    - noninvasive lobular neoplasia, such as lobular carcinoma in situ
    - ductal carcinoma in situ
    - invasive breast carcinoma
      * invasive breast carcinoma of no special type
      * microinvasive carcinoma
      * invasive lobular carcinoma
      * tubular carcinoma
      * cribriform carcinoma
      * mucinous carcinoma
      * mucinous cystadenocarcinoma
      * invasive micropapillary carcinoma
      * carcinoma with apocrine differentiation
      * metaplastic carcinoma
    - rare and salivary gland type tumors
      * acinic cell carcinoma
      * adenoid cystic carcinoma
      * secretory carcinoma
      * mucoepidermoid carcinoma
      * polymorphous adenocarcinoma
      * tall cell carcinoma with reversed polarity
    - neuroendocrine neoplasms, such as neuroendocrine tumor or carcinoma
  + fibroepithelial tumors, such as phyllodes tumor
  + tumors of the nipple, such as Paget disease of the nipple
  + mesenchymal tumors
    - vascular tumors
      * postradiation angiosarcoma of the breast
      * primary angiosarcoma of the breast
    - peripheral nerve sheath tumors, such as granular cell tumor
    - smooth muscle tumors, including leiomyosarcoma
    - adipocytic tumors, including liposarcoma
  + hematolymphoid tumors
    - extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (also known as MALT lymphoma)
    - follicular lymphoma
    - diffuse large B cell lymphoma
    - Burkitt lymphoma
    - breast implant associated anaplastic large cell lymphoma
  + metastatic tumors
  + tumors of male breast, such as invasive carcinoma or carcinoma in situ
  + Reference - Allison KH, Brogi E, Ellis I, et al. WHO Classification of Breast Tumours. 5th ed. Lyon, France: International Agency for Research on Cancer (IARC); 2019

Axillary lymph node evaluation

* if neoadjuvant therapy is planned[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF6778),[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__ANC_1607337114)
  + add axillary assessment with an exam, ultrasound or other imaging (if not previously done), and needle biopsy of any suspicious or clinically positive lymph nodes ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade A, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE) for ultrasound-guided FNA or core biopsy of suspicious nodes)
  + should consider marking any positive lymph nodes from biopsy with tattoo or clip to assure they are removed during surgery
* for women with clinically positive lymph nodes on physical exam at the time of diagnosis, consider confirmation of malignancy using ultrasound-guided FNA or core biopsy[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF6778)
  + if FNA or core biopsy negative, perform sentinel lymph node mapping and excision at surgical treatment ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + if FNA or core biopsy positive, perform axillary dissection level I/II at surgical treatment unless neoadjuvant systemic therapy given and nodes become clinically negative ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
* for women that have clinically negative nodes at the time of diagnosis, perform sentinel lymph node mapping and excision at surgical treatment ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade A, Level II](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF6778),[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__ANC_1607337114)
* **ultrasound-guided needle biopsy of axillary nodes appears accurate for initial staging in patients with invasive breast cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[21597359Ann Surg 2011 Aug;254(2):243](http://pubmed.ncbi.nlm.nih.gov/21597359?dopt=Abstract)

studySummary2

* + based on systematic review without assessment of study quality Systematic Review
  + systematic review of 31 diagnostic cohort studies evaluating preoperative ultrasound-guided needle biopsy of axillary nodes for initial staging in patients with invasive breast cancer
  + reference standard was histologic evaluation
  + median prevalence of metastatic axillary nodes was 47.2%
  + pooled diagnostic accuracy of preoperative ultrasound-guided needle biopsy for detection of metastatic axillary nodes
    - sensitivity 79.6% (95% CI 74.1%-84.2%)
    - specificity 98.3% (95% CI 97.2%-99%)
    - positive predictive value 97.1% (95% CI 95.2%-98.3%)
  + PubMed21597359Annals of surgery20110801Ann Surg2542243243 Reference - [21597359Ann Surg 2011 Aug;254(2):243](http://pubmed.ncbi.nlm.nih.gov/21597359?dopt=Abstract)
  + Authors report that preoperative ultrasound-guided needle biopsy may reduce need for sentinel lymph node (SLN) biopsy in up to 20% of patients. However, the authors do not report number of patients (with negative axillary node biopsy) who would have an SLN biopsy and therefore have an additional procedure.
* **ultrasound-guided core needle biopsy may have higher sensitivity for detecting axillary lymph node metastasis compared to ultrasound-guided fine needle aspiration in women with newly diagnosed invasive breast cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[Br J Surg 2018 Sep;105(10):1244](http://pubmed.ncbi.nlm.nih.gov/29972239)

studySummary

* + Systematic Review based on systematic review with limited data from direct comparisons
  + systematic review of 6 cohort studies evaluating ultrasound-guided core needle biopsy and/or ultrasound-guided fine needle aspiration for detecting axillary lymph node metastasis in 1,353 women with newly diagnosed invasive breast cancer
  + 15% had data to directly compare ultrasound-guided core needle biopsy vs. ultrasound-guided fine needle aspiration
  + reference standard was histological examination of sentinel node biopsy or axillary lymph node dissection
  + for detecting axillary lymph node metastasis
    - ultrasound-guided core needle biopsy had
      * sensitivity 88% (95% CI 84%-91%)
      * specificity 100% (95% CI 98%-100%)
    - ultrasound-guided fine needle aspiration had
      * sensitivity 74% (95% CI 70%-78%)
      * specificity 100% (95% CI 99%-100%)
  + ultrasound-guided core needle biopsy reported to have higher risk of complications (7.1% vs. 1.3%, p < 0.001) but fewer repeat diagnostic procedures (0.5% vs. 4%, p < 0.001) compared to ultrasound-guided fine needle aspiration
  + most common complications with core needle biopsy were pain, hematoma, and bruising
  + PubMed29972239The British journal of surgeryBr J Surg20180901105101244-12531244Reference - [Br J Surg 2018 Sep;105(10):1244](http://pubmed.ncbi.nlm.nih.gov/29972239)
* see also [Sentinel Lymph Node Biopsy and Axillary Management for Breast Cancer](https://dpa-pde-oxford.shinyapps.io/evaluation/sentinel-lymph-node-biopsy-and-axillary-management-for-breast-cancer)

Tumor Subtyping, Hormone Receptor and HER2 Testing

Tumor Subtyping

* immuno/pathological subtypes determined by receptor status
  + hormone receptor (HR)-positive (that is, estrogen receptor [ER]-positive and/or progesterone receptor [PR]-positive), and human epidermal growth factor receptor 2 [HER2]-negative
  + HER2-positive and HR-negative (both ER-negative and PR-negative)
  + triple-negative (ER-negative, PR-negative, and HER2-negative)
  + triple-positive (ER-positive, PR-positive, and HER2-positive)
  + Reference - [mnh21965335pcxh67241334pmdc21965335pJ Clin Invest 2011 Oct;121(10):3789](http://pubmed.ncbi.nlm.nih.gov/21965335?dopt=Abstract) [full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3195465/)
* currently defined intrinsic molecular subtypes of breast cancer determined by gene expression profiles include
  + luminal A
    - reportedly 28%-31% prevalence
    - mostly ER positive and HER2 negative
    - proliferation status generally low and thus lower risk of recurrence
    - generally chemoresistant but endocrine sensitive
  + luminal B
    - reportedly 19%-23% prevalence
    - mostly ER positive and HER2 negative, although about 20% may be HER2 positive
    - proliferation status generally high and thus higher risk of recurrence
    - may benefit more from chemotherapy than luminal A subtype but less endocrine sensitive
  + HER2 enriched (also called HER2 positive)
    - reportedly 12%-21% prevalence
    - about 51% ER negative and HER2 positive and 15% ER positive and HER2 positive
    - about 16% are ER positive and HER2 negative and 18% are triple-negative by gene expression, but are considered HER2 enriched based on immunohistochemical (IHC) staining
  + basal-like
    - reportedly 11%-23% prevalence
    - mostly triple-negative tumors, but 11%-19% may be ER positive and 9%-13% may be HER2 positive
  + claudin-low
    - reportedly about 7%-14% prevalence
    - mostly high-grade and triple-negative tumors, although about 12%-33% are reportedly ER positive
  + normal breast-like, reportedly 3%-10% prevalence
  + Reference - [21147047Mol Oncol 2011 Feb;5(1):5](http://pubmed.ncbi.nlm.nih.gov/21147047?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5528267/)
* surrogate subtypes based on HER2 and HR status (determined by IHC testing) as well as proliferation measures commonly used due to accessibility of this information compared to gene expression profiles required for intrinsic subtyping

| Table 6: Surrogate Subtypes Based on HER2 and HR Status | | | | |
| --- | --- | --- | --- | --- |
| **Surrogate Intrinsic Subtype** | **HR Status** | **HER2 Status** | **Ki67 Status** | **Molecular Signature** |
| Luminal A-like | * + ER positive   + PR positive (high) | Negative | Low | Low-risk |
| Luminal B-like (HER2 negative) | * + ER positive   + PR positive (low)\* | Negative | High\* | High-risk |
| Luminal B-like (HER2 positive) | * + ER positive   + PR positive or negative | Positive | High or low | NA |
| HER2 enriched | * + ER negative   + PR negative | Positive | NA | NA |
| Basal-like | * + ER negative   + PR negative | Negative | NA | NA |
| Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NA, not available; PR, progesterone receptor.\* Either PR positive (low) or Ki67 high.  Reference - [26314782Ann Oncol 2015 Sep;26 Suppl 5:v8](http://pubmed.ncbi.nlm.nih.gov/26314782?dopt=Abstract). | | | | |

* **tumor subtype associated with site of metastatic spread**

Cohort Study[Am J Clin Pathol 2015 Apr;143(4):471](http://pubmed.ncbi.nlm.nih.gov/25779997/)

studySummary

* + Cohort Study based on retrospective cohort study
  + 531 patients with breast cancer metastases (either at diagnosis or subsequently) who received systemic therapy between 1997 and 2010 were evaluated
  + 390 patients (73%) had solitary metastases and 141 patients (27%) had multiple metastases; common sites of metastases included
    - bone in 48%
    - liver in 27%
    - lung in 23%
    - central nervous system (CNS) in 17%
    - pleura in 7%
  + surrogate subtypes defined as
    - luminal if ER-positive and/or PR-positive; luminal A if HER2-negative in addition, luminal B if HER2-positive in addition
    - HER2 if ER-negative, PR-negative and HER2-positive
    - triple negative if ER-negative, PR-negative and HER2-negative
  + tumor subtype associated with decreased risk of CNS metastases
    - luminal A subtype
      * compared to HER2 subtype (OR 0.36, 95% CI 0.13-0.99)
      * compared to triple negative subtype (OR 0.36, 95% CI 0.14-0.98)
    - luminal B subtype
      * compared to HER2 subtype (OR 0.48, 95% CI 0.22-1.01)
      * compared to triple negative subtype (OR 0.48, 95% CI 0.23-0.99)
  + PubMed25779997American journal of clinical pathologyAm J Clin Pathol201504011434471-8471Reference - [Am J Clin Pathol 2015 Apr;143(4):471](http://pubmed.ncbi.nlm.nih.gov/25779997/)

Hormone Receptor Testing and Prediction of Therapeutic Response

* PubMed31928404Journal of clinical oncology : official journal of the American Society of Clinical OncologyJ Clin Oncol2020042038121346-13661346tumor estrogen receptor (ER) predicts potential benefit from endocrine therapy; tumor progesterone receptor (PR) is primarily prognostic
  + positive ER test (≥1%) predicts benefit from endocrine therapy; data is limited in patients with low positive ER (1-10%)
  + negative ER test (<1%) predicts no benefit from endocrine therapy
  + Reference - [J Clin Oncol 2020 Apr 20;38(12):1346](http://pubmed.ncbi.nlm.nih.gov/31928404)
* hormone receptor (HR) status for estrogen and progesterone receptors is usually performed by immunohistochemical (IHC) staining[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF6778)
* Oncologic\_DiseaseAmerican Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) recommendations for IHC testing of estrogen and progesterone receptors in breast cancer (J Clin Oncol 2020 Apr 20)06/12/2020 11:50:38 AMAmerican Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) recommendations for IHC testing of estrogen and progesterone receptors in breast cancer
  + estrogen receptor (ER) and progesterone receptor (PR) testing indicated for all invasive breast cancers and breast cancer recurrences
  + validated immunohistochemical (IHC) is the only recommended test for evaluating benefit from endocrine therapy ([ASCO/CAP Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))
  + optimal HR testing
    - perform on large core biopsies (multiple if possible) if they are representative of tumor (grade and type) at resection ([ASCO/CAP Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))
    - specimen handling ([ASCO/CAP Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))
      * place tissue obtained from biopsy or resection in 10% neutral buffered formalin as soon as possible for 6-72 hours of fixation
      * record time specimen removed, type of fixative, time placed in fixative, and length of time in fixative
      * do not use unstained slides cut > 6 weeks earlier
    - definitions of ER and PR testing results ([ASCO/CAP Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))
      * positive defined as ≥ 1% of tumor cell nuclei are immunoreactive; for estrogen receptor, report 1% - 10% as low positive (limited data on benefit in patients with low positive ER)
      * negative defined as < 1% of tumor cell nuclei are immunoreactive
      * uninterpretable defined as any of
        + inadequate sample (severe artifact or insufficient number cancer cells)
        + internal or external controls without appropriate staining
        + preanalytic variables (such as [specimen handling](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#TOPIC_WVC_NSP_XLB__LI_LMK_ZV5_BLB1)) interfered with accuracy
    - external controls should include negative, positive and low positive controls
    - report internal controls for cases with 0% - 10% staining, if no internal controls comment on positive external control ([ASCO/CAP Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))
    - laboratory must provide documentation of ([ASCO/CAP Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))
      * initial validation of positive and negative ER or PR categories and concordance (90% for positive, and 95% for negative ER/PR) with clinically validated assays
      * ongoing internal quality assurance procedures
      * participation in external proficiency testing
      * accreditation through a valid accrediting agency every 2 years
  + PubMed31928404Journal of clinical oncology : official journal of the American Society of Clinical OncologyJ Clin Oncol20200113JCO1902309JCO1902309Reference - [J Clin Oncol 2020 Apr 20;38(12):1346](http://pubmed.ncbi.nlm.nih.gov/31928404)
* **HR receptor status conversion between primary tumor and distant metastases may be common in patients with metastatic breast cancer**

Systematic Review[J Natl Cancer Inst 2018 Jun 1;110(6):568](http://pubmed.ncbi.nlm.nih.gov/29315431/)

studySummary

* + Systematic Review based on systematic review of observational studies
  + systematic review of 39 observational studies with data to assess discordance of HER2, estrogen receptor (ER) alpha, and progesterone receptor (PR) status between primary breast tumors to paired distant breast cancer metastases, excluding regional lymph nodes
    - mean time between primary tumor and matched distant metastasis was 51 months in analysis of 28 studies
    - 86.2% of tumors were of ductal type in 14 studies
  + pooled incidence of ER alpha conversion
    - 19.3% (95% CI 15.8%-23.4%) overall in analysis of 27 studies with 1,948 patients
    - 22.5% (95% CI 16.4%-30%) from positive to negative in analysis of 20 studies with 1,101 patients
    - 21.5% (95% CI 18.1%-25.5%) from negative to positive in analysis of 20 studies 514 patients
  + pooled incidence of PR conversion
    - 30.9% (95% CI 26.6%- 35.6%) overall in analysis of 24 studies with 1,730 patients
    - 49.4% (95% CI 40.5%- 58.2%) from positive to negative in analysis of 18 studies with 827 patients
    - 15.9% (95% CI 11.3%- 22%) from negative to positive in analysis of 18 studies with 630 patients
  + PubMed29315431Journal of the National Cancer InstituteJ Natl Cancer Inst201806011106568-580568Reference - [J Natl Cancer Inst 2018 Jun 1;110(6):568](http://pubmed.ncbi.nlm.nih.gov/29315431/)

HER2 Testing and Prediction of Therapeutic Response

* *HER2* (also called *ERBB2*) gene reported to have amplified expression in 15%-20% of primary breast cancers ([J Clin Oncol 2013 Nov 1;31(31):3997](http://pubmed.ncbi.nlm.nih.gov/24101045?dopt=Abstract))
* PubMed29846122Journal of clinical oncology : official journal of the American Society of Clinical OncologyJ Clin Oncol2018071036202105-21222105HER2 predicts for potential benefit from HER2 targeted therapies ([J Clin Oncol 2018 Jul 10;36(20):2105](http://pubmed.ncbi.nlm.nih.gov/29846122))
* American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) recommendations for HER2 testing in breast cancer
  + HER2 testing recommended for every newly diagnosed invasive breast cancer to guide decisions about pursuing HER2 targeted therapy ([ASCO/CAP Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))
  + HER2 testing of metastatic site also recommended if metastatic recurrence occurs and tissue sample available ([ASCO/CAP Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))
  + optimal HER2 testing ([ASCO/CAP Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))
    - performed with FDA-approved immunohistochemistry (IHC) or in situ hybridization (ISH); list of cleared or approved companion diagnostic devices for use of anti-HER2 targeted therapy with trastuzumab can be found at [United States FDA](https://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm301431.htm)
    - laboratories accredited by CAP or other accrediting entity may use laboratory developed tests, but must document and make available the analytical performance and validity of its assay
  + IHC
    - positive test defined as IHC 3+ and based on complete, intense circumferential membrane staining in > 10% of tumor cells ([ASCO/CAP Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))
    - equivocal test defined as IHC 2+ and based on weak/moderate complete membrane staining in > 10% of tumor cells ([ASCO/CAP Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE)); in case of IHC 2+ result, perform ISH using same specimen or retest with new specimen using either IHC or ISH ([ASCO/CAP Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))
    - negative test defined as either ([ASCO/CAP Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))
      * IHC 1+ and based on incomplete, faint membrane staining within > 10% of tumor cells
      * IHC 0 and based on either no staining, or incomplete, faint membrane staining in ≤ 10% of tumor cells
  + ISH
    - dual probe assay preferred over single probe assay
    - pathologist should scan entire ISH slide prior to counting ≥ 20 cells or use IHC to define areas of potential HER2 amplification ([ASCO/CAP Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))
      * if second population of HER2 amplified cells and cell population > 10% of tumor cells on the slide, must perform and report on a separate counting of ≥ 20 nonoverlapping cells
      * if brightfield ISH used, comparison between pattern in tumor cells and normal breast should be performed when counting to avoid counting artifactual patterns
    - positive test defined as ([ASCO/CAP Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))
      * in single probe assay, average HER2 copy number ≥ 6 signals/cell
      * in dual probe assay, HER2/CEP17 ratio ≥ 2 and average HER2 copy number ≥ 4 signals/cell
    - negative test defined as ([ASCO/CAP Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))
      * in single probe assay, average HER2 copy number < 4 signals/cell
      * in dual probe assay, HER2/CEP17 ratio < 2 and average HER2 copy number < 4 signals/cell
    - equivocal test requiring further testing including IHC (if not already assessed) using same tissue sample from ISH, and view both ISH and IHC concomitantly
      * in single probe assay, average HER2 copy number ≥ 4 but < 6 signals/cell ([ASCO/CAP Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))
        + test positive if either or both

concurrent IHC 3+

concurrent dual-probe ISH is HER2/CEP17 ratio ≥ 2 and average HER2 copy number ≥ 4 signals/cell

* + - * + test negative if either or both

concurrent IHC 0 or 1+

concurrent dual-probe ISH is HER2/CEP17 ratio < 2 and average HER2 copy number < 4 signals/cell

* + - * + perform dual probe assay for final result if IHC 2+
      * in dual probe assay
        + if HER2/CEP17 ratio ≥ 2 and average HER2 copy number < 4 signals/cell ([ASCO/CAP Strong recommendation, Intermediate-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))

test positive if IHC 3+

test negative if IHC 0 or 1+ and include comment "evidence is currently limited on efficacy of HER2 targeted therapy in patients with HER2/CEP17 ratio of ≥ 2.0 and average HER2 copy number < 4.0 signals/cell"

perform recount of ≥ 20 cells by observer blinded to previous results if IHC 2+

test negative if recount remains HER2/CEP17 ratio ≥ 2 and average HER2 copy number < 4 signals/cell and include comment "evidence is currently limited on efficacy of HER2 targeted therapy in patients with HER2/CEP17 ratio of ≥ 2.0 and average HER2 copy number < 4.0 signals/cell"

adjudicate result through internal procedure if recount changes ISH category

* + - * + if HER2/CEP17 ratio < 2 and average HER2 copy number ≥ 6 signals/cell ([ASCO/CAP Strong recommendation, Intermediate-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))

test positive if IHC 3+

test negative if IHC 0 or 1+ and include comment "insufficient evidence on efficacy of HER2 targeted therapy in patients with HER2/CEP17 ratio of < 2.0 in absence of protein overexpression"

perform recount of ≥ 20 cells by observer blinded to previous results if IHC 2+

test positive if recount remains HER2/CEP17 ratio is < 2 and average HER2 copy number ≥ 6 signals/cell

adjudicate result through internal procedure if recount changes ISH category

* + - * + if HER2/CEP17 ratio < 2 and average HER2 copy number ≥ 4 but < 6 signals/cell ([ASCO/CAP Strong recommendation, Intermediate-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))

test positive if IHC 3+

test negative if IHC 0 or 1+ and include comment "evidence is currently limited on efficacy of HER2 targeted therapy in patients with HER2/CEP17 ratio of < 2.0 and average HER2 copy number ≥ 4.0 but < 6 signals/cell in absence of protein overexpression (IHC 3+)"

perform recount of ≥ 20 cells by observer blinded to previous results if IHC 2+

test negative if recount remains HER2/CEP17 ratio < 2 and average HER2 copy number ≥ 4 but < 6 signals/cell and include comment "evidence is limited on efficacy of HER2 targeted therapy in patients with HER2/CEP17 ratio of < 2.0 and average HER2 copy number ≥ 4.0 but < 6 signals/cell in absence of protein overexpression (IHC 3+)"

adjudicate result through internal procedure if recount changes ISH category

* + for both IHC and ISH, technical issues prevent a report of positive, negative, or equivocal, such as
    - for IHC ([ASCO/CAP Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))
      * controls not as expected
      * artifacts (crush or edge artifacts) make interpretation difficult
      * normal breast ductal cells have strong membrane straining (internal control)
    - for ISH ([ASCO/CAP Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))
      * controls not as expected
      * observer cannot find and count ≥ 2 areas of invasive tumor
      * > 25% of signals are unscorable due to weak signal
      * > 10% of signals occur over cytoplasm
      * poor nuclear resolution
      * strong autofluorescence
  + repeat HER2 testing based on possible discordance
    - if initial core needle biopsy is negative for HER2, may order new HER2 testing on excision specimen if any of the following are true ([ASCO/CAP Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))
      * tumor grade 3
      * only small amount of invasive tumor in core biopsy specimen
      * resection specimen contains high-grade carcinoma that is morphologically distinct from core biopsy specimen
      * ISH and IHC testing of core biopsy specimen are both equivocal for HER2
      * potential handling error of core biopsy specimen may have occurred or pathologist believes testing error resulted in negative result
    - for histologic grade 1 carcinoma if initial HER2 test was positive and meets any of the following criteria, new HER2 testing should be ordered; if initial HER2 test was negative, new HER2 testing should not be ordered
      * infiltrating ductal or lobular carcinoma that is estrogen receptor positive and progesterone receptor positive
      * at least 90% pure tubular, mucinous, or cribriform histology
      * at least 90% pure adenoid cystic carcinoma and often triple negative
  + Reference - [J Clin Oncol 2018 Jul 10;36(20):2105](http://pubmed.ncbi.nlm.nih.gov/29846122?dopt=Abstract)
* National Comprehensive Cancer Network (NCCN) endorses the ASCO/CAP recommendations for HER2 testing in breast cancer ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF6778)
* **HER2 receptor status conversion between primary tumor and distant metastases may be common in patients with metastatic breast cancer**

Systematic Review[J Natl Cancer Inst 2018 Jun 1;110(6):568](http://pubmed.ncbi.nlm.nih.gov/29315431/)

studySummary

* + Systematic Review based on systematic review of observational studies
  + systematic review of 39 observational studies with data to assess discordance of HER2, estrogen receptor (ER) alpha, and progesterone receptor (PR) status between primary breast tumors to paired distant breast cancer metastases, excluding regional lymph nodes
    - mean time between primary tumor and matched distant metastasis was 51 months in analysis of 28 studies
    - 86.2% of tumors were of ductal type in 14 studies
  + pooled incidence of HER2 conversion
    - 10.3% (95% CI 7.8%- 13.6%) overall in analysis of 35 studies with 2,440 patients
    - 21.3% (95% CI 14.3%-30.5%) from positive to negative in analysis of 29 studies with 563 patients
    - 9.5% (95% CI 7.4%-12.1%) from negative to positive in analysis of 29 studies with 1,486 patients
  + PubMed29315431Journal of the National Cancer InstituteJ Natl Cancer Inst201806011106568-580568Reference - [J Natl Cancer Inst 2018 Jun 1;110(6):568](http://pubmed.ncbi.nlm.nih.gov/29315431/)

Prognostic Assessment and Predictive Factors for Treatment Decision-making

Gene expression profiles and biomarker testing

* multigene expression assays (for instance, MammaPrint, Oncotype DX, Prosigna, and EndoPredict) validated for prognosis, may help to predict benefit from adjuvant chemotherapy for patients at intermediate risk (N0-N1 disease) with luminal tumors but Oncotype DX is the only one validated to predict response to chemotherapy ([ESMO Grade A, Level IV](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))[1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF5142),[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF6778),[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__ANC_1607337114)
* American Society of Clinical Oncology (ASCO) clinical practice guideline for use of biomarkers to guide decisions on adjuvant systemic therapy for women with early stage invasive breast cancer
  + biomarker assays to determine benefit of adjuvant systemic treatment by hormone receptor (HR), human epidermal growth factor receptor 2 (HER2), and nodal status
    - Oncotype DX (21-gene recurrence score)
      * high recurrence score may identify patients with the greatest gain in survival with addition of adjuvant chemotherapy
      * low recurrence score may identify patients with little gain in survival with addition of adjuvant chemotherapy
      * should be used for women with HR-positive/HER2-negative and lymph node-negative breast cancer ([ASCO Evidenced-based, Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
      * should not be used for women with
        + HR-positive/HER2-negative and lymph node-positive breast cancer ([ASCO Evidenced-based, Moderate recommendation, Intermediate-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE)); 21-gene recurrence score may be prognostic and predictive in patients with positive lymph nodes, however patients with positive lymph nodes have higher recurrence than those with negative lymph nodes and similar scores; this difference may alter the recurrence score at which benefit of addition of chemotherapy may outweigh harm

This recommendation is controversial as the National Comprehensive Cancer Network (NCCN) recommends considering the 21-gene recurrence score in select patients with HR-positive/HER2-negative breast cancer and 1-3 positive lymph nodes.

* + - * + HER2-positive or triple-negative breast cancer ([ASCO Informal consensus, Strong recommendation, Insufficient evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
    - EndoPredict (12-gene risk score)
      * may be used for women with HR-positive/HER2-negative and lymph node-negative breast cancer ([ASCO Evidenced-based, Moderate recommendation, Intermediate-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
      * should not be used for women with
        + HR-positive/HER2-negative and lymph node-positive breast cancer ([ASCO Evidenced-based, Moderate recommendation, Insufficient evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
        + HER2-positive or triple-negative breast cancer ([ASCO Informal consensus, Strong recommendation, Insufficient evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
    - MammaPrint (70-gene assay)
      * low score in women with high clinical risk (per MINDACT categorization) may identify a group with good prognosis leaving little potential chemotherapy benefit
      * may be used for women with
        + HR-positive/HER2-negative, lymph node-negative breast cancer and high clinical risk per MINDACT categorization ([ASCO Evidenced-based, Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
        + HR-positive/HER2-negative, 1-3 lymph node-positive breast cancer and high clinical risk per MINDACT categorization ([ASCO Evidenced-based, Moderate recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
      * should not be used for women with
        + HR-positive/HER2-negative, lymph node-negative and low clinical risk per MINDACT categorization ([ASCO Evidenced-based, Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
        + HR-positive/HER2-negative, 1-3 lymph node-positive and low clinical risk per MINDACT categorization ([ASCO Informal consensus, Moderate recommendation, Low-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
        + HER2-positive ([ASCO Informal consensus, Moderate recommendation, Low-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
        + HR-negative/HER2-negative (triple-negative) breast cancer ([ASCO Informal consensus, Strong recommendation, Insufficient evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
    - PAM50 risk of recurrence score
      * high score may identify patients appropriate to receive adjuvant systemic therapy and low score selects patients for whom systemic therapy may not be indicated
      * should be used in combination with additional clinical indicators in women with HR-positive/HER2-negative and lymph node-negative breast cancer ([ASCO Evidenced-based, Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
      * should not be used for women with
        + HR-positive/HER2-negative and lymph node-positive breast cancer ([ASCO Evidenced-based, Moderate recommendation, Intermediate-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
        + HER2-positive or triple-negative breast cancer ([ASCO Informal consensus, Strong recommendation, Insufficient evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
    - Breast Cancer Index
      * may identify patients with good response to 5-10 years of endocrine therapy alone
      * may be used for women with HR-positive/HER2-negative and lymph node-negative breast cancer ([ASCO Evidenced-based, Moderate recommendation, Intermediate-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
      * should not be used for women with
        + HR-positive/HER2-negative and lymph node-positive breast cancer ([ASCO Informal consensus, Strong recommendation, Insufficient evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
        + HER2-positive or triple-negative breast cancer ([ASCO Informal consensus, Strong recommendation, Insufficient evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
    - Mammostrat (5-protein assay) should not be used for women with
      * HR-positive/HER2-negative and lymph node-negative or node-positive breast cancer ([ASCO Evidenced-based, Moderate recommendation, Intermediate-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
      * HER2-positive or triple-negative breast cancer ([ASCO Informal consensus, Strong recommendation, Insufficient evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
    - Immunohistochemistry (IHC) 4 should not be used for women with
      * HR-positive/HER2-negative and lymph node-negative or node-positive breast cancer ([ASCO Evidenced-based, Moderate recommendation, Intermediate-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
      * HER2-positive or triple-negative breast cancer ([ASCO Informal consensus, Strong recommendation, Insufficient evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
    - urokinase plasminogen activator (uPA) and plasminogen activator inhibitor type 1 (PAI-1)
      * not generally useful in treatment setting
      * might be used for women with HR-positive/HER2-negative and lymph node-negative breast cancer ([ASCO Evidenced-based, Weak recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
      * might not be used for women with HER2-positive or triple-negative breast cancer ([ASCO Informal consensus, Weak recommendation, Insufficient evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
    - circulating tumor cells should not be used ([ASCO Evidenced-based, Strong recommendation, Intermediate-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
    - tumor infiltrating lymphocytes should not be used for women with
      * HR-positive/HER2-negative and lymph node-negative or node-positive breast cancer ([ASCO Informal consensus, Strong recommendation, Insufficient evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
      * HER2-positive or triple-negative breast cancer ([ASCO Evidenced-based, Strong recommendation, Intermediate-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
    - Ki-67 labeling index by IHC should not be used ([ASCO Evidenced-based, Moderate recommendation, Intermediate-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
  + genetic expression profiles and biomarkers not recommended to determine specific systemic treatment
    - protein Tau mRNA expression or mRNA expression by IHC should not be used to determine usefulness of adjuvant paclitaxel ([ASCO Evidenced-based, Moderate recommendation, Intermediate-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
    - HER1/epidermal growth factor receptor (EGFR) expression by IHC should not be used to determine usefulness of adjuvant paclitaxel ([ASCO Evidenced-based, Moderate recommendation, Low-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
    - *TOP2A* gene amplification and TOP2A protein expression by IHC should not be used to determine usefulness of adjuvant anthracycline-based chemotherapy ([ASCO Evidenced-based, Moderate recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
    - *HER2* and *TOP2A* coamplification, CEP17 duplication, TIMP-1, FOXP3, or p53 protein overexpression should not be used to determine usefulness of adjuvant anthracycline-based chemotherapy ([ASCO Evidenced-based, Moderate recommendation, Intermediate-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
  + disease stage, comorbidities, and patient preferences should be considered when making treatment decisions
  + Reference - [cxh114122701pmdc26858339pJ Clin Oncol 2016 Apr 1;34(10):1134](http://pubmed.ncbi.nlm.nih.gov/26858339?dopt=Abstract) [full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4933134/), update on the use of MammaPrint can be found in [cxh124647933pmdc28692382pJ Clin Oncol 2017 Aug 20;35(24):2838](http://pubmed.ncbi.nlm.nih.gov/28692382?dopt=Abstract) [full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5846188/)
* National Comprehensive Cancer Network (NCCN) guideline for use of germline testing and biomarkers to guide decisions on targeted therapy
  + hormone receptor ([HR], estrogen receptor [ER] and progesterone [PR]) expression ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - predicts benefit from endocrine therapy
    - testing should be done in all women with newly diagnosed primary or metastatic disease
    - testing performed with immunohistochemistry (IHC) on tumor tissue
    - see [Endocrine Therapy for Early and Locally Advanced Breast Cancer](https://dpa-pde-oxford.shinyapps.io/management/endocrine-therapy-for-early-and-locally-advanced-breast-cancer) and [Management of Hormone Receptor (HR) Positive, HER2 Negative Metastatic Breast Cancer](https://dpa-pde-oxford.shinyapps.io/management/management-of-hormone-receptor-hr-positive-her2-negative-metastatic-breast-cancer) for additional information
  + HER2 overexpression ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - predicts benefit from HER2-targeted therapy
    - testing should be done in all women with newly diagnosed primary or metastatic disease
    - testing performed with either IHC or in situ hybridization (ISH) on tumor tissue
    - see [HER2 Targeted Therapy for Early and Locally Advanced Breast Cancer](https://dpa-pde-oxford.shinyapps.io/management/her2-targeted-therapy-for-early-and-locally-advanced-breast-cancer) and [Management of HER2 Positive Metastatic Breast Cancer](https://dpa-pde-oxford.shinyapps.io/management/management-of-her2-positive-metastatic-breast-cancer) for additional information
  + *BRCA1* and *BRCA2* mutation ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - predicts benefit from poly adenosine diphosphate ribose polymerase (PARP) inhibitor therapies (such as olaparib or talazoparib)
    - testing may be considered with any disease subtype (although FDA approved only for HER2 negative breast cancer)
    - testing performed with germline sequencing
  + *PIK3CA* mutation ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - predicts benefit from therapy with alpelisib pus fulvestrant
    - testing should be done in patients with HR-positive/HER2-negative disease
    - testing can be performed with either
      * polymerase chain reaction (PCR)
        + samples can be from tumor tissues or circulating tumor DNA from peripheral blood (liquid biopsy)
        + if liquid biopsy testing is negative, testing on tumor tissues recommended
      * molecular panel
  + PD-L1 expression ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - predicts benefit from therapy with atezolizumab plus albumin-bound paclitaxel
    - testing should be done in women with HR-negative/HER2-negative disease
    - testing performed with IHC of tumor-infiltrating immune cells (≥ 1% expression considered positive)
  + *NTRK* fusion mutation ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - predicts benefit from larotrectinib or entrectinib therapies
    - testing should be done in women with any disease subtype
    - testing performed with fluorescence in situ hybridization (FISH), next-generation sequencing, or PCR on tumor tissues
  + microsatellite instability-high (MSI-H)/mismatch repair deficiency (dMMR) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - predicts benefit from pembrolizumab therapy
    - testing should be done in women with any disease subtype
    - testing performed with IHC, or PCR on tumor tissues
  + Reference - Breast Cancer, Version 4.2020 in NCCN Clinical Practice Guideline in Oncology 2020 May 8 from [NCCN website](http://www.nccn.org/professionals/physician_gls) (free registration required)

Prognostic and predictive models

* models available online which may assist in estimating absolute benefits expected from systemic adjuvant endocrine therapy and chemotherapy to aid in shared decision-making about benefits and harms of systemic therapy[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__GENREF6778),[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-A822BD1F-B064-4D7C-B580-8B3453CE36BB__ANC_1607337114)
  + [PREDICT](http://www.predict.nhs.uk/predict.html) Tool
  + [Nottingham Prognostic Index](http://www.pmidcalc.org/?sid=3689666&newtest=Y)
* **insufficient evidence to evaluate prediction models for identifying women with early stage breast cancer who may not benefit from adjuvant therapy**

Systematic Review[cxh93618499pmdc24344212pJ Clin Oncol 2014 Jan 20;32(3):238](http://pubmed.ncbi.nlm.nih.gov/24344212?dopt=Abstract)

studySummary

* + based on systematic review of prognostic studies limited by clinical heterogeneity Systematic Review
  + systematic review of 47 prognostic studies evaluating models for estimating risk of recurrence or death in women with early stage breast cancer
  + 27 validation studies of most common risk prediction models
    - Nottingham Prediction Index (8 studies) and Adjuvant! (6 studies) based on clinical prognosticators
    - MammaPrint (8 studies) and Oncotype DX (5 studies) based on biomolecular features
  + most women received systemic treatments following assessment, but treatments varied and not all women were hospitalized
  + prediction models reported to be less accurate in women < 50 or > 75 years old and in Asian women
  + PubMed24344212Journal of clinical oncology : official journal of the American Society of Clinical Oncology20140120J Clin Oncol323238238 Reference - [cxh93618499pmdc24344212pJ Clin Oncol 2014 Jan 20;32(3):238](http://pubmed.ncbi.nlm.nih.gov/24344212?dopt=Abstract)
* PROGNOSTIC\_AND\_PREDICTIVE\_MODELS\_\_LI\_ZR4\_NNH\_3TBEU04252204/25/2022 06:55:04 AMevidenceUpdatelowplusOncologic\_DiseaseRSClin tool that adds tumor grade, tumor size, and age to Oncotype DX 21-gene recurrence score stratifies risk of distant recurrence in adults with hormone receptor positive, human epidermal growth factor receptor 2 negative, lymph node negative breast cancer in patients receiving endocrine therapy with or without chemotherapy (J Clin Oncol 2021 Feb 20)

**RSClin tool that adds tumor grade, tumor size, and age to Oncotype DX 21-gene recurrence score stratifies risk of distant recurrence in adults with hormone receptor positive, human epidermal growth factor receptor 2 negative, lymph node negative breast cancer in patients receiving endocrine therapy with or without chemotherapy (**[**level 1 [likely reliable] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Prediction Rule[J Clin Oncol 2021 Feb 20;39(6):557](https://pubmed.ncbi.nlm.nih.gov/33306425)[Full Text](https://ascopubs.org/doi/10.1200/JCO.20.03007?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed)

studySummary

* + Prediction Rulebased on prognostic cohort study with independent derivation and validation cohorts
  + derivation cohort included 10,004 adults with hormone receptor positive, HER2 negative, lymph node negative breast cancer who had endocrine therapy alone in TAILORx (median age 56 years) or NSABP B-14 (median age 59 years) trials or endocrine therapy plus chemotherapy in TAILORx trial (median age 56 years)
  + 4.5% in derivation cohort developed distant recurrence
  + RSClin developed using factors significantly associated with distant recurrence in derivation cohort
    - Oncotype DX 21-gene recurrence score (0-100)
    - histologic tumor grade
    - tumor size
    - patient age at surgery
  + validation cohort included 1,098 adults (median age 59 years) with lymph node negative disease who had endocrine therapy alone (80%) or endocrine therapy plus chemotherapy (20%) from Clalit Health Registry
  + 5.3% in validation cohort developed distant recurrence
  + data from 550 adults who had chemotherapy in NSABP B-20 trial (median age 51 years) were included to adjust for effect of chemotherapy in patients from TAILORx trial who had endocrine therapy plus chemotherapy
  + 10-year risk of distant recurrence in validation cohort by RSClin (estimated from figure)
    - 3% of patients in first quintile
    - 4% of patients in second quintile
    - 5% of patients in third quintile
    - 7% of patients in fourth quintile
    - 14% of patients in fifth quintile
  + estimated absolute benefit of chemotherapy in derivation cohort for 55 year old patient with 21-gene recurrence score 11-50
    - 0%-15% with 1.5 cm intermediate-grade tumor
    - 1%-33% with 2.5 cm poor-grade tumor
  + online calculator to estimate 10-year risk of distant recurrence and absolute benefit of chemotherapy can be found at [Oncotype IQ Physician Portal](https://online.genomichealth.com/)
  + PubMed33306425Journal of clinical oncology : official journal of the American Society of Clinical OncologyJ Clin Oncol20210220396557-564557Reference - [J Clin Oncol 2021 Feb 20;39(6):557](https://pubmed.ncbi.nlm.nih.gov/33306425)[full-text](https://ascopubs.org/doi/10.1200/JCO.20.03007?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed), editorial can be found in [J Clin Oncol 2021 Feb 20;39(6):545](https://pubmed.ncbi.nlm.nih.gov/33306424)[full-text](https://ascopubs.org/doi/10.1200/JCO.20.03234?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed), comments can be found in [J Clin Oncol 2021 Jun 10;39(17):1946](https://pubmed.ncbi.nlm.nih.gov/33793293)[full-text](https://ascopubs.org/doi/10.1200/JCO.21.00178?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed) and [J Clin Oncol 2021 Jun 10;39(17):1947](https://pubmed.ncbi.nlm.nih.gov/33793318)[full-text](https://ascopubs.org/doi/10.1200/JCO.21.00424?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed)

Other Diagnostic Testing

Triple Test Score

* In higher resource areas with access to modern mammography, ultrasound, and core needle biopsy devices, the triple test score largely has been replaced by algorithms.
* triple test score is combination of physical examination, imaging, and tissue sampling developed to help physicians interpret discordant results on the individual components of the 3 tests ([15887452Am Fam Physician 2005 May 1;71(9):1731](http://pubmed.ncbi.nlm.nih.gov/15887452?dopt=Abstract)[full-text](http://www.aafp.org/afp/2005/0501/p1731.html))
* original description of triple test score
  + individual scores (range 1-3 points) given for each result of physical examination, mammography, and fine needle aspiration, based on following
    - 1 point = benign
    - 2 points = suspicious
    - 3 points = malignant
  + individual scores combined for final triple test score (range 3-9 points), with interpretation of total score as follows
    - 3 or 4 points = benign mass
    - 5 points = excisional biopsy recommended for definitive diagnosis
    - ≥ 6 points = malignancy, definitive therapy recommended
  + performance of triple test score in original description (derivation cohort with 259 patients with 261 palpable breast masses 1991-1997)
    - score 3-4 in 152 masses (58%) - 100% were benign
    - score 5 in 21 masses (8%) - 38% were malignant
    - score 6-9 in 88 masses (34%) - 100% were malignant
  + Reference - [9749842Arch Surg 1998 Sep;133(9):930](http://pubmed.ncbi.nlm.nih.gov/9749842?dopt=Abstract)
* **triple test score validated to be accurate for diagnosing breast cancer if score ≥ 6 and rule out breast cancer if score 3-4 (**[**level 1 [likely reliable] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cohort Study[Arch Surg 2001 Sep;136(9):1008](http://pubmed.ncbi.nlm.nih.gov/11529822-usefulness-of-the-triple-test-score-for-palpable-breast-masses-discussion-1012-3/?dopt=Abstract)[Full Text](http://archsurg.jamanetwork.com/article.aspx?articleid=392091)Cohort Study[Ann Saudi Med 2003 May;23(3-4):158](http://pubmed.ncbi.nlm.nih.gov/16985306-accuracy-of-the-triple-test-in-the-diagnosis-of-palpable-breast-masses-in-saudi-females/?dopt=Abstract)Cohort Study[JNMA J Nepal Med Assoc 2008 Oct;47(172):189](http://pubmed.ncbi.nlm.nih.gov/19079392-accuracy-of-triple-test-score-in-the-diagnosis-of-palpable-breast-lump/?dopt=Abstract)

studySummary

* + Cohort StudyCohort StudyCohort Study based on 3 diagnostic cohort studies
  + diagnostic cohort of 479 women > 40 years old with 484 palpable breast masses in Oregon, United States 1991-2000
    - triple test evaluated was physical examination, mammogram, and fine needle aspiration
    - 149 cases confirmed malignant by biopsy with histology (reference standard)

| Diagnostic Performance of Triple Test Elements | | |
| --- | --- | --- |
|  | **Sensitivity** | **Specificity** |
| Physical examination | 87% | 80% |
| Mammography | 91% | 78% |
| Fine needle aspiration | 92% | 96% |

* + - outcomes based on triple test score
      * 315 masses (65%) had triple test score 3-4 - malignancy in none (specificity 100%)
      * 39 masses (8%) had triple test score 5 - malignancy in 19 masses (49%)
      * 130 masses (27%) had triple test score 6-9 - malignancy in 100% (sensitivity 100%)
    - PubMed11529822Archives of surgery (Chicago, Ill. : 1960)Arch Surg2001090113691008-121008Reference - [Arch Surg 2001 Sep;136(9):1008](http://pubmed.ncbi.nlm.nih.gov/11529822-usefulness-of-the-triple-test-score-for-palpable-breast-masses-discussion-1012-3/?dopt=Abstract)[full-text](http://archsurg.jamanetwork.com/article.aspx?articleid=392091)
  + diagnostic cohort of 140 women with palpable breast masses in Saudi Arabia 1998-1999
    - triple test evaluated was physical examination, mammogram, and fine needle aspiration cytology
    - histologic confirmation by open biopsy was reference standard

| Diagnostic Performance of Test Components | | | |
| --- | --- | --- | --- |
|  | **Physical Examination** | **Mammogram** | **Fine Needle Aspiration Cytology** |
| Sensitivity | 82.6% | 87.5% | 91.7% |
| Specificity | 97.3% | 97.3% | 100% |
| Positive predictive value | 86.4% | 87.5% | 100% |
| Negative predictive value | 96.5% | 97.3% | 98.3% |

* + - triple test associated with 100% accuracy when all 3 tests had consistent results (all malignant or all benign)
    - PubMed16985306Annals of Saudi medicineAnn Saudi Med20030501233-4158-61158Reference - [Ann Saudi Med 2003 May;23(3-4):158](http://pubmed.ncbi.nlm.nih.gov/16985306-accuracy-of-the-triple-test-in-the-diagnosis-of-palpable-breast-masses-in-saudi-females/?dopt=Abstract)
  + diagnostic cohort of 50 women with palpable breast lump in Nepal
    - triple test evaluated was physical examination, mammogram, and fine needle aspiration cytology
    - 19 classified as benign - 100% were benign
    - 31 classified as malignant - 30 lumps (97%) were malignant
    - PubMed19079392JNMA; journal of the Nepal Medical AssociationJNMA J Nepal Med Assoc2008100147172189-92189Reference - [JNMA J Nepal Med Assoc 2008 Oct;47(172):189](http://pubmed.ncbi.nlm.nih.gov/19079392-accuracy-of-triple-test-score-in-the-diagnosis-of-palpable-breast-lump/?dopt=Abstract)

Diagnostic Evaluation During Pregnancy or Lactation

Considerations Specific to Diagnostic Evaluation During Pregnancy or Lactation

* considerations for workup and diagnosis during pregnancy or lactation
  + breast cancer diagnosis is often delayed during pregnancy, as neither patient nor physician suspect malignancy (NCCN guidelines on breast cancer, version 3.2021 [NCCN website](https://www.nccn.org/professionals/physician_gls/default.aspx) [free registration required])
  + most palpable masses that are biopsied in pregnant or lactating women are benign (> 80%); benign palpable masses may
    - occur due to enlargement of preexisting benign masses or development of new masses due to pregnancy and lactation (such as lactating adenomas and galactoceles)
    - present with concerning features on imaging, warranting biopsy for confirmation
    - PubMed30392595Journal of the American College of Radiology : JACRJ Am Coll Radiol201811011511SS263-S275S263Reference - [J Am Coll Radiol 2018 Nov;15(11S):S263](http://pubmed.ncbi.nlm.nih.gov/30392595)[PDF](https://acsearch.acr.org/docs/3102382/Narrative/)
  + imaging appearance of pregnancy-associated breast cancer is similar to breast cancer in nonpregnant women, however necrosis may be more common due to increased incidence of triple negative disease; may also have misleading imaging appearance similar to benign mass with relatively circumscribed margins, parallel orientation, and posterior acoustic enhancement ([J Am Coll Radiol 2018 Nov;15(11S):S263](http://pubmed.ncbi.nlm.nih.gov/30392595)[PDF](https://acsearch.acr.org/docs/3102382/Narrative/))
  + PubMed31776799Current treatment options in oncologyCurr Treat Options Oncol2019112720128686human epidermal growth factor 2 (HER2) positive and triple negative disease are reported to be more prevalent in pregnant women compared to nonpregnant women ([Curr Treat Options Oncol 2019 Nov 27;20(12):86](http://pubmed.ncbi.nlm.nih.gov/31776799))
* imaging-specific considerations
  + generally staging is limited in pregnant women unless findings would alter treatment approach
  + radiation risk due to imaging
    - > 50,000 microGy considered the threshold for teratogenic effects related to exposure of ionizing radiation to a fetus
    - for context, typical fetal background exposure during normal development is about 1,000 microGy in women without breast cancer
    - fetal exposure from mammography < 0.03 microGy and shielding decreases further
  + ultrasound
    - ultrasound can help differentiate between solid and cystic lesions and avoids ionizing radiation
    - **ultrasound has excellent sensitivity for detection of malignant breast lesions in women who are pregnant, lactating, or postpartum (**[**level 1 [likely reliable] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Diagnostic Cohort Study[AJR Am J Roentgenol 2011 Mar;196(3):716](http://pubmed.ncbi.nlm.nih.gov/21343518)

studySummary

* + - * Diagnostic Cohort Study based on diagnostic cohort study
      * 126 pregnant, lactating, or postpartum women (mean age 32 years) had diagnostic mammogram and/or breast ultrasound
      * reference standard was biopsy-proven pathologic abnormality or > 12 months of radiographic or clinical follow-up
      * 4 women (3.2%) had malignant lesion based on reference standard (all presenting with a palpable mass)
      * 122 women (97%) had ultrasound
      * diagnostic performance of ultrasound [BI-RADS category 4 or 5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#DIAGNOSTIC_MAMMOGRAPHY) was
        + sensitivity 100%
        + specificity 86%
        + positive predictive value 19%
        + negative predictive value 100%
      * PubMed21343518AJR. American journal of roentgenologyAJR Am J Roentgenol201103011963716-22716Reference - [AJR Am J Roentgenol 2011 Mar;196(3):716](http://pubmed.ncbi.nlm.nih.gov/21343518)
  + mammography
    - if strong suspicion or diagnosis of breast cancer already made, mammography may help evaluate extent of disease, visualize suspicious microcalcifications, and evaluate contralateral breast
    - limited sensitivity for visualization of masses in pregnancy/lactation due to increase in breast density responding to hormonal shifts; may be difficult to visualize small masses due to heterogeneous breast density (50-75% of breast dense) and extreme density (>75% of breast dense) limiting mammographic sensitivity overall
    - minimal risk to fetus with shielding technique
    - exposure from mammogram with shield = 0.03 microGy
    - **diagnostic mammogram has excellent sensitivity and specificity for detection of malignant breast lesions in women who are pregnant, lactating, or postpartum (**[**level 1 [likely reliable] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

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studySummary

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      * 126 pregnant, lactating, or postpartum women (mean age 32 years) had diagnostic mammogram and/or breast ultrasound
      * reference standard was biopsy-proven pathologic abnormality or > 12 months of radiographic or clinical follow-up
      * 4 women (3.2%) had malignant lesion based on reference standard (all presenting with a palpable mass)
      * 85 women (67%) had diagnostic mammogram
      * all 4 women with a malignant lesion had microcalcifications on diagnostic mammogram; in addition, 1 had a mass and 1 had architectural distortion
      * diagnostic performance of mammogram [BI-RADS category 4 or 5](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#DIAGNOSTIC_MAMMOGRAPHY) was
        + sensitivity 100%
        + specificity 93%
        + positive predictive value 40%
        + negative predictive value 100%
      * PubMed21343518AJR. American journal of roentgenologyAJR Am J Roentgenol201103011963716-22716Reference - [AJR Am J Roentgenol 2011 Mar;196(3):716](http://pubmed.ncbi.nlm.nih.gov/21343518)
  + MRI
    - gadolinium-based contrast might be teratogenic
    - use of gadolinium contrast likely safe in women who are postpartum or lactating, but small amounts are excreted into breast milk raising potential for toxicity or allergic reactions
    - hypervascularity and changes due to lactation may increase background enhancement making interpretation difficult
  + PubMed28232597The oncologistOncologist20170301223324-334324Reference - [Oncologist 2017 Mar;22(3):324](http://pubmed.ncbi.nlm.nih.gov/28232597)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5344634/)

Recommendations for Diagnostic Evaluation and Staging During Pregnancy or Lactation

* TOPIC\_LSR\_NSQ\_2PB\_\_LI\_IGG\_R1F\_JPBGSU04212104/21/2021 04:15:58 PMguidelineSummaryUpdatestandardOncologic\_DiseaseNational Comprehensive Cancer Network (NCCN) 2021 guidelines for workup of breast cancer in women who are pregnant include (NCCN website)National Comprehensive Cancer Network (NCCN) 2021 guidelines for workup of breast cancer in women who are pregnant include
  + considerations for initial assessment and staging workup include
    - physical exam should include special attention to breast and regional lymph nodes
    - mammogram can be performed safely (with shielding)
    - ultrasound of breast and regional lymph nodes may be useful in evaluating extent of disease or guiding biopsy
    - biopsy can be performed through fine needle aspiration for cytological evaluation of suspicious mass or lymph nodes, however core needle biopsy is preferred to obtain adequate tissue for confirmation of histology and hormone receptor (HR)/human epidermal growth factor 2 (HER2) status
    - minimize fetal exposure to radiation during staging
    - detection of metastases may affect treatment plan and patient decision regarding pregnancy termination
    - additional evaluation should include maternal fetal medicine consult for
      * assessment of preexisting maternal risks such as hypertension, diabetes, and previous pregnancy complications
      * ultrasound of fetus to assess of growth, development, and age; this is useful as estimation of delivery date can aid in the planning of systemic chemotherapy
      * counseling regarding maintenance or termination of the pregnancy
  + recommendations for workup include
    - chest x-ray with abdominal shielding ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); likely adequate for staging
    - perform abdominal ultrasound to evaluate for liver metastases (if indicated by symptoms or blood work) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - consider magnetic resonance imaging (MRI) without contrast of spine to evaluate for bone metastases (if indicated by symptoms) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - CT scans and nuclear medicine scans are contraindicated during pregnancy
  + Reference - NCCN guidelines on breast cancer (version 3.2021 [NCCN website](https://www.nccn.org/guidelines/category_1) [free registration required])
* American College of Radiology (ACR) 2018 guidelines
  + for pregnant women with a palpable breast mass, perform ultrasound as initial imaging ([ACR Rating 7,8, or 9](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE)); if findings are suspicious for malignancy or no etiology determined, follow with diagnostic mammography ([ACR Rating 4, 5, or 6](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE))
  + for women with suspicious nipple discharge during pregnancy or lactation
    - retroareolar ultrasound is preferred as initial imaging to assess for etiology of nipple discharge including papilloma or breast mass ([ACR Rating 7-9](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE)); techniques that may improve detection of nipple discharge etiology include peripheral compression, 2-handed compression, and rolled nipple
    - diagnostic mammography or digital breast tomosynthesis (DBT) with retroareolar magnification views may be considered for initial imaging or performed in addition to ultrasound ([ACR Rating 7-9](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE)); in general, reported to have sensitivity of 74%-90% for detection of malignancy in pregnant and/or lactating women
    - magnetic resonance imaging (MRI) and molecular breast imaging (MBI) are not recommended for initial evaluation of nipple discharge in pregnant and/or lactating women ([ACR Rating 1-3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE))
  + for locoregional staging of breast cancer diagnosed during pregnancy, perform diagnostic mammogram and ultrasound of axilla ([ACR Rating 7,8, or 9](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACRGRADE))
  + PubMed30392595Journal of the American College of Radiology : JACRJ Am Coll Radiol201811011511SS263-S275S263Reference - [ACR 2018 PDF](https://acsearch.acr.org/docs/3102382/Narrative/) in [J Am Coll Radiol 2018 Nov;15(11S):S263](http://pubmed.ncbi.nlm.nih.gov/30392595)

Management

ManagementManagement

Management of early or operable breast cancer

* before treatment for early breast cancer, perform assessment for treatment planning
* management requires a multidisciplinary team specializing in and dedicated to treating breast cancer, and including (at minimum) ≥ 1 each of surgeon, radiation oncologist, medical oncologist, radiologist, pathologist, and breast nurse ([ESMO Grade A, Level IV](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
* neoadjuvant systemic therapy
  + neoadjuvant systemic therapy is indicated for patients with operable breast cancer and
    - desire breast-conserving surgery, however mastectomy is required due to tumor size ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
    - have clinically positive lymph nodes, likely to become negative with neoadjuvant systemic therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + chemotherapy and endocrine therapy may each be used alone or in combination with human epidermal growth factor receptor 2 (HER2) targeted therapy in the neoadjuvant setting; use of each modality is based on tumor subtype, comorbidities and extent of disease
    - neoadjuvant chemotherapy
      * is an option for patients with triple-negative or HER2 positive breast cancer
      * may benefit some patients with hormone receptor (HR) positive breast cancer, especially if high-risk luminal disease
    - neoadjuvant endocrine therapy
      * is an option for patients with HR positive breast cancer ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * may be considered as sole neoadjuvant therapy for patients with estrogen receptor (ER) positive disease based on comorbidity status or low-risk luminal biology ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - neoadjuvant HER2 targeted therapy is an option for patients with HER2 positive tumors, particularly if HR negative, due to higher likelihood of pathologic complete response ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
* locoregional therapy includes surgery to the breast and axilla and radiation
  + surgery to the breast includes either breast-conserving surgery or mastectomy; choice between breast-conserving surgery or mastectomy is based on patient preferences, disease characteristics, and plans for adjuvant radiation therapy
  + locoregional therapy options include either
    - breast-conserving therapy by lumpectomy with surgical axillary staging ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)), followed by radiation therapy according to lymph node status
    - total mastectomy with surgical axillary staging ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)) with or without breast reconstruction ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)), and with or without postmastectomy radiation therapy according to lymph node status, tumor size, and surgical margins
  + surgical axillary staging options include either or both sentinel lymph node biopsy or axillary lymph node dissection
    - for patients with clinically negative lymph nodes at time of diagnosis, perform sentinel lymph node mapping and excision ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade A, Level II](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
      * if negative sentinel lymph node, no further axillary surgery ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade A, Level II](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
      * if positive sentinel lymph node and
        + only with micrometastasis, no further axillary surgery ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade B, Level II](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE) for no further axillary surgery if tangential radiation given)
        + all the following criteria are met, no further axillary surgery recommended, otherwise perform level I/II axillary lymph node dissection ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade A, Level II](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))

no preoperative systemic therapy

tumor size < 5 cm

≤ 2 positive sentinel lymph nodes

breast-conserving therapy planned

whole-breast radiation planned

* + - for patients with clinically positive lymph nodes at time of diagnosis, consider ultrasound-guided fine needle aspiration (FNA) or core needle biopsy of the suspicious lymph node ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * if FNA or core biopsy negative, perform sentinel lymph node mapping and excision ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)), preferably after any neoadjuvant systemic therapy
      * if FNA or core biopsy positive and no neoadjuvant systemic therapy or remains positive following neoadjuvant systemic therapy, perform level I/II axillary lymph node dissection ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * if FNA or core biopsy positive, but becomes clinically negative following neoadjuvant systemic therapy, may consider sentinel lymph node mapping and excision ([NCCN Category 2B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)), otherwise axillary lymph node dissection should be performed ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - for patients with sentinel lymph node that cannot be identified, perform level I/II axillary lymph node dissection (unless woman will have mastectomy and radiation therapy, in which case, axillary radiation therapy may replace axillary dissection) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
* adjuvant systemic therapy
  + recommendations for use of adjuvant systemic therapy are based on tumor size, nodal status, tumor histology, HR status, HER2 receptor status, and multigene assays
  + National Comprehensive Cancer Network (NCCN) recommendations for systemic adjuvant treatment
    - for HR positive and HER2 positive early breast cancer
      * with pT1-T3 and pN0 or pN1mi (≤ 2 mm axillary lymph node metastasis) disease
        + if tumor ≤ 0.5 cm including microinvasive

if pN0, consider adjuvant endocrine therapy with or without adjuvant chemotherapy plus [trastuzumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/trastuzumab) ([NCCN Category 2B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

if pN1mi, consider either adjuvant endocrine therapy alone ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)) or adjuvant chemotherapy plus trastuzumab plus endocrine therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

* + - * + if tumor 0.6-1 cm, consider either adjuvant endocrine therapy alone ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)) or adjuvant chemotherapy plus trastuzumab plus endocrine therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + if tumor > 1 cm, offer adjuvant chemotherapy plus trastuzumab ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)) plus endocrine therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * with lymph node-positive (any metastases > 2 mm to any ipsilateral axillary lymph nodes) disease, options include
        + offer adjuvant chemotherapy plus [trastuzumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/trastuzumab) ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)) and endocrine therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)) or adjuvant chemotherapy plus trastuzumab plus [pertuzumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/pertuzumab) plus endocrine therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + if high risk of recurrence, consider extended therapy with [neratinib](https://dpa-pde-oxford.shinyapps.io/drug-monograph/neratinib) after completion of adjuvant trastuzumab with or without pertuzumab
    - for HR negative and HER2 positive early breast cancer
      * with pT1-T3 and pN0 or pN1mi (≤ 2 mm axillary lymph node metastasis) disease
        + if tumor ≤ 0.5 cm including microinvasive

if pN0, consider adjuvant chemotherapy plus [trastuzumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/trastuzumab) or observation alone ([NCCN Category 2B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

if pN1mi, consider adjuvant chemotherapy plus trastuzumab ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

* + - * + if tumor 0.6-1 cm, consider adjuvant chemotherapy plus trastuzumab ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + if tumor > 1 cm, offer adjuvant chemotherapy plus trastuzumab ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * with lymph node-positive (any metastases > 2 mm to any ipsilateral axillary lymph nodes) disease, offer adjuvant chemotherapy plus trastuzumab ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)) or adjuvant chemotherapy plus trastuzumab plus [pertuzumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/pertuzumab) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - for HR positive and HER2 negative early breast cancer
      * if ductal, lobular, mixed, or metaplastic histology
        + with pT1-T3 and pN0 or pN1mi (≤ 2 mm axillary lymph node metastasis) disease

if tumor ≤ 0.5 cm including microinvasive

if pN0, consider adjuvant endocrine therapy ([NCCN Category 2B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

if pN1mi, consider 21-gene reverse transcriptase polymerase chain reaction (RT-PCR) assay to aid in decision regarding addition of chemotherapy in patients with 1-3 positive lymph nodes and offer adjuvant endocrine therapy alone ([NCCN Category 2B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)) or adjuvant chemotherapy followed by endocrine therapy ([NCCN Category 2B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

if tumor > 0.5 cm, consider 21-gene RT-PCR assay ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

if 21-gene RT-PCR assay not done, offer adjuvant endocrine therapy alone or adjuvant chemotherapy followed by endocrine therapy ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

if recurrence score < 18, offer adjuvant endocrine therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

if recurrence score 18-30, offer adjuvant endocrine therapy alone or adjuvant chemotherapy followed by endocrine therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

if recurrence score 11-25, adjuvant endocrine therapy alone and adjuvant chemotherapy followed by endocrine therapy may have similar 9-year overall survival and invasive disease-free survival based on TAILORx trial, but adjuvant chemotherapy followed by endocrine therapy might slightly improve invasive disease-free survival in women ≤ 50 years old with recurrence scores 16-25

if recurrence score ≥ 31, offer adjuvant chemotherapy followed by endocrine therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

* + - * + with lymph node-positive (any metastases > 2 mm to any ipsilateral axillary lymph nodes) disease, consider 21-gene RT-PCR assay to aid in decision regarding addition of chemotherapy in select patients with 1-3 positive lymph nodes; otherwise offer adjuvant chemotherapy followed by endocrine therapy ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * if tubular, mucinous, or papillary (favorable) histology
        + with pT1-T3 and pN0 or pN1mi (≤ 2 mm axillary lymph node metastasis) disease

if tumor < 1 cm, consider adjuvant endocrine therapy for risk reduction ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

if tumor 1-2.9 cm, consider adjuvant endocrine therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

if tumor ≥ 3 cm, offer adjuvant endocrine therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

* + - * + with lymph node-positive (any metastases > 2 mm to any ipsilateral axillary lymph nodes) disease, offer adjuvant endocrine therapy with or without adjuvant chemotherapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - for HR negative and HER2 negative early breast cancer
      * with pT1-T3 and pN0 or pN1mi (≤ 2 mm axillary lymph node metastasis) disease
        + if tumor ≤ 0.5 cm including microinvasive

if pN0, no adjuvant therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

if pN1mi, consider adjuvant chemotherapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

* + - * + if tumor 0.6-1 cm, consider adjuvant chemotherapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + if tumor > 1 cm, offer adjuvant chemotherapy ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * with lymph node-positive (any metastases > 2 mm to any ipsilateral axillary lymph nodes) disease, offer adjuvant chemotherapy ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + European Society for Medical Oncology (ESMO) recommendations for systemic adjuvant treatment of early and locally advanced breast cancer
    - HER2 positive
      * if ER positive and progesterone receptor (PR) either positive or negative
        + combination of chemotherapy plus [trastuzumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/trastuzumab) plus endocrine therapy recommended ([ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
        + if chemotherapy is contraindicated or refused, combination of trastuzumab plus endocrine therapy may be considered for systemic therapy without chemotherapy ([ESMO Grade A, Level V](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
      * if HR negative (both ER and PR negative), combination of chemotherapy plus trastuzumab recommended ([ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
    - HER2 negative
      * if high-risk ER positive and PR either positive or negative (luminal B), chemotherapy plus endocrine therapy recommended ([ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE)); when deciding for treatment, consider factors such as level of ER expression, proliferation, genetic risk, tumor burden, and patient preference
      * if low-risk ER positive and PR either positive or negative (luminal A), chemotherapy not recommended ([ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
      * if triple negative, chemotherapy recommended ([ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE)) unless low-risk histology (secretory juvenile, apocrine, or adenoid cystic)
  + American Society of Clinical Oncology (ASCO) guideline on use of Onco*type* DX for systemic therapy decision making
    - Oncotype DX to guide adjuvant chemotherapy plus endocrine therapy
      * for patients with node-negative breast cancer
        + for patients with Oncotype DX recurrence score ≥ 26, offer adjuvant endocrine therapy plus chemotherapy ([ASCO Evidence-based, Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
        + for patients ≤ 50 years old with Oncotype DX recurrence score 16-25, consider adjuvant endocrine therapy plus chemotherapy ([ASCO Evidence-based, Moderate recommendation, Intermediate-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
      * for patients with 1-3 positive lymph nodes
        + for patients who are postmenopausal with Oncotype DX recurrence score ≥ 26, offer adjuvant endocrine therapy plus chemotherapy ([ASCO Evidence-based, Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
        + for patients who are premenopausal, consider not performing Oncotype DX ([ASCO Evidence-based, Moderate recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
      * for patients with ≥ 4 positive lymph nodes, there is insufficient evidence to recommend use of Oncotype DX to guide adjuvant chemotherapy and endocrine therapy ([ASCO Informal consensus, Moderate recommendation, Insufficient evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCOGRADE))
      * PubMed35439025Journal of clinical oncology : official journal of the American Society of Clinical OncologyJ Clin Oncol2022060140161816-18371816Reference - [J Clin Oncol 2022 Jun 1;40(16):1816](https://pubmed.ncbi.nlm.nih.gov/35439025)
* surveillance
  + perform history and physical 1-4 times per year, as clinically indicated for 5 years, then annually thereafter ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade A, Level V](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
  + annual ipsilateral and/or contralateral mammogram, to begin 6-12 months after completion of radiation therapy (suspicious findings on physical exam or surveillance imaging may indicate more frequent mammograms or ultrasound) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade A, Level II](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
  + for patients on adjuvant endocrine therapy
    - routine blood tests are indicated for surveillance of patients on endocrine therapy due to potential side-effects of these drugs, particularly in lipid profile ([ESMO Grade A, Level V](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
    - for patients on [tamoxifen](https://dpa-pde-oxford.shinyapps.io/drug-monograph/tamoxifen), annual gynecological exam by experienced gynecologist recommended, if uterus present ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade B, Level V](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE), with gynecological ultrasound as necessary); counsel women to report vaginal spotting or bleeding
    - for patients on aromatase inhibitors, regular bone density evaluation recommended ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
    - during follow up, assess and encourage adherence to adjuvant endocrine therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + periodically screen for changes in family history, and refer for genetic counseling as appropriate ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + monitor for adverse events associated with therapy
* see [Management of Early and Locally Advanced Breast Cancer](https://dpa-pde-oxford.shinyapps.io/management/management-of-early-and-locally-advanced-breast-cancer) for details

Management of inoperable locally advanced noninflammatory breast cancer

* before treatment for locally advanced breast cancer, perform assessment for treatment planning
* management requires a multidisciplinary team specializing in and dedicated to treating breast cancer, and including (at minimum) ≥ 1 each of surgeon, radiation oncologist, medical oncologist, radiologist, pathologist, and breast nurse ([ESMO Grade A, Level IV](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
* most cases of locally advanced breast cancer require a combined treatment approach including systemic therapy, surgery, and radiation therapy ([ESO/ESMO Grade 1A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
* neoadjuvant systemic therapy
  + offer neoadjuvant systemic therapy to all patients with inoperable locally advanced breast cancer ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); systemic therapy, not surgery or radiation therapy, should be offered as initial treatment in these patients ([ESO/ESMO Expert opinion](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOGRADE), 100% consensus)
    - chemotherapy or endocrine therapy may each be used alone or in combination with human epidermal growth factor receptor 2 (HER2) targeted therapy in the neoadjuvant setting; use of each modality is based on tumor subtype, comorbidities, and extent of disease
      * neoadjuvant chemotherapy is preferred
      * neoadjuvant endocrine therapy
        + is an option for patients with hormone receptor (HR) positive breast cancer ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + may be considered as sole neoadjuvant therapy for patients with estrogen receptor (ER) positive disease based on comorbidity status or low-risk luminal biology ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * neoadjuvant HER2 targeted therapy should be added for patients with HER2 positive tumors ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - all chemotherapy regimens generally used in the adjuvant setting may be used in the neoadjuvant setting ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
* locoregional therapy includes surgery to the breast and axilla and radiation
  + surgery to the breast includes either breast-conserving surgery or mastectomy; choice between breast-conserving surgery or mastectomy is based on patient preferences and disease characteristics
  + locoregional therapy options include either
    - breast-conserving therapy by lumpectomy plus level I/II axillary dissection plus whole breast radiation therapy with or without boost radiation to tumor bed, plus radiation to infraclavicular region, supraclavicular area, internal mammary nodes, and any part of axillary bed at risk ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - total mastectomy plus level I/II axillary dissection plus radiation therapy to chest wall, infraclavicular region, supraclavicular area, internal mammary nodes and any part of axillary bed at risk, with or without breast reconstruction ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
* adjuvant therapy for women with locally advanced breast cancer includes all the following
  + adjuvant chemotherapy
    - for all patients, complete any planned chemotherapy if not completed in the neoadjuvant setting ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - for patients with triple-negative tumor and residual invasive cancer after neoadjuvant therapy with taxane, alkylator, and anthracycline based chemotherapy, consider adjuvant capecitabine ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + adjuvant radiation therapy to breast/chest wall, infraclavicular region, supraclavicular area, internal mammary nodes, and any part of axillary bed at risk ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + adjuvant endocrine therapy for patients with HR positive (ER and/or progesterone receptor positive) breast cancer ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - radiation therapy may be given safely during endocrine therapy treatment ([ESMO Grade B, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
    - chemotherapy and endocrine therapy should not be given concurrently; administer sequentially with chemotherapy followed by endocrine therapy ([ESMO Grade D, Level II](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
  + adjuvant HER2 targeted therapy for patients with HER2 positive breast cancer
    - complete up to 1 year of HER2 targeted therapy with [trastuzumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/trastuzumab) ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)) with or without [pertuzumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/pertuzumab) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - HER2 targeted therapy may be given concurrently with radiation therapy and/or endocrine therapy as appropriate ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if HR positive breast cancer and high risk of recurrence, consider extended therapy with [neratinib](https://dpa-pde-oxford.shinyapps.io/drug-monograph/neratinib) after completion of adjuvant trastuzumab with or without pertuzumab; benefit or toxicities of extended adjuvant neratinib following pertuzumab therapy are not known
* surveillance
  + perform history and physical 1-4 times per year, as clinically indicated for 5 years, then annually thereafter ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade A, Level V](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
  + annual ipsilateral and/or contralateral mammogram, to begin 6-12 months after completion of radiation therapy (suspicious findings on physical exam or surveillance imaging may indicate more frequent mammograms or ultrasound) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade A, Level II](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
  + for patients on adjuvant endocrine therapy
    - routine blood tests are indicated for surveillance of patients on endocrine therapy due to potential side-effects of these drugs, particularly in lipid profile ([ESMO Grade A, Level V](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
    - for patients on [tamoxifen](https://dpa-pde-oxford.shinyapps.io/drug-monograph/tamoxifen), annual gynecological exam by experienced gynecologist recommended, if uterus present ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade B, Level V](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE), with gynecological ultrasound as necessary); counsel women to report vaginal spotting or bleeding
    - for patients on aromatase inhibitors, regular bone density evaluation recommended ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))
    - during follow-up, assess and encourage adherence to adjuvant endocrine therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + periodically screen for changes in family history, and refer for genetic counseling as appropriate ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + monitor for adverse events associated with therapy
* see [Management of Early and Locally Advanced Breast Cancer](https://dpa-pde-oxford.shinyapps.io/management/management-of-early-and-locally-advanced-breast-cancer) for details

Management of inflammatory breast cancer

* management consists of trimodality therapy starting with neoadjuvant systemic therapy followed by mastectomy with axillary dissection, and postmastectomy radiation therapy; trimodality therapy should not start with surgery
* neoadjuvant systemic therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + anthracycline plus taxane is preferred neoadjuvant chemotherapy combination for inflammatory breast cancer, options include
    - dose-dense [doxorubicin](https://dpa-pde-oxford.shinyapps.io/topic/an:dmp2:T908383) plus [cyclophosphamide](https://dpa-pde-oxford.shinyapps.io/drug-monograph/cyclophosphamide) (ddAC) followed by paclitaxel every 2 weeks (preferred option for inflammatory breast cancer)
    - ddAC followed by paclitaxel every week (preferred option for inflammatory breast cancer)
  + if tumor is human epidermal growth factor receptor 2 (HER2) positive, HER2 targeted therapy ([trastuzumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/trastuzumab) with or without [pertuzumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/pertuzumab)) is added to the neoadjuvant chemotherapy concurrent with the taxane and continued for a year
* assess treatment response to neoadjuvant therapy
  + accurate assessment of breast tumor and regional lymph node response to preoperative systemic therapy is challenging and should include physical exam and repeat imaging (such as mammography and/or magnetic resonance imaging) of abnormal findings identified at time of initial tumor staging
  + early evaluation of treatment response after 2 cycles of neoadjuvant therapy may give information about resistance to primary chemotherapy
* for patients with a response to neoadjuvant therapy, following completion proceed with
  + total mastectomy with level I/II axillary lymph node dissection ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - immediate breast reconstruction contraindicated in patients with inflammatory breast cancer
    - optional delayed breast reconstruction following radiation
  + postmastectomy radiation therapy to improve locoregional control of disease due to high risk of local recurrence
    - postmastectomy radiation therapy to chest wall, infraclavicular region, supraclavicular area, internal mammary nodes, and any part of axillary node area at risk recommended ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - radiation therapy typically starts about 4-6 weeks after mastectomy
  + postoperative systemic therapy
    - complete chemotherapy regimen if not completed preoperatively, and if hormone receptor (HR) positive give endocrine therapy following completion of chemotherapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - complete up to 1 year of HER2 targeted therapy if HER2 positive ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); may be given concurrently with radiation therapy and with endocrine therapy if indicated ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
* for patients with little to no response to neoadjuvant chemotherapy
  + consider additional neoadjuvant chemotherapy and/or preoperative radiation therapy to achieve response, or enrollment in clinical trial ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + for patients unresponsive to additional neoadjuvant chemotherapy or preoperative radiation therapy, consider individualized treatment or enrollment in clinical trial ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + mastectomy generally not recommended if no response
* surveillance for recurrence includes annual mammography to detect new contralateral breast cancer
* see [Inflammatory breast cancer](https://dpa-pde-oxford.shinyapps.io/condition/inflammatory-breast-cancer) for details

Management of locoregional recurrence of breast cancer

* before treatment
  + assessment for presence of metastatic disease is necessary to differentiate isolated locoregional recurrences from metastatic disease
  + patients with metastases beyond regional lymph nodes should be treated as metastatic recurrence with systemic therapy or palliative locoregional therapy
* for optimal outcomes, a multidisciplinary approach is important so that all possible treatment options are considered ([ESO/ESMO Expert opinion](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOGRADE), 100% consensus)
* management of local only recurrence is based on initial treatment approach
  + for patients initially treated with breast-conserving surgery and radiation therapy
    - offer total mastectomy plus axillary lymph node staging (if level I/II axillary dissection not done previously) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - may consider reirradiation of portion or all the chest wall in select cases ([ESO/ESMO Expert opinion](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOGRADE), 97% agreement)
    - if initial axillary surgery was sentinel lymph node biopsy, may be technically feasible to repeat sentinel node biopsy, however accuracy is unproven
      * level I and II axillary dissection is preferred
      * sentinel lymph node biopsy may be considered but is discouraged
    - consider systemic therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + for patients initially treated with mastectomy
    - if initial treatment included radiation therapy and level I/II axillary dissection, options include
      * surgical resection if possible ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESO/ESMO Grade 1B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOGRADE))
      * may consider reirradiation of portion or all the chest wall in select cases ([ESO/ESMO Expert opinion](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOGRADE), 97% agreement)
      * if surgical resection not technically feasible, consider systemic therapy to best response, then surgical resection if possible
    - for patients without prior radiation therapy, options include
      * surgical resection if possible plus radiation therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESO/ESMO Grade 1B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOGRADE))
      * if surgical resection not technically feasible, consider systemic therapy to best response, then surgical resection if possible
    - consider systemic therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESO/ESMO Grade 1B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOGRADE))
  + for patients who are not candidates for surgical resection, options include
    - systemic therapy followed by surgical resection ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)), radical radiation therapy, or systemic therapy alone
    - palliative systemic therapy (following principles for metastatic breast cancer) ([ESO/ESMO Expert opinion](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOGRADE), 97% consensus)
* management of regional only or local and regional recurrence is based on site of recurrence (treat with curative intent whenever possible)
  + axillary recurrence - surgical resection if possible plus radiation therapy if possible ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); consider systemic therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + supraclavicular recurrence - radiation therapy if possible ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); consider systemic therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + internal mammary node recurrence - radiation therapy if possible ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); consider systemic therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + local breast or chest wall recurrence - local therapy to breast or chest wall
  + for patients with disease not suitable for local treatment with curative intent, palliative systemic therapies options would be as given for metastatic disease ([ESO/ESMO Expert opinion](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOGRADE), 97% consensus)
* see [Locoregional recurrence of breast cancer](https://dpa-pde-oxford.shinyapps.io/management/management-of-locoregional-recurrence-of-breast-cancer) for details

Management of metastatic breast cancer

* The following is an excerpt from [Management of Metastatic Breast Cancer](https://dpa-pde-oxford.shinyapps.io/management/management-of-metastatic-breast-cancer); please see topic for details.
  + metastatic breast cancer is breast cancer that has spread beyond the breast to other organs (most often bones, lungs, liver, or brain); refers to either breast cancer with metastasis at the time of initial diagnosis, often called de novo stage IV breast cancer, or to a metastatic recurrence
  + metastatic breast cancer is considered incurable with currently available therapies; goals of therapy include increased survival and maintenance of quality of life
  + all patients should be offered enrollment in a clinical trial; for a list of trials recruiting patients with advanced breast cancer, see [clinicaltrials.gov](https://clinicaltrials.gov/ct2/results?term=advanced+breast+cancer&recr=Recruiting&rslt=&type=Intr&cond=&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&gndr=&rcv_s=&rcv_e=&lup_s=&lup_e=)
  + assessment for treatment planning includes history and physical exam, blood tests (complete blood count and comprehensive metabolic panel), imaging, and biopsy of metastatic site if possible
  + for patients with metastatic breast cancer, treatment typically involves systemic therapy with endocrine therapy or chemotherapy with or without human epidermal growth factor receptor 2 (HER2) targeted therapy and other targeted or biologic therapies
  + surgery and/or radiation therapy may be used with the goal of palliation of symptoms including prevention and treatment of bone fractures and spinal cord compression, or for definitive locoregional therapy for de novo stage IV breast cancer or oligometastatic disease
  + systemic therapy recommendations
    - for HR positive and HER2 negative metastatic disease: endocrine therapy, chemotherapy, and targeted therapy should be individualized based on menopausal status, prior exposure to endocrine therapy, burden of disease, and biomarkers
      * if visceral crisis, consider initial chemotherapy and/or targeted therapy; continue until disease progression or unacceptable toxicity ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * if no visceral crisis
        + offer endocrine therapy with or without cyclin dependent kinase 4/6 (CDK4/6) inhibitor and for premenopausal women, offer addition of ovarian ablation or suppression ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESO/ESMO Grade A, Expert opinion](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOESMO2018GRADE)); if progressed on prior endocrine therapy, offer a different first-line endocrine therapy regimen
        + for premenopausal women, may consider selective estrogen receptor modulator (tamoxifen or toremifene) if no prior endocrine therapy within a year ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESO/ESMO Grade D, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOESMO2018GRADE)) for tamoxifen if patient declines ovarian suppression/ablation)
        + continue endocrine therapy regimen until disease progression or unacceptable toxicity
      * if disease progression or unacceptable toxicity on first-line endocrine therapy
        + consider either

a different endocrine therapy with or without targeted therapy if not endocrine refractory ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESO/ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOESMO2018GRADE))

systemic therapy with chemotherapy and/or targeted therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

* + - * + if no benefit following 3 sequential endocrine therapies or symptomatic visceral disease occurs, offer chemotherapy and/or targeted therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

most patients are candidates for multiple lines of palliative systemic therapy

use shared decision-making at each reassessment to evaluate value of ongoing treatment, risks and benefits of additional chemotherapy, performance status, and patient preferences

* + - * if disease progression or unacceptable toxicity on first-line chemotherapy or beyond
        + offer another line of chemotherapy and/or targeted therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

most patients are candidates for multiple lines of palliative systemic therapy

use shared decision-making at each reassessment to evaluate value of ongoing treatment, risks and benefits of additional chemotherapy, performance status, and patient preferences

* + - * + if progression occurs and no additional systemic therapy is warranted (based on clinical factors and patient preference), continue supportive care without further chemotherapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * if germline *BRCA* mutation, offer poly adenosine diphosphate ribose polymerase (PARP) inhibitor such as olaparib or talazoparib after progression on endocrine therapy plus CDK4/6 inhibitor ([ESO/ESMO Grade B, Expert opinion](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOESMO2018GRADE))
    - for HR positive and HER2 positive metastatic disease: endocrine therapy, chemotherapy, and targeted therapy should be individualized based on menopausal status, biomarkers, and prior exposure to endocrine therapy, chemotherapy or other agents
      * options include any of the following
        + endocrine therapy with or without HER2 targeted therapy and for premenopausal women, consider addition of ovarian ablation or suppression ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ASCO Moderate recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE) for select cases; [ESO/ESMO Grade B, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOESMO2018GRADE)); if prior endocrine therapy within 1 year, consider different endocrine therapy
        + for premenopausal women, selective estrogen receptor (ER) modulator without ovarian ablation or suppression plus HER2 targeted therapy
        + chemotherapy plus HER2 targeted therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ASCO Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE); [ESO/ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOESMO2018GRADE)); when chemotherapy ends, endocrine therapy may be added to HER2 targeted therapy
        + other HER2 targeted therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + other targeted therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * continue therapy until disease progression or unacceptable toxicity ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * for disease progression or unacceptable toxicity
        + if first-line therapy was endocrine therapy, consider a different endocrine therapy (if not endocrine refractory) with or without HER2 targeted therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

if no benefit following up to 3 sequential endocrine therapy regimens with or without HER2 targeted therapy or symptomatic visceral disease present, offer chemotherapy plus HER2 targeted therapy regimens ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

if progression occurs and no additional systemic therapy is warranted (based on clinical factors and patient preference), continue supportive care without further HER2 targeted therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

* + - * + if first-line therapy was chemotherapy plus HER2 targeted therapy, offer a different chemotherapy plus HER2 targeted therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ASCO Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE); [ESO/ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOESMO2018GRADE)); when chemotherapy ends, endocrine therapy may be added to HER2 targeted therapy
        + continue second-line and beyond therapy until progression ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE), [ESO/ESMO Grade A, Level II](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOESMO2018GRADE))

most patients are candidates for multiple lines of palliative systemic therapy

use shared decision-making at each reassessment to evaluate value of ongoing treatment, risks and benefits of additional chemotherapy, performance status, and patient preferences

* + - * + if progression occurs and no additional systemic therapy is warranted (based on clinical factors and patient preference), continue supportive care without further HER2 targeted therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * acceptable trastuzumab substitutes
      * pertuzumab, trastuzumab and hyaluronidase-zzxf subcutaneous injection may be substituted for intravenous pertuzumab plus intravenous trastuzumab
    - for HR negative and HER2 positive metastatic disease: treatment typically involves combination of HER2 targeted therapy and chemotherapy or other targeted therapy individualized based on biomarkers, prior therapies, burden of metastatic disease, and balance of toxicities
      * systemic therapy options include
        + chemotherapy plus HER2 targeted therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ASCO Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE); [ESO/ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOESMO2018GRADE))
        + parp inhibitors (olaparib or talazoparib) may be considered if germline *BRCA* 1/2 mutation ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); FDA approval for HER2 negative only, but NCCN panel recommends for all subtypes
      * continue until progression or unacceptable toxicity occurs, then consider a different line of chemotherapy plus HER2 targeted therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESO/ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOESMO2018GRADE))
        + most patients are candidates for multiple lines of palliative systemic therapy
        + use shared decision-making at each reassessment to evaluate value of ongoing treatment, risks and benefits of additional chemotherapy, performance status, and patient preferences
        + may consider other targeted therapy options ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * if progression occurs and no additional systemic therapy is warranted (based on clinical factors and patient preference), continue supportive care without further HER2 targeted therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * acceptable trastuzumab substitutes
      * pertuzumab, trastuzumab and hyaluronidase-zzxf subcutaneous injection may be substituted for intravenous pertuzumab plus intravenous trastuzumab
    - for HR negative and HER2 negative (triple negative) metastatic disease: treatment typically involves chemotherapy and/or targeted therapy individualized based on biomarkers, prior therapies, burden of metastatic disease, and balance of toxicities
      * offer chemotherapy and/or targeted therapy until progression or unacceptable toxicity ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * if progression or unacceptable toxicity, offer another line of chemotherapy and/or targeted therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + most patients are candidates for multiple lines of palliative systemic therapy
        + use shared decision-making at each reassessment to evaluate value of ongoing treatment, risks and benefits of additional chemotherapy, performance status, and patient preferences
      * if progression occurs and no additional systemic therapy is warranted (based on clinical factors and patient preference), continue supportive care without further cytotoxic therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + for metastasis to bone, multidisciplinary treatment approach includes
    - discussing goals of therapy (incorporating shared decision-making) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - bone-modifying agents, with calcium and vitamin D supplement, for all patients with bone metastases ([ASCO Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE); [NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESO/ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOESMO2018GRADE))
    - surgery for patients with high risk for developing fracture or spinal cold compression ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - radiation therapy for potential definitive therapy of bone oligometastases, palliation of pain, or therapy for impending fracture or spinal cord compression ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ASTRO Strong recommendation, High-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASTRO2012GRADE))
    - systemic therapy, including endocrine therapy, chemotherapy, and targeted or biologic therapies based on menopausal status, biomarkers, prior therapies used, burden of metastatic disease, and balance of toxicities ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - supportive care ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ESO/ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOESMO2018GRADE))
    - see [Management of Breast Cancer Metastatic to Bone](https://dpa-pde-oxford.shinyapps.io/management/management-of-breast-cancer-metastatic-to-bone) for additional information
  + for metastasis to brain (see [Management of Breast Cancer Metastatic to Brain](https://dpa-pde-oxford.shinyapps.io/management/management-of-breast-cancer-metastatic-to-brain) for additional information)
    - palliative and supportive care is appropriate for all patients with brain metastases ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - consider clinical trial if available ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ASCO Moderate recommendation, Low-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASCO2017GRADE))
    - consider steroids for patients symptomatic from brain metastases or spinal cord compression ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [EANO Good practice point](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__EANOGRADE)); do not offer routine prophylactic antiseizure medications ([EANO Good practice point](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__EANOGRADE)), although may consider perioperatively ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - multimodal treatment approach based on performance status, prognosis, number, size and location of brain metastasis
      * for single metastasis and good prognosis (survival ≥ 3 months), options include
        + surgical resection (if resectable) ([ESO/ESMO Grade B, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOESMO2018GRADE), [EANO Level A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__EANOGRADE) if systemic disease absent or stable; [EANO Good practice point](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__EANOGRADE) if systemic disease active but treatment options available) followed by stereotactic radiosurgery (SRS) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE);[ASTRO Level 3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASTRO2012GRADE); [EANO Level C](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__EANOGRADE))
        + SRS alone; particularly for metastasis ≤ 3-4 cm ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ASTRO Level 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASTRO2012GRADE); [ESO/ESMO Grade B, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOESMO2018GRADE); [EANO Level B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__EANOGRADE))
        + surgical resection (if resectable) plus WBRT ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ASTRO Level 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASTRO2012GRADE); [ESO/ESMO Grade C, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOESMO2018GRADE); [EANO Level A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__EANOGRADE))
        + SRS plus WBRT, particularly for metastasis ≤ 3-4 cm, but addition of WBRT to SRS generally not recommended due to increased neurocognitive deficits with no survival benefits ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ASTRO Level 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASTRO2012GRADE); [EANO Level A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__EANOGRADE))
      * for multiple metastases and good prognosis (survival ≥ 3 months)
        + if no mass effect, options include

SRS alone, particularly if all metastases are ≤ 3-4 cm ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE), [ASTRO Level 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASTRO2012GRADE); [EANO Level B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__EANOGRADE))

surgical resection ([EANO Level A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__EANOGRADE)) followed by SRS (preferred) or WBRT ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

SRS plus WBRT, particularly for metastasis ≤ 3-4 cm, but addition of WBRT to SRS generally not recommended due to increased neurocognitive deficits with no survival benefits ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ASTRO Level 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASTRO2012GRADE))

WBRT alone, particularly if all metastases ≤ 3-4 cm ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ASTRO Level 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASTRO2012GRADE))

* + - * + if significant mass effect, options include

surgical resection of metastasis causing mass effect followed by WBRT, SRS, or systemic therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ASTRO Level 3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASTRO2012GRADE) for resection followed by WBRT)

WBRT ([ASTRO Level 3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASTRO2012GRADE))

systemic therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

* + - * for patients with poor prognosis
        + WBRT ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [ASTRO Level 3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASTRO2012GRADE); [EANO Level B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__EANOGRADE))
        + SRS in select patients with limited brain metastases ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + palliative and supportive care ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)) with or without WBRT ([ASTRO Level 3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ASTRO2012GRADE); [EANO Level B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__EANOGRADE))
      * for local recurrence
        + if limited recurrence and favorable prognosis, options include

surgical resection followed by SRS or radiation therapy (RT) to resection cavity ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE); [EANO Level C](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__EANOGRADE))

SRS, single dose ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE) if no prior RT; [NCCN Category 2B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE) if prior radiation at same site; [EANO Level C](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__EANOGRADE)) or fractionated stereotactic RT ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

WBRT for large tumors if no prior RT ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

systemic therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

* + - * + if diffuse or extensive recurrence, may consider

WBRT if no prior WBRT ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)

systemic therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

* + - * for leptomeningeal metastases, offer treatment based on risk status
        + choice of treatment options including intra-CSF therapy, systemic therapy, radiation therapy, and supportive care should be based on prognostic evaluation and multidisciplinary discussion as no standard ([ESO/ESMO Expert Opinion](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOESMO2018GRADE))
        + for patients with good risk status, treatment options include

systemic chemotherapy with CNS penetration such as high dose methotrexate ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

intra-CSF chemotherapy or targeted therapy

may consider intrathecal therapy in highly selected patients with unobstructed CSF flow, evidence of malignant cells in CSF, and stable systemic disease; intrathecal therapy has risk of significant toxicity ([ESO/ESMO Expert Opinion](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOESMO2018GRADE))

addition of intrathecal therapy to systemic therapy does not improve overall survival, quality of life or clinical meaningful CSF progression ([ESO/ESMO Grade D, Level II](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOESMO2018GRADE))

strongly consider use of Ommaya reservoir/intraventricular catheter ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

breast cancer intra-CSF regimen options include methotrexate and trastuzumab (if HER2 positive) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

if symptoms or imaging suggest CSF flow blockage, perform CSF flow scan prior to initiation of intra-CSF therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); if flow abnormality confirmed, options include

fractionated external beam radiation therapy to painful or metastatic sites of obstruction with repeat CSF flow scan to evaluate whether flow abnormality has resolved ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

high-dose methotrexate (systemic chemotherapy) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

SRS or WBRT and/or involved-field radiation therapy to bulky disease and neurologically symptomatic sites (for example cranial neuropathies or painful sites); craniospinal radiation therapy carries significant toxicity and should not be used for breast cancer) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

consider focal radiation therapy for symptomatic circumscribed lesions ([ESO/ESMO Expert Opinion](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOESMO2018GRADE))

may consider WBRT for extensive nodular or symptomatic LMD ([ESO/ESMO Expert Opinion](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESOESMO2018GRADE))

palliative or best supportive care (if patient does not wish for further treatment)

* + - * + for patients with poor risk status, options include ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

palliative or best supportive care

consider palliative involved-field radiation therapy to neurologically symptomatic or painful sites (including spine and intracranial disease)

* + - * systemic therapy options with CNS penetration include
        + cisplatin, etoposide, cisplatin plus etoposide, or high-dose methotrexate (consider glucarpidase (carboxypeptidase G2) for prolonged methotrexate clearance to reduce methotrexate-induced nephrotoxicity) ([NCCN Category 2B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + if HER2 positive cancer

capecitabine plus lapatinib or neratinib ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

paclitaxel plus neratinib ([NCCN Category 2B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

capecitabine ([NCCN Category 2B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

tucatinib plus trastuzumab plus capecitabine only if prior ≥1 anti-HER2 regimen ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

* + - follow with brain MRI every 2-3 months for 1-2 years, and then every 4-6 months thereafter ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + surveillance includes periodic assessment of varied combinations of symptoms, physical exam findings, routine laboratory tests, imaging studies, and blood biomarkers where appropriate
    - optimal frequency of repeat testing uncertain, and primarily based on monitoring strategies utilized in breast cancer clinical trials
    - depending on dynamics of disease, location and extent of metastatic involvement, and type of treatment, evaluation of response to therapy generally done every 2-4 months for endocrine therapy or after 2-3 cycles for chemotherapy
  + see [Management of Metastatic Breast Cancer](https://dpa-pde-oxford.shinyapps.io/management/management-of-metastatic-breast-cancer) for details

Management of breast cancer during pregnancy

* considerations for breast cancer during pregnancy
  + considerations for surgery during pregnancy
    - breast-conserving surgery possible if timing of radiation is postpartum (NCCN version 3.2021 [NCCN website](https://www.nccn.org/professionals/physician_gls/default.aspx) [free registration required])
    - obstetrical and prenatal specialists must be onsite for surgery ≥ 25 weeks of gestation (NCCN version 3.2021 [NCCN website](https://www.nccn.org/professionals/physician_gls/default.aspx) [free registration required])
    - anesthetic considerations
      * considerations for fetus
        + in most cases, the fetus is largely unaffected, with no blood loss and limited stress or hemodynamic alterations related to surgery
        + surgical risks for fetus may include

intraoperative hypoxemia or asphyxia due to decreased uterine blood flow, maternal hypotension, excessive maternal mechanical ventilation, maternal hypoxia, or depression of fetal cardiovascular system or central nervous system due to anesthetic agents passing through the placental barrier

potential exposure to teratogenic agents

risk for preterm delivery related to stress of surgical procedure or medications (highest in 3rd trimester)

* + - * considerations for mother
        + consider maternal physiologic factors such as hypercoagulability, delayed gastric emptying, increased blood volume and cardiac output, decreased functional residual capacity of the lungs, and decreased serum cholinesterase activity
        + rapid sequence induction of anesthesia may be preferred over standard induction due to pregnancy-associated gastroesophageal reflux
        + for surgery during the 3rd trimester

placing patient in 15 degree left lateral tilt position is helpful to avoid aortocaval compression

intraoperative fetal monitoring is useful

* + - * PubMed28232597The oncologistOncologist20170301223324-334324Reference - [Oncologist 2017 Mar;22(3):324](http://pubmed.ncbi.nlm.nih.gov/28232597)
  + considerations for sentinel lymph node biopsy during pregnancy
    - decision to use sentinel lymph node biopsy should be similar to patients who are not pregnant
    - radiolabeled sulfur colloid appears safe
      * uterine dose of radiation from use of radiolabeled sulfur colloid reported as 1.67 microGy (normal background radiation averages 8.2 microGy daily)
      * PubMed28232597The oncologistOncologist20170301223324-334324Reference - [Oncologist 2017 Mar;22(3):324](http://pubmed.ncbi.nlm.nih.gov/28232597)
    - use of blue dye contraindicated
    - Reference - NCCN guidelines on breast cancer (version 3.2021 [NCCN website](https://www.nccn.org/professionals/physician_gls/default.aspx) [free registration required])
  + considerations for chemotherapy treatment during pregnancy
    - chemotherapy should not be given during first trimester due to increase risk of fetal malformation
    - most experience with chemotherapy during pregnancy is from regimens using combinations of [doxorubicin](https://dpa-pde-oxford.shinyapps.io/topic/an:dmp2:T908383), [cyclophosphamide](https://dpa-pde-oxford.shinyapps.io/drug-monograph/cyclophosphamide), and [fluorouracil](https://dpa-pde-oxford.shinyapps.io/drug-monograph/fluorouracil)
    - limited data on use of taxanes during pregnancy; [paclitaxel](https://dpa-pde-oxford.shinyapps.io/drug-monograph/paclitaxel) weekly after first trimester acceptable if clinically indicated by disease status
    - administration of chemotherapy after week 35 of pregnancy or within 3 weeks of planned delivery reported to increase risk of hematologic complications during delivery
    - fetal monitoring before each cycle of chemotherapy may be useful
    - Reference - NCCN guidelines on breast cancer (version 3.2021 [NCCN website](https://www.nccn.org/professionals/physician_gls/default.aspx) [free registration required])
  + adjuvant endocrine therapy, human epidermal growth factor receptor 2 (HER2) targeted therapy, and radiation therapy should not be used during any trimester of pregnancy, but may be offered in postpartum period if indicated by disease status ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)) (NCCN version 3.2021 [NCCN website](https://www.nccn.org/professionals/physician_gls/default.aspx) [free registration required])
* MANAGEMENT\_OF\_BREAST\_CANCER\_IN\_PREGNANCY\_\_LI\_DFN\_RG2\_JPBGSU04212104/21/2021 01:43:37 PMguidelineSummaryUpdatestandardOncologic\_DiseaseNational Comprehensive Cancer Network (NCCN) 2021 recommendations for breast cancer during pregnancy (NCCN website) National Comprehensive Cancer Network (NCCN) 2021 recommendations for breast cancer during pregnancy
  + for pregnant women with confirmed breast cancer diagnosis, considerations and selection of optimal local and systemic therapy are similar to those in nonpregnancy associated breast cancer; however, timing and selection of chemotherapy, endocrine therapy, and radiation therapy is different for pregnant and nonpregnant women
  + communication between oncologist and maternal fetal medicine specialist essential at every visit and for every treatment decision point
  + treatment of pregnant women with confirmed breast cancer diagnosis and no distant metastases on staging is based on gestational trimester
    - in first trimester
      * discuss nontherapeutic pregnancy termination ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); maternal fetal medicine consultation should include review of treatment options and possibility of pregnancy termination
      * for women who choose to continue pregnancy consider mastectomy plus axillary staging as primary treatment ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + if late in first trimester, may consider neoadjuvant chemotherapy to begin in the second trimester; otherwise, offer adjuvant chemotherapy in second trimester ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + adjuvant radiation therapy and/or endocrine therapy may only be added postpartum ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - in second trimester or early third trimester, options include
      * mastectomy or breast-conserving surgery plus axillary staging, followed by adjuvant chemotherapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); adjuvant radiation therapy and/or endocrine therapy may only be added postpartum ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * neoadjuvant chemotherapy followed by mastectomy or breast-conserving surgery plus axillary staging ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); adjuvant radiation therapy and/or endocrine therapy may only be added postpartum ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - in late third trimester, consider mastectomy or breast-conserving surgery plus axillary staging, followed by adjuvant chemotherapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); adjuvant radiation therapy and/or endocrine therapy may only be added postpartum ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + Reference - NCCN guidelines on breast cancer (version 3.2021 [NCCN website](https://www.nccn.org/guidelines/category_1) [free registration required])

Management of breast cancer in older women

Recommendations From Professional Organizations

* National Comprehensive Cancer Network (NCCN) recommendations on pretreatment evaluation
  + if no concerns from patients, family or clinician on tolerability of anticancer therapies, consider evaluation with geriatric screening tools ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - screening tools include
      * abbreviated comprehensive geriatric assessment
      * Barber questionnaire
      * Fried Frailty Criteria
      * Geriatric-8
      * Groningen Frailty Index
      * Triage Risk Screening Tool
      * Vulnerable Elders Survey
    - if normal results from screening tools, consider standard management as appropriate for fit patients ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if abnormal results consider comprehensive geriatric assessment (CGA) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)), including evaluation of
      * functional status
      * socioeconomic status
      * psychosocial status
      * comorbidities
      * cognitive function
      * nutritional status
      * polypharmacy
      * medication review
    - if abnormal results from CGA
      * if modifiable impairments, consider treatments to resolve impairments ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * if non-modifiable impairments, consider either
        + alternative options of therapies with lower, acceptable toxicity level ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + [supportive care](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-79410BC4-6932-4AEC-9DD7-5AB021B7BF9D) only if no alternative options of therapies ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + if there are concerns from patients, family or clinician on tolerability of anticancer therapies, consider CGA ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if modifiable impairments, consider treatments to resolve impairments ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - if non-modifiable impairments, consider either
      * alternative options of therapies with lower, acceptable toxicity level ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * [supportive care](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-79410BC4-6932-4AEC-9DD7-5AB021B7BF9D) only if no alternative options of therapies ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
  + Reference - NCCN guidelines on older adult oncology from [NCCN website](http://www.nccn.org/professionals/physician_gls/) (free registration required)
* National Institute for Health and Care Excellence recommendations on adjuvant radiation therapy after breast-conserving therapy with lumpectomy
  + consider no radiation therapy in women who meet all the following criteria
    - have had breast-conserving surgery for invasive cancer with clear margins
    - have very low absolute risk of local recurrence (women ≥ 65 years old with tumors ≤ 2 cm, N0, ER-positive, HER2-negative and grade 1-2)
    - willing to take adjuvant endocrine therapy for ≥ 5 years
  + discuss risks and benefits of omitting radiation in women meeting the above criteria, including
    - 5-year risk of local recurrence rate 5% without radiation vs. 1% with radiation
    - no difference in overall survival at 10 years
    - no increase in serious late effects of radiation therapy if given
  + Reference - [NICE 2018 July:NG101](https://www.nice.org.uk/guidance/ng101)[PDF](https://www.nice.org.uk/guidance/ng101/resources/early-and-locally-advanced-breast-cancer-diagnosis-and-management-pdf-66141532913605)

Treatment Considerations for Early Breast Cancer in Older Women

* considerations for primary endocrine therapy
  + primary endocrine therapy alone for women with hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative disease
    - reported to have equal overall survival benefits compared to surgery (with or without addition of endocrine therapies), although local disease progression reported to be higher
    - helpful in women with short life expectancy (tumor control effective for about 18-24 months) and substantial comorbidity
  + for initially HR-positive/HER2-negative unresectable disease, endocrine therapy may reduce tumor size to allow subsequent mastectomy or breast-preserving treatment
  + aromatase inhibitors may be preferable over tamoxifen because of lower reported recurrence risk with no elevated risk for thromboembolism or uterine cancer
  + References -
    - PubMed28731946Cancer journal (Sudbury, Mass.)Cancer J20170701234231-237231[Cancer J 2017 Jul/Aug;23(4):231](http://pubmed.ncbi.nlm.nih.gov/28731946)
    - PubMed26869650Journal of oncology practiceJ Oncol Pract20160201122123-32123[J Oncol Pract 2016 Feb;12(2):123](http://pubmed.ncbi.nlm.nih.gov/26869650)
* considerations for surgical treatments
  + partial or total mastectomy may not be beneficial for women with significant comorbidities and short life expectancy; alternatives may include
    - [primary endocrine therapy alone](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#TOPIC_Y2P_FHN_DMB__LI_VPS_WQM_DMB) for women with HR-positive/HER2-negative disease
    - minimally invasive alternatives
      * may include
        + cryotherapy
        + laser irradiation
        + microwave irradiation
        + radiofrequency ablation
        + high-intensity focused ultrasound ablation
      * considered investigational only because of limited evidence
      * may be helpful for women with favorable disease (tumor size < 2-3 cm located ≥1 cm from skin or chest wall with little to no in situ component)
  + omission of sentinel lymph node biopsy
    - may be appropriate in women if any of following
      * favorable, clinically node-negative disease
      * treatment decisions unlikely to be affected by additional information
      * presence of serious comorbidity
    - evidence of effects on survival conflicting
    - reported to have short-term reduction of adverse effects, such as restriction of arm movement, pain, and numbness
  + References -
    - PubMed28731946Cancer journal (Sudbury, Mass.)Cancer J20170701234231-237231[Cancer J 2017 Jul/Aug;23(4):231](http://pubmed.ncbi.nlm.nih.gov/28731946)
    - PubMed26869650Journal of oncology practiceJ Oncol Pract20160201122123-32123[J Oncol Pract 2016 Feb;12(2):123](http://pubmed.ncbi.nlm.nih.gov/26869650)
* considerations for radiation therapy
  + omission of adjuvant radiation therapy
    - in older women with estrogen receptor (ER) positive breast cancer measuring ≤ 3 cm in size who are treated with endocrine therapy, radiation therapy has no survival benefit; radiation therapy after lumpectomy reported to reduce the risk of local recurrence from 10% to 2%
    - in older women with ER negative breast cancer, radiation more beneficial as recurrence rates higher without radiation and often occur within first few years after treatment; survival benefit reported 5-10 years after treatment
  + for women with high risk of locoregional recurrence or if unwilling to omit adjuvant radiation therapy after breast-conserving surgery, alternatives for minimization of radiation include
    - hypofractionated accelerated whole breast irradiation has become standard care
      * given as 250-270 cGy over 15-21 daily irradiation
      * reported to have similar overall survival and local recurrence rates and cosmetic outcomes compared to conventional fractionation
    - partial breast irradiation
      * radiation targeted to lumpectomy bed with margin
      * typical course is ≤ 5 days
      * in appropriately selected women, reported to have similar survival, local recurrence rate, and cosmetic outcome compared to whole-breast irradiation
    - omission of radiation boost
      * omission of 10-16 Gy to tumor bed after whole-body irradiation
      * benefit on ipsilateral breast tumor recurrence rate reduction reported to be smaller in older women compared to younger women
  + References -
    - PubMed28731946Cancer journal (Sudbury, Mass.)Cancer J20170701234231-237231[Cancer J 2017 Jul/Aug;23(4):231](http://pubmed.ncbi.nlm.nih.gov/28731946)
    - PubMed26869650Journal of oncology practiceJ Oncol Pract20160201122123-32123[J Oncol Pract 2016 Feb;12(2):123](http://pubmed.ncbi.nlm.nih.gov/26869650)
* considerations for adjuvant endocrine therapy, chemotherapy and HER2-targeted therapy
  + evaluation to determine benefits of adjuvant chemotherapy includes
    - [Oncotype DX recurrence score](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GENE_EXPRESSION_PROFILES_AND_BIOMARKER_TESTING__ANC_699172262) (applicable to older women)
      * if low recurrence score, endocrine therapy alone is appropriate
      * if high recurrence score, addition of chemotherapy to endocrine therapy beneficial
    - [PREDICT tool](https://breast.predict.nhs.uk/predict.html), which includes prediction of overall survival benefit of trastuzumab for HER2-positive disease
  + planning of adjuvant therapy use should include evaluation of
    - potential therapy-related toxicities, including
      * neuropathy (from taxane use)
      * decreased ejection fraction and congestive heart failure (from anthracyclines and trastuzumab use)
      * myelodysplasia and acute leukemia (from anthracycline use)
    - potential for hospitalization from chemotherapy-related toxicities
  + use of adjuvant therapy based on specific disease subtype and life expectancy
    - omission of all adjuvant therapy may be appropriate for women with
      * HR-positive/HER-negative, node-negative, low-grade tumor < 1 cm
      * life expectancy < 5 years
    - for women with HR-positive/HER2-negative disease and life expectancy > 5 years
      * for most women, adjuvant endocrine therapy may be appropriate
        + common regimen is aromatase inhibitor or tamoxifen for 2-3 years followed by aromatase inhibitor
        + explanation of goals and toxicity of endocrine therapy necessary at follow-up due to low adherence rate of therapy
      * addition of adjuvant chemotherapy to endocrine therapy
        + may be omitted if low [Oncotype DX recurrence score](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GENE_EXPRESSION_PROFILES_AND_BIOMARKER_TESTING__ANC_699172262) and considered if high recurrence score
        + may be appropriate if [estimated benefit of chemotherapy ≥ 5%](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#TOPIC_Y2P_FHN_DMB__LI_ZBF_JYM_DMB)
    - for women with HR-negative/HER2-negative disease and life expectancy > 5 years, as most recurrences are within 5 years, adjuvant chemotherapy
      * may be appropriate if [estimated benefit of chemotherapy 3%-5%](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#TOPIC_Y2P_FHN_DMB__LI_ZBF_JYM_DMB) at 5 years
      * should be given if [estimated benefit of chemotherapy > 5%](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#TOPIC_Y2P_FHN_DMB__LI_ZBF_JYM_DMB) at 5 years
    - for women with HER2-positive disease and life expectancy > 5 years, most recurrences occur within 5 years
      * for HR-positive disease, adjuvant endocrine therapy is appropriate
      * adjuvant chemotherapy and HER2-targeted therapy may be appropriate if [estimated benefit of chemotherapy ≥ 3%](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#TOPIC_Y2P_FHN_DMB__LI_ZBF_JYM_DMB) at 5 years
  + alternative chemotherapy regimens
    - capecitabine (with possible lower toxicity) reported to have lower overall survival compared to combination of cyclophosphamide plus methotrexate plus fluorouracil (CMF), or cyclophosphamide plus doxorubicin
    - docetaxel reported to have greater toxicity and lower quality of life with no overall survival benefit compared to CMF regimens
  + References -
    - PubMed28731946Cancer journal (Sudbury, Mass.)Cancer J20170701234231-237231[Cancer J 2017 Jul/Aug;23(4):231](http://pubmed.ncbi.nlm.nih.gov/28731946)
    - PubMed26869650Journal of oncology practiceJ Oncol Pract20160201122123-32123[J Oncol Pract 2016 Feb;12(2):123](http://pubmed.ncbi.nlm.nih.gov/26869650)
  + TOPIC\_Y2P\_FHN\_DMB\_\_LI\_X24\_34J\_MYBEU08172308/17/2023 04:09:33 PMevidenceUpdatelowplusOncologic\_Diseaseprimary endocrine therapy may have similar overall survival and breast cancer-specific survival compared to primary surgical therapy in older female patients with breast cancer (Br J Surg 2023 Mar 30)

**primary endocrine therapy may have similar overall survival and breast cancer-specific survival compared to primary surgical therapy in older female patients with breast cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[36718056Br J Surg 2023 Mar 30;110(4):420](http://pubmed.ncbi.nlm.nih.gov/36718056?dopt=Abstract)

studySummary

* + - Systematic Review based on systematic review with wide confidence intervals
    - systematic review of 5 randomized trials and 9 cohort studies (6 retrospective and 3 prospective) comparing primary endocrine therapy vs. primary surgical therapy in 14,254 female patients ≥ 65 years old with breast cancer
      * primary surgical therapy included surgery plus adjuvant endocrine therapy in all patients in 7 studies or in some patients in 3 studies, and surgery alone in 3 studies
      * 6 studies included patients with estrogen receptor positive tumors only
    - median study duration was 8 years
    - all trials had high risk of bias in domains of performance and detection
    - in meta-analysis of randomized trials
      * no significant difference in
        + overall survival (hazard ratio [HR] 1.12, 95% CI 0.97-1.28) in analysis of 5 trials, not significant, but CI cannot exclude differences that may be clinically important
        + breast cancer-specific survival (HR 1.14, 95% CI 0.54-2.39) in analysis of 2 trials, but CI includes possibility of benefit or harm
      * primary endocrine therapy associated with increased local failure (HR 3.26, 95% CI 2.2-4.82) in analysis of 3 trials
    - Reference - [36718056Br J Surg 2023 Mar 30;110(4):420](http://pubmed.ncbi.nlm.nih.gov/36718056?dopt=Abstract)
  + TOPIC\_Y2P\_FHN\_DMB\_\_LI\_V5B\_R3K\_SPBEU05242105/24/2021 02:03:57 PMevidenceUpdatestandardGeriatrics Oncologic\_DiseaseCARG-BC score helps stratify risk of grade 3-5 chemotherapy toxicity in adults ≥ 65 years old with early-stage breast cancer having standard chemotherapy regimen (J Clin Oncol 2021 Feb 20)

**Cancer and Aging Research Group-Breast Cancer (CARG-BC) score helps stratify risk of grade 3-5 chemotherapy toxicity in adults ≥ 65 years old with early-stage breast cancer having standard chemotherapy regimen (**[**level 1 [likely reliable] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Prediction Rule[J Clin Oncol 2021 Feb 20;39(6):608](http://pubmed.ncbi.nlm.nih.gov/33444080)

studySummary

* + - Prediction Rulebased on prognostic cohort study with independent derivation and validation cohorts
    - derivation cohort included 283 patients ≥ 65 years old (median age 70 years, 98.9% women) with stage I-III breast cancer scheduled for neoadjuvant or adjuvant standard chemotherapy at 1 of 16 institutions (24 patients with missing data were excluded from model development)
    - validation cohort included 190 similar patients (median age 70 years, 100% women) from same institutions
    - overall, 87.7% had polychemotherapy, 82.7% had treatment in adjuvant setting, 74.2% had prophylactic white blood cell growth factor therapy, 33.8% had anthracycline, 4.4% had prior radiation therapy, and 2.5% had reduced-dose chemotherapy
    - 46.2% had grade 3-5 chemotherapy toxicity in derivation cohort and 44.7% in validation cohort
    - CARG-BC score derived using 8 factors significantly associated with grade 3-5 chemotherapy toxicity in derivation cohort (total score 0-24 points)
      * patient and tumor characteristics
        + stage II or III breast cancer = 3 points
        + ≥ 1 fall in past 6 months = 4 points
        + "Does your health limit you in walking > 1 mile?"

somewhat or very limited = 3 points

not limited at all = 0 points

* + - * + "How often is someone available to give you good advice about a crisis?"

none, little, or some of time = 3 points

most or all of time = 0 points

* + - * laboratory tests
        + abnormal liver function (normal defined as all liver tests within normal limits for ranges at each institution) = 3 points
        + hemoglobin ≤ 13 g/dL for men and ≤ 12 g/dL for women = 3 points
      * treatment
        + anthracycline use = 1 point
        + planned treatment duration > 3 months = 4 points
    - risk of grade 3-5 chemotherapy toxicity

| Grade 3-5 Chemotherapy Toxicity by Risk Category in Derivation and Validation Cohorts | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Risk Category** | **Score** | **Derivation Cohort** | | **Validation Cohort** | |
| **Number of Patients** | **Grade 3-5 Chemotherapy Toxicity** | **Number of Patients** | **Grade 3-5 Chemotherapy Toxicity** |
| Low | 0-5 points | 93 | 19% | 59 | 27% |
| Intermediate | 6-11 points | 159 | 54% | 98 | 45% |
| High | ≥ 12 points | 31 | 87% | 33 | 76% |

* + - secondary outcomes in analysis of combined derivation and validation cohorts comparing CARB-BC score low- vs. intermediate- vs. high-risk groups (p < 0.001 for each comparing low- vs. combined intermediate- and high-risk groups)
      * hospitalization in 11% vs. 27% vs. 38%
      * early discontinuation in 13% vs. 26% vs. 39%
      * dose reduction in 14% vs. 25% vs. 38%
      * dose delay in 9% vs. 30% vs. 50%
    - PubMed33444080Journal of clinical oncology : official journal of the American Society of Clinical OncologyJ Clin Oncol20210220396608-618608Reference - HOPE with Breast Cancer study ([J Clin Oncol 2021 Feb 20;39(6):608](http://pubmed.ncbi.nlm.nih.gov/33444080))
  + TOPIC\_Y2P\_FHN\_DMB\_\_LI\_VXW\_PVY\_NXBEU05222305/22/2023 09:20:25 AMevidenceUpdatestandardOncologic\_Diseaseamong patients aged 65-86 years with stage I-III breast cancer and HER2 negative disease, lower performance status (Karnofsky Score < 90), treatment with anthracycline-based or CMF regimen, and age ≥ 76 years each associated with increased risk of receiving lower relative dose intensity (low RDI) of neoadjuvant or adjuvant chemotherapy (J Clin Oncol 2023 Jan 10)

**among patients aged 65-86 years with stage I-III breast cancer and HER2 negative disease, lower performance status (Karnofsky Score < 90), treatment with anthracycline-based or CMF regimen, and age ≥ 76 years each associated with increased risk of receiving lower relative dose intensity (low RDI) of neoadjuvant or adjuvant chemotherapy**

Cohort Study[J Clin Oncol 2023 Jan 10;41(2):316](https://pubmed.ncbi.nlm.nih.gov/36455189)

studySummary

* + - Cohort Studybased on cohort study
    - 501 patients ≥ 65 years old from HOPE with Breast Cancer study receiving neoadjuvant (17%) or adjuvant (83%) chemotherapy for stage I-III breast cancer were assessed
    - 322 patients aged 65-86 years (median 69 years, 74% non-Hispanic White) without HER2 positive disease or HER2 equivocal disease treated with trastuzumab, treatment with nonstandard regimens, upfront dose reduction, or change of treatment after treatment initiation were included in analysis
    - chemotherapy regimens included docetaxel plus cylcophosphamide (TC) in 47%, anthracycline-based regimens in 47%, and CMF in 7%
    - 21% received low RDI of chemotherapy, defined as RDI < 85% of intended standard dose
    - factors associated with increased risk of low RDI in multivariate analysis
      * physician-rated Karnofsky Performance Status < 90 (adjusted odds ratio [OR] 4.32, 95% CI 1.98-9.42)
      * anthracycline-based regimens or CMF compared to TC (adjusted OR 3.47, 95% CI 1.71-7.05)
      * age ≥ 76 years (adjusted OR 2.57, 95% CI 1.12-5.91)
    - PubMed36455189Journal of clinical oncology : official journal of the American Society of Clinical OncologyJ Clin Oncol20230110412316-326316Reference - [J Clin Oncol 2023 Jan 10;41(2):316](https://pubmed.ncbi.nlm.nih.gov/36455189)

Treatment Considerations for Metastatic Breast Cancer in Older Women

* management strategies based on subtype of disease
  + for women with HR-positive/HER2-negative disease
    - endocrine therapy should be standard modality
    - aromatase inhibitor preferable to tamoxifen (due to no elevated risk of elevated risk for thromboembolism or uterine cancer)
    - for first-line therapy, addition of palbociclib to endocrine therapy reported to increase progression-free survival
    - for second-line therapy. addition of palbociclib and everolimus to endocrine therapy may improve progression-free survival but limited evidence on survival benefits and toxicity profiles in older women
  + for women refractory to endocrine therapy or with HR-negative/HER2-negative (triple negative) disease
    - palliative chemotherapy may be appropriate, especially in symptomatic disease
    - possible chemotherapy agents
      * capecitabine (relatively safe for older women)
      * weekly paclitaxel (but serious toxicities reported in 15%)
      * albumin-bound paclitaxel
      * eribulin (reported to have increased risk of neuropathy)
      * liposomal doxorubicin
      * gemcitabine
  + for women with HER2-positive disease
    - therapy options may include
      * trastuzumab monotherapy (higher risk of cardiac toxicity than in younger women)
      * taxane plus trastuzumab (higher risk of cardiac toxicity than in younger women)
      * taxane plus trastuzumab and pertuzumab reported to increase survival compared to taxane plus trastuzumab (higher risk of cardiac toxicity than in younger women)
      * ado-trastuzumab emtansine (reported to have favorable toxicity profile)
    - limited evidence of all therapy options in older women
  + PubMed26869650Journal of oncology practiceJ Oncol Pract20160201122123-32123Reference - [J Oncol Pract 2016 Feb;12(2):123](http://pubmed.ncbi.nlm.nih.gov/26869650)
* palliative and supportive care
  + early palliative care with team including primary care physician, social worker, and palliative care specialist helpful for improving quality of life and survival
  + referral for early hospice care
    - may be appropriate if risk of cancer therapy outweighs benefits, especially for women with metastatic disease
    - may improve survival and support for patients and families
  + PubMed26869650Journal of oncology practiceJ Oncol Pract20160201122123-32123Reference - [J Oncol Pract 2016 Feb;12(2):123](http://pubmed.ncbi.nlm.nih.gov/26869650)

Complications and Prognosis

Prognosis

Complications

* **survivors of breast cancer have modestly increased risk for clinical fractures**

Cohort Study[mdc15767532pArch Intern Med 2005 Mar 14;165(5):552](http://pubmed.ncbi.nlm.nih.gov/15767532?dopt=Abstract)

studySummary

* + based on prospective 5-year follow-up of 5,298 breast cancer survivors and 80,848 women with no cancer history at baseline Cohort Study
  + fracture was assessed through annual self-reports, with hip fracture confirmed by medical record review
  + compared to women with no cancer history, breast cancer survivors had higher incidence of
    - forearm or wrist fracture (adjusted hazard ratio [HR] 1.4, 95% CI 1.2-1.6)
    - fracture other than hip, vertebral, forearm, or wrist (HR 1.3, 95% CI 1.2-1.4)
    - vertebral fracture in women diagnosed before age 55 years (HR 1.8, 95% CI 1.3-2.5)
    - all fractures combined (HR 1.3, 95% CI 1.2-1.4)
  + PubMed15767532Archives of internal medicine20050314Arch Intern Med1655552552 Reference - [mdc15767532pArch Intern Med 2005 Mar 14;165(5):552](http://pubmed.ncbi.nlm.nih.gov/15767532?dopt=Abstract)
* **primary invasive breast cancer associated with increased risk of second primary cancer**

Systematic Review[25448459Gynecol Oncol 2015 Jan;136(1):158](http://pubmed.ncbi.nlm.nih.gov/25448459?dopt=Abstract)

studySummary

* + based on systematic review of observational studies Systematic Review
  + systematic review of 15 retrospective cohort studies evaluating risk of second primary cancer in 1,433,780 women with primary invasive breast cancer
  + patient population, primary cancer definition, and types of second primary cancers varied across studies
  + compared to general population, primary invasive breast cancer associated with increased risk of second primary cancer (pooled standardized incidence ratio 1.15, 95% CI 1.04-1.27) in analysis of 13 studies with 1,135,517 women, results limited by significant heterogeneity
  + in subgroup analyses
    - women < 50 years old at breast cancer diagnosis had significantly increased risk of second primary cancer compared to women ≥ 50 years old
    - similar risk of second primary cancer regardless of time since breast cancer diagnosis (< 10 years or ≥ 10 years)
  + PubMed25448459Gynecologic oncology20150101Gynecol Oncol1361158158 Reference - [25448459Gynecol Oncol 2015 Jan;136(1):158](http://pubmed.ncbi.nlm.nih.gov/25448459?dopt=Abstract)
* complications of breast surgery include
  + bleeding
  + infection (cellulitis or abscess)
  + seroma
  + lymphedema
  + nerve injury
* risk for cardiovascular diseases increased by some breast cancer treatments
  + radiation therapy to left chest wall - increased risk for cardiovascular events
  + aromatase inhibitors - possible increased risk for cardiovascular events
  + [tamoxifen](https://dpa-pde-oxford.shinyapps.io/drug-monograph/tamoxifen) - increased risk for deep vein thrombosis and cerebrovascular disease
  + anthracyclines - increased risk for heart failure
  + [trastuzumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/trastuzumab) - increased risk for heart failure
  + risk increased with tamoxifen
  + Reference - [17568031N Engl J Med 2007 Jun 14;356(24):2505](http://pubmed.ncbi.nlm.nih.gov/17568031?dopt=Abstract), commentary can be found in [17823995N Engl J Med 2007 Sep 6;357(10):1053](http://pubmed.ncbi.nlm.nih.gov/17823995?dopt=Abstract)
* case report and literature review of paraneoplastic cerebellar degeneration as presentation of breast cancer can be found in [a9h35703500pInt Semin Surg Oncol 2008 Apr 21;5:8](http://pubmed.ncbi.nlm.nih.gov/18426566?dopt=Abstract)[full-text](http://www.issoonline.com/content/5/1/8)
* paraneoplastic stiff person syndrome and limbic encephalitis with anti-amphiphysin antibodies associated with invasive ductal carcinoma in case report ([22931320N Engl J Med 2012 Aug 30;367(9):851](http://pubmed.ncbi.nlm.nih.gov/22931320?dopt=Abstract))

Prognosis

Survival and Mortality

* **estimated global breast cancer mortality 626,679 in 2018**

Population-based Surveillance[CA Cancer J Clin 2018 Nov;68(6):394](http://pubmed.ncbi.nlm.nih.gov/30207593?dopt=Abstract)

studySummary

* + based on population-based cancer registries, vital registration data, and mortality data from 185 countries or territories with total population > 150,000 during 2018Population-based Surveillance
  + mortality
    - estimated global breast cancer mortality 626,679
    - age-standardized rate (ASR) 13 per 100,000 women
    - cumulative global lifetime risk of death (ages 0-74 years) 1.41%

| Estimated Global Breast Cancer Mortality by Gl obal Region, 2018 | |
| --- | --- |
| **Region** | **Age-Standardized Rates per 100,000** |
| **Americas** | |
| North America | 12.6 |
| Central America | 10.1 |
| Caribbean | 18.1 |
| South America | 13.4 |
| **Africa** |  |
| Northern Africa | 18.4 |
| Western Africa | 17.8 |
| Middle Africa | 15.8 |
| Eastern Africa | 15.4 |
| Southern Africa | 15.6 |
| **Europe** | |
| Western Europe | 15.5 |
| Northern Europe | 14.1 |
| Southern Europe | 13.3 |
| Eastern Europe | 15.5 |
| **Asia** | |
| Western Asia | 13.6 |
| South Central Asia | 13.6 |
| Eastern Asia | 8.6 |
| South-Eastern Asia | 14.1 |
| **Oceana** | |
| Australia/New Zealand | 12.6 |
| Melanesia | 25.5 |
| Micronesia/Polynesia | 19.1 |

* + CA: a cancer journal for clinicians20181101CA Cancer J Clin686394394 Reference - GLOBOCAN 2018 ([CA Cancer J Clin 2018 Nov;68(6):394](http://pubmed.ncbi.nlm.nih.gov/30207593?dopt=Abstract))
* TOPIC\_SB4\_F3T\_1MB\_\_LI\_WKP\_WFQ\_DVBEU10112210/11/2022 12:43:15 PMevidenceUpdatestandardOncologic\_Disease5-year age-adjusted breast cancer mortality 128.3 per 100,000 female persons in United States during 2016-2020; highest breast cancer mortality in Black persons compared to persons with other races or ethnicities (CA Cancer J Clin 2022 Oct 3 early online)

**5-year age-adjusted breast cancer mortality 128.3 per 100,000 person-years for female persons in United States during 2016-2020; highest breast cancer mortality in Black persons compared to persons of other races or ethnicities**

Population-based Surveillance[5-year age-adjusted incidence stratified by race](https://seer.cancer.gov/statistics-network/explorer/application.html?site=55&data_type=1&graph_type=10&compareBy=race&chk_race_1=1&chk_race_6=6&chk_race_5=5&chk_race_4=4&chk_race_9=9&chk_race_8=8&series=9&sex=3&age_range=1&stage=101&advopt_precision=1&advopt_show_ci=on&hdn_view=1#tableWrap)Population-based Surveillance[CA Cancer J Clin 2022 Oct 3 early online](https://pubmed.ncbi.nlm.nih.gov/36190501)[Full Text](https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21754)

studySummary

* + Population-based SurveillancePopulation-based Surveillance based on population-based surveillance
  + annual population-based surveillance information on incidence (during 2015-2019) and mortality (during 2016-2020) of breast cancer in female persons in the United States from Surveillance, Epidemiology, and End Results (SEER) database was evaluated
    - incidence and mortality rates were age-adjusted to standard population of United States in 2000
    - 5-year age-adjusted incidence and mortality of breast cancer

| 5-year Age-adjusted Incidence (in 2015-2019) and Mortality Rates (in 2016-2020) by Race and Ethnicity | | |
| --- | --- | --- |
| **Race/Ethnicity** | **Incidence (per 100,000 Person-years)** | **Mortality (per 100,000 Person-years)** |
| All races | 128.3 | 19.6 |
| American Indian and Alaska Native (non-Hispanic) | 111.3 | 17.6 |
| Asian and Pacific Islander (non-Hispanic) | 106.9 | 11.7 |
| Black (non-Hispanic) | 129.6 | 27.6 |
| Hispanic (any race) | 99.9 | 13.7 |
| White (non-Hispanic) | 137.6 | 19.7 |

* + - PubMed36190501CA: a cancer journal for cliniciansCA Cancer J Clin20221003Reference - SEER Cancer Statistics Review (accessed 2022-10-11) on
      * [5-year age-adjusted incidence stratified by race](https://seer.cancer.gov/statistics-network/explorer/application.html?site=55&data_type=1&graph_type=10&compareBy=race&chk_race_1=1&chk_race_6=6&chk_race_5=5&chk_race_4=4&chk_race_9=9&chk_race_8=8&series=9&sex=3&age_range=1&stage=101&advopt_precision=1&advopt_show_ci=on&hdn_view=1#tableWrap)
      * [5-year age-adjusted mortality stratified by race](https://seer.cancer.gov/statistics-network/explorer/application.html?site=55&data_type=2&graph_type=10&compareBy=race&chk_race_1=1&chk_race_6=6&chk_race_5=5&chk_race_4=4&chk_race_9=9&chk_race_8=8&series=9&sex=3&age_range=1&advopt_precision=1&advopt_show_ci=on&hdn_view=1#tableWrap)
  + during 2016-2020, compared to White persons (non-Hispanic), higher mortality in Black persons (non-Hispanic)
    - for ages 20-29 years (mortality rate ratio [MRR] 2.36, 95% CI not reported, p < 0.05)
    - for ages 30-39 years (MRR 1.86, 95% CI not reported, p < 0.05)
    - for ages 40-49 years (MRR 1.84, 95% CI not reported, p < 0.05)
    - for ages 50-59 years (MRR 1.67, 95% CI not reported, p < 0.05)
    - for ages 60-69 years (MRR 1.45, 95% CI not reported, p < 0.05)
    - for ages 70-79 years (MRR 1.23, 95% CI not reported, p < 0.05)
    - age ages ≥ 80 years (MRR 1.1, 95% CI not reported, p < 0.05)
    - PubMed36190501CA: a cancer journal for cliniciansCA Cancer J Clin20221003Reference - [CA Cancer J Clin 2022 Oct 3 early online](https://pubmed.ncbi.nlm.nih.gov/36190501)[full-text](https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21754)
* age-standardized mortality 20.9 per 100,000 person-years for breast cancer in women in Australia in 2014 ([a9h108929809t pcxh108929809t pmdc26264473pAsia Pac J Clin Oncol 2015 Sep;11(3):208](http://pubmed.ncbi.nlm.nih.gov/26264473?dopt=Abstract) )
* 5-year relative survival rates from CONCORD study (1.9 million adults with first primary invasive cancer from 101 cancer registries in 31 countries) can be found in [18639491Lancet Oncol 2008 Aug;9(8):730](http://pubmed.ncbi.nlm.nih.gov/18639491?dopt=Abstract)
* 20-year cause-specific survival with inflammatory breast cancer increased from 9% of 134 patients from 1975 to 1977 to 20% of 416 patients from 1993 to 1995 ([mnh16242046paph31614021pa9h31614021pafh31614021pcxh31614021pmdc16242046pBMC Cancer 2005 Oct 22;5:137](http://pubmed.ncbi.nlm.nih.gov/16242046?dopt=Abstract) [full-text](http://www.biomedcentral.com/1471-2407/5/137))
* **estimated progression-free survival 7.6 months and overall survival 21.7 months in women starting first-line chemotherapy for metastatic breast cancer**

Systematic Review[mdc21189397pJ Clin Oncol 2011 Feb 1;29(4):456](http://pubmed.ncbi.nlm.nih.gov/21189397?dopt=Abstract)

studySummary

* + based on systematic review without assessment of trial quality Systematic Review
  + systematic review of 36 randomized trials evaluating survival outcomes in 13,083 women having first-line chemotherapy for metastatic breast cancer
  + survival in women with metastatic breast cancer having first-line chemotherapy in analysis of 36 trials with 13,083 women
    - mean of median progression-free survival 7.6 months (interquartile range 6 months-9 months)
    - mean of median overall survival 21.7 months (interquartile range 18.2 months-24 months)
  + overall survival significantly longer in trials with higher proportions of women with estrogen-receptor positive tumors (p = 0.001) and in trials of trastuzumab-treated HER2-positive tumors (p = 0.001)
  + PubMed21189397Journal of clinical oncology : official journal of the American Society of Clinical Oncology20110201J Clin Oncol294456456 Reference - [mdc21189397pJ Clin Oncol 2011 Feb 1;29(4):456](http://pubmed.ncbi.nlm.nih.gov/21189397?dopt=Abstract) , editorial can be found in [mdc21189394pJ Clin Oncol 2011 Feb 1;29(4):347](http://pubmed.ncbi.nlm.nih.gov/21189394?dopt=Abstract)

Prognostic tools

* [Adjuvant! clinical prognostic tool](http://www.adjuvantonline.com/index.jsp)
  + requires online registration by medical professional
  + accurately predicts 10-year overall survival, breast cancer-specific survival, and event-free survival
  + predicts recurrence rates (based on standard efficacy) after adjuvant chemotherapy, endocrine therapy, or both to predict amount of absolute benefit of therapy
  + validated in study with 4,083 women with stage I and II breast cancer
  + References
    - [mdc15837986pJ Clin Oncol 2005 Apr 20;23(12):2716](http://pubmed.ncbi.nlm.nih.gov/15837986?dopt=Abstract) , commentary can be found in Evidence-Based Medicine 2005 Nov-Dec;10(6):186
    - [19801202Lancet Oncol 2009 Nov;10(11):1070](http://pubmed.ncbi.nlm.nih.gov/19801202?dopt=Abstract)
  + Adjuvant! clinical prognostic tool does not provide risk predictions based on human epidermal growth factor receptor type 2 (HER2/neu) status.
* **Adjuvant! may not accurately predict survival in elderly women with breast cancer**

Cohort Study[24836274Lancet Oncol 2014 Jun;15(7):722](http://pubmed.ncbi.nlm.nih.gov/24836274?dopt=Abstract)

studySummary

* + based on validation cohort study with 2,012 women ≥ 65 years old with breast cancer fulfilling Adjuvant! criteria Cohort Study
  + 2,012 women ≥ 65 years old with breast cancer fulfilling Adjuvant! criteria
  + 45% died and 16% had recurrence during follow-up
  + Adjuvant! overestimated 10-year survival when using comorbidity status "average for age" and underestimated survival when using individualized comorbidity status
  + PubMed24836274The Lancet. Oncology20140601Lancet Oncol157722722 Reference - [24836274Lancet Oncol 2014 Jun;15(7):722](http://pubmed.ncbi.nlm.nih.gov/24836274?dopt=Abstract), editorial can be found in [24872094Lancet Oncol 2014 Jun;15(7):672](http://pubmed.ncbi.nlm.nih.gov/24872094?dopt=Abstract)
* **in women < 55 years old with lymph node-negative breast cancer and Adjuvant!-predicted 10-year breast cancer-specific survival ≥ 95%, mitotic activity index may further stratify high-risk and low-risk patients (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Diagnostic Cohort Study[mdc21189388pJ Clin Oncol 2011 Mar 1;29(7):852](http://pubmed.ncbi.nlm.nih.gov/21189388?dopt=Abstract)

studySummary2

* + based on derivation cohort study without validation Diagnostic Cohort Study
  + 516 women < 55 years old with lymph node-negative breast cancer were assessed using mitotic activity index (MAI) and Adjuvant! prognostic tool
  + median follow-up 118 months
  + 122 women had Adjuvant!-predicted 10-year breast cancer-specific survival ≥ 95%
    - observed breast cancer-specific survival 91%
    - breast cancer-specific survival stratified by MAI (p < 0.001)
      * 99% in 74 women with MAI < 3
      * 79% in 48 women with MAI ≥ 3
  + 394 women had Adjuvant!-predicted 10-year breast cancer-specific survival < 95%
    - observed breast cancer-specific survival 74%
    - breast cancer-specific survival stratified by MAI (p < 0.001)
      * 92% in 86 women with MAI < 3
      * 70% in 308 women with MAI ≥ 3
  + PubMed21189388Journal of clinical oncology : official journal of the American Society of Clinical Oncology20110301J Clin Oncol297852852 Reference - [mdc21189388pJ Clin Oncol 2011 Mar 1;29(7):852](http://pubmed.ncbi.nlm.nih.gov/21189388?dopt=Abstract)
* [Finprog](http://www.finprog.org/) is an online system to enter individual patient data and predict overall survival based on data from 2,032 breast cancer patients in Finland followed for 8-11 years ([12511459BMJ 2003 Jan 4;326(7379):29](http://pubmed.ncbi.nlm.nih.gov/12511459?dopt=Abstract)[full-text](http://www.bmj.com/content/326/7379/29.full)), editorial can be found in [12511432BMJ 2003 Jan 4;326(7379):2](http://pubmed.ncbi.nlm.nih.gov/12511432?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/12511432/), commentary can be found in [12689987BMJ 2003 Apr 12;326(7393):822](http://pubmed.ncbi.nlm.nih.gov/12689987?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/12689987/)
* **prognostic score predicts 5-year disease-specific survival after surgery as first intervention for stage I-IIIA breast cancer (**[**level 1 [likely reliable] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Diagnostic Cohort Study[mdc22084362pJ Clin Oncol 2011 Dec 10;29(35):4654](http://pubmed.ncbi.nlm.nih.gov/22084362?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/22084362/)

studySummary1

* + based on derivation and validation cohort study Diagnostic Cohort Study
  + derivation cohort included 3,728 patients with stage I-IIIA breast cancer who had surgery as first intervention and who were followed for mean of 6.6 years
  + validation cohort included 26,711 similar patients who were followed for mean of 5.9 years
  + 5-year disease-specific survival
    - 97.4% for derivation cohort
    - 93.2% for validation cohort
  + 6 prognostic scores based on 6 risk factors were evaluated in derivation cohort
  + risk factors associated with 5-year disease-specific survival in derivation cohort and points assigned to derive prognostic score (total score 0-4 points)
    - pathologic stage - 0 points if stage I, 1 point if stage IIA-IIB, 2 points if stage IIIA
    - nuclear grade - 0 points if grade I-II, 1 point if grade III
    - estrogen receptor status - 0 points if positive, 1 point if negative
  + 5-year disease-specific survival by prognostic score in derivation and validation cohorts

| Results | | |
| --- | --- | --- |
| **Score** | **Derivation Cohort** | **Validation Cohort** |
| 0 points | 99.5% | 98.5% |
| 1 point | 98.9% | 95.2% |
| 2 points | 96.1% | 86.3% |
| 3 points | 86.2% | 72.2% |
| 4 points | 65.2% | 54.2% |

* + PubMed22084362Journal of clinical oncology : official journal of the American Society of Clinical Oncology20111210J Clin Oncol293546544654 Reference - [mdc22084362pJ Clin Oncol 2011 Dec 10;29(35):4654](http://pubmed.ncbi.nlm.nih.gov/22084362?dopt=Abstract) [full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/22084362/)
* **lymph vascular space invasion tumor burden ≥ 60 has high specificity but low sensitivity for prediction of disease relapse in women with node-negative breast cancer (**[**level 1 [likely reliable] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Diagnostic Cohort Study[24114856Ann Oncol 2013 Dec;24(12):2994](http://pubmed.ncbi.nlm.nih.gov/24114856?dopt=Abstract)

studySummary1

* + based on derivation and validation cohort study Diagnostic Cohort Study
  + derivation cohort included 120 women with node-negative breast cancer who had immunohistochemical stained breast cancer tissue samples assessed for lymph vascular space invasion tumor burden (number of lymph vascular space invasion foci × number of tumor cells in largest tumor embolus)
  + validation cohort included 238 similar women
  + prevalence of disease relapse was 38.3% overall
  + lymph vascular space invasion tumor burden ≥ 60 was optimal cutoff for prediction of disease relapse in comparative analysis
  + for prediction of disease relapse, lymph vascular space invasion tumor burden with cutoff ≥ 60 had sensitivity 23.9% and specificity 94.6%
  + lymph vascular space invasion tumor burden ≥ 60 associated with reduced survival compared to lymph vascular space invasion tumor burden < 60 in analysis of validation cohort (hazard ratio for mortality 2.4, 95% CI 1.37-4.09)
  + PubMed24114856Annals of oncology : official journal of the European Society for Medical Oncology20131201Ann Oncol241229942994 Reference - [24114856Ann Oncol 2013 Dec;24(12):2994](http://pubmed.ncbi.nlm.nih.gov/24114856?dopt=Abstract)

Prognostic factors

Race and ethnicity

* **breast cancer mortality generally highest among non-Hispanic Black women and lowest among Asian/Pacific Islander women in the United States**

Population-based Surveillance[CA Cancer J Clin 2019 Jan;69(1);7](http://pubmed.ncbi.nlm.nih.gov/30620402?dopt=Abstract)[Full Text](https://onlinelibrary.wiley.com/doi/full/10.3322/caac.21551)

studySummary

* + based on annual report of cancer status in United States with data 2012-2016 for death ratesPopulation-based Surveillance
  + age-adjusted breast cancer death rates per 100,000 women by race/ethnicities
    - all women 20.6
    - non-Hispanic Black women 28.9
    - non-Hispanic White women 20.6
    - American Indian/Alaska Native women 14.5
    - Hispanic women 14.3
    - Asian/Pacific Islander women 11.3
  + CA: a cancer journal for clinicians20190101CA Cancer J Clin7 Reference - [CA Cancer J Clin 2019 Jan;69(1);7](http://pubmed.ncbi.nlm.nih.gov/30620402?dopt=Abstract)[full-text](https://onlinelibrary.wiley.com/doi/full/10.3322/caac.21551)
* **5-year relative survival rates by stage and race in United States from 2008 to 2014**

|  | **Localized Disease\*** | **Regional Disease\*\*** | **Metastatic Disease\*\*\*** |
| --- | --- | --- | --- |
| All women | 99% | 85% | 27% |
| White women | 99% | 86% | 28% |
| Black women | 95% | 77% | 20% |
| \* Localized disease is stage I and II if negative lymph node(s).\*\* Regional disease is stage II and III if positive lymph node(s).\*\*\* Metastatic disease is stage IV. | | | |

* + Reference - [CA Cancer J Clin 2019 Jan;69(1);7](http://pubmed.ncbi.nlm.nih.gov/30620402?dopt=Abstract)[full-text](https://onlinelibrary.wiley.com/doi/full/10.3322/caac.21551)
* **mortality of breast cancer may be highest in African American women in United States**
  + female breast cancer mortality by ethnicity in United States

| Table 7: Incidence and Mortality in United States | |
| --- | --- |
| **Ethnic Group** | **Mortality Rates per 100,000 (2010-2014)** |
| Non-Hispanic White women | 21.1 |
| African American women | 30 |
| Hispanic/Latina women | 14.4 |
| American Indian/Alaska Native women | 14.1 |
| Asian American/Pacific Islander women | 11.3 |

* + Reference - [mnh28055103pcxh120669112t pmdc28055103pCA Cancer J Clin 2017 Jan;67(1):7](http://pubmed.ncbi.nlm.nih.gov/28055103?dopt=Abstract) [full-text](http://onlinelibrary.wiley.com/doi/10.3322/caac.21387/full)
* **breast cancer mortality higher among Black women than White women < 65 years old in the United States**

Cohort Study[19084242J Surg Res 2009 May 1;153(1):105](http://pubmed.ncbi.nlm.nih.gov/19084242?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/19084242/)

studySummary

* + based on retrospective cohort study Cohort Study
  + 20,424 Black women and 204,506 White women diagnosed with first primary breast cancer from 1988 to 2003 were analyzed
  + hazard ratios comparing Black women vs. White women
    - for breast cancer mortality 1.9 (95% CI 1.83-1.96)
    - all-cause mortality 1.52 (95% CI 1.48-1.55)
  + Black women had increased risk of breast cancer mortality for each stage 0-IV and unstaged cancer and for each age group < 40 years old, aged 40-49 years, and aged 50-64 years
  + increased risk not found for Black women ≥ 65 years old
  + PubMed19084242The Journal of surgical research20090501J Surg Res1531105105 Reference - [19084242J Surg Res 2009 May 1;153(1):105](http://pubmed.ncbi.nlm.nih.gov/19084242?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/19084242/)
* **breast cancer mortality at 7 years after diagnosis with stage I breast cancer appears higher in Black women than in non-Hispanic White women in the United States**

Population-based Surveillance[cxh100436460pmdc25585328pJAMA 2015 Jan 13;313(2):165](http://pubmed.ncbi.nlm.nih.gov/25585328?dopt=Abstract)

studySummary

* + based on analysis of 373,563 women (mean age 61 years) with invasive breast cancer diagnosed from 2004 to 2011 in Surveillance, Epidemiology, and End Results (SEER) database in United States Population-based Surveillance
  + median follow-up 38 months
  + stage I breast cancer at diagnosis in 48%
  + actuarial 7-year mortality due to stage I breast cancer 6.2% in Black women vs. 3% in non-Hispanic White women (adjusted hazard ratio [HR] 1.57, 95% CI 1.4-1.75)
  + no significant differences in mortality comparing non-Hispanic White women vs. Hispanic women, or women of Japanese or South Asian descent
  + mortality significantly lower in women of Chinese descent vs. non-Hispanic White women
  + presence of nodal metastases and distant metastases more common with breast cancer tumors ≤ 2 cm in African American women compared to non-Hispanic White women (p < 0.001 for each)
  + PubMed25585328JAMA20150113JAMA3132165165 Reference - [cxh100436460pmdc25585328pJAMA 2015 Jan 13;313(2):165](http://pubmed.ncbi.nlm.nih.gov/25585328?dopt=Abstract) , editorial can be found in [cxh100436455pmdc25585323pJAMA 2015 Jan 13;313(2):141](http://pubmed.ncbi.nlm.nih.gov/25585323?dopt=Abstract)
* **differences in survival between Black and White older women with breast cancer may be associated with differences in presentation factors (comorbidities and tumor characteristics) and differences in treatment**

Cohort Study[mdc23917289pJAMA 2013 Jul 24;310(4):389](http://pubmed.ncbi.nlm.nih.gov/23917289?dopt=Abstract)

studySummary

* + based on cohort studyCohort Study
  + 7,375 Black women ≥ 65 years old with breast cancer diagnosed from 1991 to 2005 were compared to 22,125 matched White women with breast cancer from the United States SEER database
    - mean age at diagnosis 76 years
    - matching was based on
      * demographic factors (including age and year of diagnosis)
      * presentation factors at diagnosis (including comorbidities and tumor characteristics) plus demographics
      * treatment received plus presentation factors plus demographics
  + 5-year overall survival in Black women was 55.9%
  + difference in 5-year survival in White women compared to Black women (p < 0.001 for each)
    - +12.9% in White women matched for demographics alone
    - +4.4% in White women matched for presentation factors plus demographics
    - +3.6% in White women matched for treatment received plus presentation factors plus demographics
  + PubMed23917289JAMA20130724JAMA3104389389 Reference - [mdc23917289pJAMA 2013 Jul 24;310(4):389](http://pubmed.ncbi.nlm.nih.gov/23917289?dopt=Abstract) , editorial can be found in [mdc23917286pJAMA 2013 Jul 24;310(4):376](http://pubmed.ncbi.nlm.nih.gov/23917286?dopt=Abstract)
* **British women of Black race with breast cancer may present at a younger age and have more aggressive tumors than British women of White race**

Cohort Study[mnh18182985paph28611088pa9h28611088pbyh28611088pafh28611088pcxh28611088pmdc18182985pBr J Cancer 2008 Jan 29;98(2):277](http://pubmed.ncbi.nlm.nih.gov/18182985?dopt=Abstract)[Full Text](http://dx.doi.org/10.1038/sj.bjc.6604174)

studySummary

* + based on retrospective cohort study Cohort Study
  + 445 women with invasive breast cancer presenting to 1 clinic in London from 1994 to 2005
  + comparing Black women vs. White women
    - median age at presentation 46 years vs. 67 years presentation at younger age (p = 0.001)
    - presence of grade 3 tumors in 62% vs. 42% (p = 0.02)
    - proportion of women < 60 years old who have
      * estrogen receptor (ER)-negative tumors 39% vs. 21% (p = 0.03)
      * triple-negative tumors 25% vs. 12% (p = 0.09)
    - Black women had poorer survival with tumors ≤ 2 cm (hazard ratio 2.9, 95% CI 0.98-8.6, p = 0.05)
  + PubMed18182985British journal of cancer20080129Br J Cancer982277277 Reference - [mnh18182985paph28611088pa9h28611088pbyh28611088pafh28611088pcxh28611088pmdc18182985pBr J Cancer 2008 Jan 29;98(2):277](http://pubmed.ncbi.nlm.nih.gov/18182985?dopt=Abstract) [full-text](http://dx.doi.org/10.1038/sj.bjc.6604174)
* **breast cancer diagnosed without screening or during screening interval associated with 80% 10-year survival (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cohort Study[23160783BMJ 2012 Nov 16;345:e7536](http://pubmed.ncbi.nlm.nih.gov/23160783?dopt=Abstract)[Full Text](http://www.bmj.com/content/345/bmj.e7536?view=long&pmid=23160783)

studySummary2

* + based on retrospective cohort study Cohort Study
  + 7,116 women aged 50-72 years with diagnosis of invasive breast cancer in Norway from 1996 to 2006 were evaluated
    - 26% had diagnosis between 1 of 2 mammography screenings or ≤ 2 years and 2 months after last normal screening (interval group)
    - 74% had diagnosis prior to invitation for mammography screening (nonscreened group)
  + at baseline, interval group had slightly more lobular cancers, large tumors (diameter > 20 mm), negative axillary lymph nodes, and stage II (vs. stage I) disease (p < 0.001 for each)
  + mean follow-up of 3.6 years in interval group and 6.3 years in nonscreened group
  + 10-year survival rate 79.1% for women with interval cancers vs. 76.8% for women who did not receive screening (hazard ratio 0.98, 95% CI 0.84-1.15, p = 0.53)
  + PubMed23160783BMJ (Clinical research ed.)20121116BMJ345e7536e7536 Reference - [23160783BMJ 2012 Nov 16;345:e7536](http://pubmed.ncbi.nlm.nih.gov/23160783?dopt=Abstract)[full-text](http://www.bmj.com/content/345/bmj.e7536?view=long&pmid=23160783)

Tumor characteristics and extent

* **larger tumor diameter and greater number of positive nodes at diagnosis each associated with increasing risk of distant recurrence 5-20 years after diagnosis in women with estrogen receptor-positive early stage breast cancer who were disease-free after 5 years of endocrine therapy**

Randomized Trial[29117498N Engl J Med 2017 Nov 9;377(19):1836](http://pubmed.ncbi.nlm.nih.gov/29117498?dopt=Abstract)

studySummary

* + based on meta-analysis of observational data from randomized trials Randomized Trial
  + individual patient data meta-analysis of 88 randomized trials with data to assess risk factors for distant recurrence in 62,923 women with estrogen receptor-positive early stage breast cancer who were disease-free after scheduled endocrine therapy (tamoxifen or aromatase inhibitors)
  + all women were scheduled to receive 5-year endocrine therapy, but authors state that "substantial minority" did not complete treatment
  + rates of distant recurrence 5-20 years after diagnosis
    - stage T1 (tumor diameter ≤ 2 cm)
      * with no nodes involved, 13%
      * with 1-3 nodes involved, 20%
      * with 4-9 nodes involved, 34%
    - stage T2 (tumor diameter 2-5 cm)
      * with no nodes involved, 19%
      * with 1-3 nodes involved, 26%
      * with 4-9 nodes involved, 41%
  + increasing tumor diameter and increasing number of positive nodes at diagnosis each significantly associated with increasing risk of distant recurrence and breast cancer-related death at 5-20 years after diagnosis
  + no significant association between progesterone receptor status or HER2 status and risk of distant recurrence in analysis controlling for tumor diameter and number of nodes
  + PubMed29117498The New England journal of medicine20171109N Engl J Med3771918361836 Reference - [29117498N Engl J Med 2017 Nov 9;377(19):1836](http://pubmed.ncbi.nlm.nih.gov/29117498?dopt=Abstract)
* **risk factors for breast cancer mortality include higher histologic grade, larger tumor size, ipsilateral breast tumor recurrence, and lymphatic invasion**

Cohort Study[16859523Breast Cancer Res 2006 Jul 19;8(4):R44](http://pubmed.ncbi.nlm.nih.gov/16859523?dopt=Abstract)[Full Text](http://breast-cancer-research.com/content/8/4/R44)

studySummary

* + based on prospective cohort study of 1,540 consecutive women aged 18-75 years with node-negative breast cancer followed for up to 12 years Cohort Study
  + 98 ipsilateral breast tumor recurrences (6.4%) and 117 deaths (7.4%) occurred
  + risk factors for ipsilateral breast cancer recurrence included
    - age < 40 years (relative risk [RR] 1.89, 95% CI 1-3.58)
    - presence of intraductal disease (RR 1.81, 95% CI 1.15-2.85)
    - histological grade (G2 or G3 vs. G1) (RR 1.59, 95% CI 0.87-2.94)
  + risk factors for disease-specific mortality included
    - histologic grade (G2 or G3 vs. G1) (RR 8.59, 95% CI 2.09-35.36)
    - tumor size > 2 cm (vs. < 1 cm) (RR 2.94, 95% CI 1.56-5.56)
    - ipsilateral breast tumor recurrence (RR 2.58, 95% CI 1.05-3.64)
    - progesterone receptor status (negative or equivocal vs. positive or unknown) (RR 2.15, 95% CI 1.36-3.39)
    - lymphatic invasion (RR 1.78, 95% CI 1.17-2.72)
  + PubMed16859523Breast cancer research : BCR20060719Breast Cancer Res84R44R44 Reference - [16859523Breast Cancer Res 2006 Jul 19;8(4):R44](http://pubmed.ncbi.nlm.nih.gov/16859523?dopt=Abstract)[full-text](http://breast-cancer-research.com/content/8/4/R44)
* **survival varies with histologic type**

Cohort Study[Arch Intern Med 2003 Oct 13;163(18):2149](http://pubmed.ncbi.nlm.nih.gov/14557212-risk-of-mortality-by-histologic-type-of-breast-cancer-among-women-aged-50-to-79-years/?dopt=Abstract)

studySummary

* + Cohort Study based on retrospective cohort study of 164,958 women aged 50-79 years with 1 of 7 histologic types of invasive breast cancer in 9 cancer registries from 1974 to 1998
  + 80.2% women had invasive ductal carcinoma, 41.3% overall mortality
  + 11.8% had invasive lobular carcinoma, 33% mortality
  + 2.4% had mucinous carcinoma, 34.7% mortality
  + 1.9% had comedocarcinoma, 29.7% mortality
  + 1.8% had medullary carcinoma, 44.8% mortality
  + 1.4% had tubular carcinoma, 18.5% mortality
  + 0.6% had papillary carcinoma, 37.2% mortality
  + PubMed14557212Archives of internal medicineArch Intern Med20031013163182149-532149 Reference - [Arch Intern Med 2003 Oct 13;163(18):2149](http://pubmed.ncbi.nlm.nih.gov/14557212-risk-of-mortality-by-histologic-type-of-breast-cancer-among-women-aged-50-to-79-years/?dopt=Abstract)
* **5-year overall survival 94% with breast cancer immunohistochemical subtype luminal A**

Cohort Study[mnh23892409pcxh89702728pmdc23892409pJ Cancer Res Clin Oncol 2013 Sep;139(9):1569](http://pubmed.ncbi.nlm.nih.gov/23892409?dopt=Abstract)

studySummary

* + based on retrospective cohort study of 3,381 women diagnosed from 2003 through 2005 with 1 of 5 breast cancer immunohistochemical subtypes Cohort Study
  + 5-year overall survival (per subtype)
    - 94.4% with luminal A
    - 89% with luminal B
    - 87% with luminal-HER2
    - 74.8% with HER2-enriched
    - 74.7% with triple-negative
  + luminal A subtype associated with significantly improved overall survival compared to other subtypes in adjusted analyses
  + PubMed23892409Journal of cancer research and clinical oncology20130901J Cancer Res Clin Oncol139915691569 Reference - [mnh23892409pcxh89702728pmdc23892409pJ Cancer Res Clin Oncol 2013 Sep;139(9):1569](http://pubmed.ncbi.nlm.nih.gov/23892409?dopt=Abstract)
  + This time period preceded the use of HER2 targeted therapy in women with early and locally advanced breast cancer. Survival in women with HER2 positive breast cancer and access to HER2 targeted therapy is improving.
* **clinical outcome with infiltrating lobular carcinoma similar to infiltrating ductal carcinoma**

Cohort Study[15084238Breast Cancer Res 2004 Feb 17;6(3):R149](http://pubmed.ncbi.nlm.nih.gov/15084238?dopt=Abstract)[Full Text](http://breast-cancer-research.com/content/6/3/R149)

studySummary

* + based on study of 4,140 patients with infiltrating lobular carcinoma compared to 45,169 patients with infiltrating ductal carcinoma Cohort Study
  + median follow-up of 87 months
  + comparing patients with infiltrating lobular carcinoma vs. patients with infiltrating ductal carcinoma
    - 5-year overall survival 85.6% vs. 84.1%
    - recurrence rate over 5 years 14.3% vs. 16.5% ("disease-free survival" rates did not account for deaths)
    - contralateral breast cancer in 20.9% vs. 11.2% (p < 0.0001)
    - after first recurrence
      * median survival 22 months vs. 19 months (p = 0.002)
      * 5-year overall survival 32.8% vs. 26.7% (p = 0.002)
  + PubMed15084238Breast cancer research : BCR20040217Breast Cancer Res63R149R149 Reference - [15084238Breast Cancer Res 2004 Feb 17;6(3):R149](http://pubmed.ncbi.nlm.nih.gov/15084238?dopt=Abstract)[full-text](http://breast-cancer-research.com/content/6/3/R149)
* **invasive medullary breast tumors associated with higher overall survival than invasive ductal breast tumors**

Cohort Study[22707751Ann Oncol 2012 Nov;23(11):2843](http://pubmed.ncbi.nlm.nih.gov/22707751?dopt=Abstract)[Full Text](http://annonc.oxfordjournals.org/content/23/11/2843.long)

studySummary

* + based on prognostic cohort study Cohort Study
  + 127 women with invasive medullary tumors and 8,096 women with invasive ductal tumors were assessed for recurrence and survival
    - all women were previously included in 1 of 13 trials assessing timing and duration of chemoendocrine therapies in women with early breast cancer
    - 47 women with medullary tumors and 1,407 women with ductal tumors had estrogen-receptor negative grade 3 tumors
    - median duration of follow-up of 14 years
  + comparing medullary tumors to ductal tumors in overall cohort
    - 14-year overall survival 66% vs. 57% (p = 0.03)
    - 14-year distant recurrence-free survival in 76% vs. 64% (p = 0.0005)
  + comparing medullary tumors to ductal tumors in women with estrogen-receptor negative grade 3 tumors
    - 14-year overall survival 74% vs. 54% (p = 0.01)
    - 14-year distant recurrence-free survival in 89% vs. 63% (p = 0.002)
  + PubMed22707751Annals of oncology : official journal of the European Society for Medical Oncology20121101Ann Oncol231128432843 Reference - [22707751Ann Oncol 2012 Nov;23(11):2843](http://pubmed.ncbi.nlm.nih.gov/22707751?dopt=Abstract)[full-text](http://annonc.oxfordjournals.org/content/23/11/2843.long)
* **asymptomatic second tumors associated with improved survival compared to symptomatic tumors in breast cancer survivors (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cohort Study[19297316Ann Oncol 2009 Sep;20(9):1505](http://pubmed.ncbi.nlm.nih.gov/19297316?dopt=Abstract)[Full Text](http://annonc.oxfordjournals.org/content/20/9/1505.long)

studySummary2

* + based on retrospective cohort study Cohort Study
  + 1,044 breast cancer survivors who had second invasive tumor ≥ 6 months after initial diagnosis were followed for median 13.7 years after first diagnosis
  + 67% of women with second cancers were asymptomatic
  + asymptomatic tumors were (compared to symptomatic)
    - smaller (p < 0.001)
    - more likely to be early-stage tumors (p < 0.0001)
    - less likely to be cancer stage pT2 or larger (p < 0.001)
    - fewer node metastases in contralateral cancer (p = 0.0001)
    - associated with increased disease-specific survival from first cancer diagnosis (p < 0.0001)
  + despite mammography being more sensitive than clinical examination (86% vs. 57%, p < 0.0001), 13.8% of second cancer cases were only identified clinically
  + PubMed19297316Annals of oncology : official journal of the European Society for Medical Oncology20090901Ann Oncol20915051505 Reference - [19297316Ann Oncol 2009 Sep;20(9):1505](http://pubmed.ncbi.nlm.nih.gov/19297316?dopt=Abstract)[full-text](http://annonc.oxfordjournals.org/content/20/9/1505.long)
* **in women with metachronous contralateral breast cancer, increased risk of breast cancer-related death with larger tumor size, positive nodal status, and short time interval to development of contralateral cancer**

Cohort Study[cxh82203233pmdc22927521pJ Clin Oncol 2012 Oct 1;30(28):3478](http://pubmed.ncbi.nlm.nih.gov/22927521?dopt=Abstract)

studySummary

* + based on prospective cohort study Cohort Study
  + from a cohort of 42,670 women with breast cancer in Sweden from 1992 to 2008, 803 women who developed metachronous contralateral breast cancer were assessed for factors associated with breast cancer-related mortality
  + 13.4% died from breast cancer in median follow-up of 9.9 years
  + in women with metachronous contralateral breast cancer, risk of breast cancer-related mortality increased with
    - larger tumor size compared to tumors ≤ 2 cm
      * for tumors 2-5 cm, hazard ratio (HR) 2.2 (95% CI 1.3-3.6)
      * for > 5 cm, HR 6.3 (95% CI 3-13)
      * for tumor of any size with extension to chest wall and/or skin, HR 4.1 (95% CI 1.5-12)
    - positive nodal status compared to negative status (HR 2.4, 95% CI 1.5-3.9)
    - contralateral breast cancer ≤ 5 years after primary tumor compared to longer latency (HR 1.7, 95% CI 1.1-2.6)
    - negative estrogen receptor status compared to positive status (HR 2.6, 95% CI 1-4.8)
    - negative progesterone receptor status compared to positive status (HR 2.4, 95% CI 1-5.9)
  + PubMed22927521Journal of clinical oncology : official journal of the American Society of Clinical Oncology20121001J Clin Oncol302834783478 Reference - [cxh82203233pmdc22927521pJ Clin Oncol 2012 Oct 1;30(28):3478](http://pubmed.ncbi.nlm.nih.gov/22927521?dopt=Abstract)
* lymph node metastases
  + **metastases ≤ 2 mm diameter in axillary lymph nodes associated with poorer survival compared with absence of metastases**

Systematic Review[20190185J Natl Cancer Inst 2010 Mar 17;102(6):410](http://pubmed.ncbi.nlm.nih.gov/20190185?dopt=Abstract)[Full Text](http://jnci.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=20190185)

studySummary

* + - based on systematic review of 58 studies evaluating prognosis of occult lymph node metastases, isolated tumor cells, and micrometastases in 297,533 persons with breast cancer Systematic Review
    - axillary lymph node metastases of ≤ 2 mm diameter associated with poorer overall survival compared with absence of metastases (pooled hazard ratio 1.44, 95% CI 1.29-1.62)
    - PubMed20190185Journal of the National Cancer Institute20100317J Natl Cancer Inst1026410410 Reference - [20190185J Natl Cancer Inst 2010 Mar 17;102(6):410](http://pubmed.ncbi.nlm.nih.gov/20190185?dopt=Abstract)[full-text](http://jnci.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=20190185)
  + **isolated tumor cells or micrometastases in regional lymph nodes associated with reduced 5-year disease-free survival in women with early-stage breast cancer not receiving adjuvant therapy**

Cohort Study[19675329N Engl J Med 2009 Aug 13;361(7):653](http://pubmed.ncbi.nlm.nih.gov/19675329?dopt=Abstract)

studySummary

* + - based on cohort study in Netherlands Cohort Study
    - all women having sentinel-node biopsy for breast cancer before 2006 for breast cancer with favorable primary-tumor characteristics and isolated tumor cells or micrometastases in regional lymph nodes were compared to women with node-negative disease from 2000 to 2001
      * 856 women with isolated tumor cells or micrometastases did not receive systemic adjuvant therapy
      * 995 women with isolated tumor cells or micrometastases received systemic adjuvant therapy
      * 856 women with node-negative disease did not receive systemic adjuvant therapy
    - women followed for median of 5.1 years
    - adjusted hazard ratio (HR) for disease events in women not receiving adjuvant therapy
      * 1.5 (95% CI 1.15-1.94) in women with isolated tumor cells vs. node-negative disease
      * 1.56 (95% CI 1.15-2.13) in women with micrometastases vs. node-negative disease
    - unadjusted 5-year disease-free survival in women not receiving adjuvant therapy
      * 85.7% with node-negative disease
      * 75.9% with micrometastases without adjuvant therapy (p = 0.002 vs. node-negative disease)
      * 77.2% with isolated tumor cells without adjuvant therapy (p < 0.001 vs. node-negative disease, not significant vs. micrometastases)
    - adjusted HR for disease events 0.57 (95% CI 0.45-0.73) in women with isolated tumor cells or micrometastases with adjuvant therapy vs. no adjuvant therapy
    - PubMed19675329The New England journal of medicine20090813N Engl J Med3617653653 Reference - [19675329N Engl J Med 2009 Aug 13;361(7):653](http://pubmed.ncbi.nlm.nih.gov/19675329?dopt=Abstract), commentary can be found in [19907048N Engl J Med 2009 Nov 12;361(20):1994](http://pubmed.ncbi.nlm.nih.gov/19907048?dopt=Abstract)
  + **axillary lymph node macrometastasis on pathology associated with small reduction in survival compared to no macrometastasis in women with clinically node-negative breast cancer**

Cohort Study[21247310N Engl J Med 2011 Feb 3;364(5):412](http://pubmed.ncbi.nlm.nih.gov/21247310?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/21247310/)

studySummary

* + - based on cohort analysis of data from NSABP-32 randomized trial Cohort Study
    - 3,887 women with invasive breast cancer and clinically negative nodes were evaluated for macrometastases ≥ 2 mm
    - 15.9% had occult metastases
    - comparing patients with detectable occult metastases vs. no detectable occult metastases at 5 years
      * overall survival 94.6% vs. 95.8% (p = 0.03)
      * cancer-free survival 86.4% vs. 89.2% (p = 0.02)
      * distant cancer-free 89.7% vs. 92.5% (p = 0.04)
    - PubMed21247310The New England journal of medicine20110203N Engl J Med3645412412 Reference - [21247310N Engl J Med 2011 Feb 3;364(5):412](http://pubmed.ncbi.nlm.nih.gov/21247310?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/21247310/)
  + **increased number of involved lymph nodes associated with decreased survival in women with endocrine-responsive breast cancer**

Cohort Study[cxh75345721pmdc22207051pAnn Surg Oncol 2012 Jun;19(6):1808](http://pubmed.ncbi.nlm.nih.gov/22207051?dopt=Abstract)

studySummary

* + - based on retrospective prognostic cohort study Cohort Study
    - 7,052 women with endocrine-responsive breast cancer from 4 randomized trials having axillary lymph node dissection were included in analysis
    - 2718 patients (39%) had node-positive disease
    - decreased overall survival in patients with
      * increased number of involved lymph nodes (p < 0.0001)
      * increased lymph node ratio (p < 0.0001), but significant association confined to women with 1-3 lymph nodes and treated with mastectomy in subgroup analysis
    - consistent results for recurrence-free survival
    - no significant association between number of removed nodes and either recurrence-free survival or overall survival
    - PubMed22207051Annals of surgical oncology20120601Ann Surg Oncol19618081808 Reference - [cxh75345721pmdc22207051pAnn Surg Oncol 2012 Jun;19(6):1808](http://pubmed.ncbi.nlm.nih.gov/22207051?dopt=Abstract)
* distant metastases
  + **bone marrow micrometastasis at time of breast cancer diagnosis associated with poor prognosis**

Meta-analysis[16120859N Engl J Med 2005 Aug 25;353(8):793](http://pubmed.ncbi.nlm.nih.gov/16120859?dopt=Abstract)[Full Text](http://www.nejm.org/doi/full/10.1056/NEJMoa050434#t=article)

studySummary

* + - based on meta-analysis of individual patient data from 9 studies with 4,703 patients with stages I-III breast cancer followed for median of 5.2 years Meta-analysis
    - 1,438 patients (30.6%) had micrometastasis
    - compared to those without micrometastases, patients with bone marrow micrometastasis had (p < 0.01 for all variables)
      * larger tumors
      * tumors with a higher histologic grade
      * more frequent lymph node metastasis
      * more hormone receptor-negative tumors
    - micrometastasis associated with reduced overall survival, breast cancer-specific survival, disease-free survival, and distant disease-free survival
    - PubMed16120859The New England journal of medicine20050825N Engl J Med3538793793 Reference - [16120859N Engl J Med 2005 Aug 25;353(8):793](http://pubmed.ncbi.nlm.nih.gov/16120859?dopt=Abstract)[full-text](http://www.nejm.org/doi/full/10.1056/NEJMoa050434#t=article), commentary can be found in [16291991N Engl J Med 2005 Nov 17;353(20):2191](http://pubmed.ncbi.nlm.nih.gov/16291991?dopt=Abstract)
  + **occult bone marrow metastases not independently associated with reduced survival in women with early stage invasive breast cancer having chemotherapy**

Cohort Study[mdc21791687pJAMA 2011 Jul 27;306(4):385](http://pubmed.ncbi.nlm.nih.gov/21791687?dopt=Abstract)[Full Text](http://jama.jamanetwork.com/article.aspx?articleid=1104148)

studySummary

* + - based on analysis of data from prospective cohort from American College of Surgeons Oncology Group (ACOSOG) Z0010 trial Cohort Study
    - 5,210 women with early stage invasive breast cancer had breast-conserving surgery and sentinel lymph node (SLN) dissection followed for median of 6.3 years
      * bone marrow aspiration at time of operation was initially optional but became mandatory midtrial
      * SLN specimens (hematoxylin-eosin negative) and bone marrow specimens were sent for immunochemical staining
      * 86.2% received systemic chemotherapy
      * 65.5% had bone marrow specimens examined by immunocytochemistry
    - bone marrow positive for tumor in 2%
    - mortality in 8.3%
    - disease progression in 7.2%
    - comparing immunohistochemical evidence of bone marrow metastases vs. no evidence of bone marrow metastases
      * overall survival at 5 years 90.1% vs. 95% (p = 0.01) in univariate analysis
      * no significant difference in overall survival at 5 years in multivariate analysis
    - PubMed21791687JAMA20110727JAMA3064385385 Reference - [mdc21791687pJAMA 2011 Jul 27;306(4):385](http://pubmed.ncbi.nlm.nih.gov/21791687?dopt=Abstract) [full-text](http://jama.jamanetwork.com/article.aspx?articleid=1104148), editorial can be found in [mdc21791695pJAMA 2011 Jul 27;306(4):436](http://pubmed.ncbi.nlm.nih.gov/21791695?dopt=Abstract)
  + **women with metastases in unusual sites and women with metastases in usual sites appear to have similar 5-year survival**

Cohort Study[18613072Cancer 2008 Aug 15;113(4):677](http://pubmed.ncbi.nlm.nih.gov/18613072?dopt=Abstract)[Full Text](http://dx.doi.org/10.1002/cncr.23612)

studySummary

* + - based on retrospective cohort study Cohort Study
    - 3,783 patients evaluated with median follow-up of 5 years
    - 85 (2.2%) had unusual metastases (defined as systemic failures occurring with frequency ≤ 1%)
    - among 764 patients with distant metastases, 5-year cumulative overall survival was 53.5% for women with unusual metastases vs. 53.4% for women without unusual metastases
    - PubMed18613072Cancer20080815Cancer1134677677 Reference - [18613072Cancer 2008 Aug 15;113(4):677](http://pubmed.ncbi.nlm.nih.gov/18613072?dopt=Abstract)[full-text](http://dx.doi.org/10.1002/cncr.23612)
  + **increasing numbers of bony metastases associated with decreased survival in women with breast cancer**

Cohort Study[11148555Cancer 2001 Jan 1;91(1):17](http://pubmed.ncbi.nlm.nih.gov/11148555?dopt=Abstract)

studySummary

* + - based on retrospective cohort of 641 women with stage I-III breast cancer Cohort Study
    - 116 women had bone metastases as sole initial site of metastatic disease
    - median survival from time of recurrence in women with bony metastases
      * 53 months with 1 lesion (p < 0.0001 vs. ≥ 3 lesions)
      * 38 months with 2 lesions (p < 0.005 vs. ≥ 3 lesions)
      * 22 months with ≥ 3 lesions
    - PubMed11148555Cancer20010101Cancer9111717 Reference - [11148555Cancer 2001 Jan 1;91(1):17](http://pubmed.ncbi.nlm.nih.gov/11148555?dopt=Abstract)
* circulating tumor cells (CTCs)
  + **increased numbers of CTCs may be associated with worse overall survival**

Cohort Study[Cancer 2008 Nov 1;113(9):2422](http://pubmed.ncbi.nlm.nih.gov/18785255-circulating-tumor-cells-in-metastatic-breast-cancer-from-prognostic-stratification-to-modification-of-the-staging-system/?dopt=Abstract)[Full Text](http://onlinelibrary.wiley.com/doi/10.1002/cncr.23852/full)

studySummary

* + - Cohort Study based on retrospective cohort study
    - 185 patients (median age 49 years) with metastatic or recurrent breast cancer evaluated
    - median survival 15 months for patients with ≥ 5 CTCs per 750 mL of whole blood vs. 28.3 months for patients with < 5 CTCs per 750 mL of whole blood (p < 0.001)
    - Reference - [18785255Cancer 2008 Nov 1;113(9):2422](http://pubmed.ncbi.nlm.nih.gov/18785255?dopt=Abstract)[full-text](http://onlinelibrary.wiley.com/doi/10.1002/cncr.23852/full)
    - PubMed18785255CancerCancer2008110111392422-302422Reference - [Cancer 2008 Nov 1;113(9):2422](http://pubmed.ncbi.nlm.nih.gov/18785255-circulating-tumor-cells-in-metastatic-breast-cancer-from-prognostic-stratification-to-modification-of-the-staging-system/?dopt=Abstract)[full-text](http://onlinelibrary.wiley.com/doi/10.1002/cncr.23852/full)
  + number of CTCs before treatment and at first follow-up significantly predicted disease progression and overall survival in prospective study of 177 patients with measurable metastatic breast cancer ([15317891N Engl J Med 2004 Aug 19;351(8):781](http://pubmed.ncbi.nlm.nih.gov/15317891?dopt=Abstract)), editorial can be found in [15317898N Engl J Med 2004 Aug 19;351(8):824](http://pubmed.ncbi.nlm.nih.gov/15317898?dopt=Abstract), commentary can be found in [15580681N Engl J Med 2004 Dec 2;351(23):2452](http://pubmed.ncbi.nlm.nih.gov/15580681?dopt=Abstract)
* **residual breast cancer following neoadjuvant chemotherapy associated with reduced distant relapse-free survival**

Cohort Study[mdc17785706pJ Clin Oncol 2007 Oct 1;25(28):4414](http://pubmed.ncbi.nlm.nih.gov/17785706?dopt=Abstract)[Full Text](http://jco.ascopubs.org/content/25/28/4414.long)

studySummary

* + based on retrospective analysis of 382 patients treated with fluorouracil, doxorubicin, and cyclophosphamide (preceded by paclitaxel in 241 patients) Cohort Study
  + residual breast cancer determined by pathologic measurement of primary tumor and nodal metastases
  + PubMed17785706Journal of clinical oncology : official journal of the American Society of Clinical Oncology20071001J Clin Oncol252844144414 Reference - [mdc17785706pJ Clin Oncol 2007 Oct 1;25(28):4414](http://pubmed.ncbi.nlm.nih.gov/17785706?dopt=Abstract) [full-text](http://jco.ascopubs.org/content/25/28/4414.long), commentary can be found in [mdc18565900pJ Clin Oncol 2008 Jun 20;26(18):3094](http://pubmed.ncbi.nlm.nih.gov/18565900?dopt=Abstract)
* in mammographic lesions < 14 mm, casting-type calcifications associated with lower long-term survival in prospective study of 343 mammograms of invasive breast cancers of size 1-14 mm ([mnh10841122p t caph2753270t c pa9h2753270t c pbyh2753270t c pafh2753270t c pbeh2753270t c phch2753270t c pnyh2753270t c pnxh2753270t c pbth2753270t c ppbh2753270t c pcxh2753270t c pmdc10841122p t cLancet 2000 Feb 5;355(9202):429](http://pubmed.ncbi.nlm.nih.gov/10841122?dopt=Abstract) ), correction can be found in Lancet 2000 Apr 15;355(9212):1372, commentary can be found in [mnh10801193p t cmdc10801193p t cLancet 2000 Apr 29;355(9214):1551](http://pubmed.ncbi.nlm.nih.gov/10801193?dopt=Abstract)

Age

* young age
  + **young age at presentation (≤ 25 years old) associated with poorer survival in women with invasive breast cancer**

Nested case-control study[23812457Obstet Gynecol 2013 Jun;121(6):1235](http://pubmed.ncbi.nlm.nih.gov/23812457?dopt=Abstract)

studySummary

* + - based on 2-phase, retrospective, nested, within-cases matched study Nested case-control study
    - 28 women ≤ 25 years old with invasive breast cancer compared with 685 older (> 25 years old) premenopausal women with invasive breast cancer
      * age ≤ 25 years at diagnosis associated with
        + more advanced stage (p = 0.012, pairwise comparisons not reported)
        + higher grade (p = 0.018, pairwise comparisons not reported)
      * no significant difference in histologic subtype, estrogen receptor status, and progesterone receptor status
    - 23 women ≤ 25 years old with invasive breast cancer compared with 23 older (> 25 years old) premenopausal women with invasive breast cancer from above study population
      * age ≤ 25 years at diagnosis associated with
        + reduced overall survival (adjusted hazard ratio [HR] for death 4.3, 95% CI 1.09-17.03)
        + reduced relapse-free survival (adjusted HR for recurrence 8.28, 95% CI 2.24-30.6)
    - PubMed23812457Obstetrics and gynecology20130601Obstet Gynecol121612351235 Reference - [23812457Obstet Gynecol 2013 Jun;121(6):1235](http://pubmed.ncbi.nlm.nih.gov/23812457?dopt=Abstract)
  + **young age not associated with increased risk of early recurrence or survival in women with early stage human epidermal growth factor receptor 2 (HER2)-positive breast cancer**

Randomized Trial[cxh88999352pmdc23752109pJ Clin Oncol 2013 Jul 20;31(21):2692](http://pubmed.ncbi.nlm.nih.gov/23752109?dopt=Abstract)

studySummary

* + - based on cohort analysis of data from randomized trial Randomized Trial
    - 3,401 women with early stage HER2- positive breast cancer from HERA trial were randomized to trastuzumab vs. observation and evaluated after median 2 years of follow-up
    - all women received surgery and/or adjuvant or neoadjuvant chemotherapy, with or without radiation therapy
    - compared to women > 40 years old, no significant differences for disease-free survival or overall survival in women ≤ 40 years old for either group
    - PubMed23752109Journal of clinical oncology : official journal of the American Society of Clinical Oncology20130720J Clin Oncol312126922692 Reference - [cxh88999352pmdc23752109pJ Clin Oncol 2013 Jul 20;31(21):2692](http://pubmed.ncbi.nlm.nih.gov/23752109?dopt=Abstract) , commentary can be found in [cxh93375658pmdc24323029pJ Clin Oncol 2014 Jan 10;32(2):161](http://pubmed.ncbi.nlm.nih.gov/24323029?dopt=Abstract)
  + **young age at presentation (< 35 years old) of breast cancer may be associated with higher mortality**

Cohort Study[mnh16857060paph29336839pa9h29336839pafh29336839pcxh29336839pmdc16857060pBMC Cancer 2006 Jul 20;6:194](http://pubmed.ncbi.nlm.nih.gov/16857060?dopt=Abstract)[Full Text](http://www.biomedcentral.com/1471-2407/6/194)

studySummary

* + - based on retrospective cohort study Cohort Study
    - 1,320 consecutive patients (mean age at presentation 50.8 years) diagnosed with breast cancer from 1990 to 2001 and followed for median of 2.9 years
    - 8.1% were aged < 35 years
    - comparing patients < 35 years old vs. patients aged 35-50 years vs. patients > 50 years old
      * development of metastasis in 32.4% vs. 22.9% vs. 22.8% (not significant)
      * 5-year survival (extrapolated from graph) 70% vs. 85% vs. 90% (p = 0.03)
    - PubMed16857060BMC cancer20060720BMC Cancer6194194 Reference - [mnh16857060paph29336839pa9h29336839pafh29336839pcxh29336839pmdc16857060pBMC Cancer 2006 Jul 20;6:194](http://pubmed.ncbi.nlm.nih.gov/16857060?dopt=Abstract) [full-text](http://www.biomedcentral.com/1471-2407/6/194)
  + **increased mortality in women < 40 years old compared to women aged 45-49 years at diagnosis of breast cancer among women not receiving adjuvant cytotoxic chemotherapy**

Cohort Study[10678859BMJ 2000 Feb 19;320(7233):474](http://pubmed.ncbi.nlm.nih.gov/10678859?dopt=Abstract)[Full Text](http://www.bmj.com/content/320/7233/474.full)

studySummary

* + - based on retrospective cohort study Cohort Study
    - 10,356 women with primary breast cancer who were aged < 50 years old at diagnosis
    - compared to women diagnosed age 45-49 years, increased risk of mortality in
      * women diagnosed age 35-39 years (adjusted relative risk [RR] 1.4, 95% CI 1.1-1.8)
      * women diagnosed at < 35 years old (RR 2.18, 95% CI 1.64-2.89)
    - association of younger age and mortality not found for women who received adjuvant cytotoxic chemotherapy
    - PubMed10678859BMJ (Clinical research ed.)20000219BMJ3207233474474 Reference - [10678859BMJ 2000 Feb 19;320(7233):474](http://pubmed.ncbi.nlm.nih.gov/10678859?dopt=Abstract)[full-text](http://www.bmj.com/content/320/7233/474.full), editorial can be found in [10678839BMJ 2000 Feb 19;320(7233):457](http://pubmed.ncbi.nlm.nih.gov/10678839?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/10678839/) (correction can be found in BMJ 2000 Apr 29;320(7243):1173), commentary can be found in [10939831BMJ 2000 Jul 1;321(7252):53](http://pubmed.ncbi.nlm.nih.gov/10939831?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/10939831/)
  + **higher risk of relapse and death in younger premenopausal women than older premenopausal women, especially if estrogen receptor-positive tumors**

Randomized Trial[mnh10866443p t caph3166027t c pa9h3166027t c pbyh3166027t c pafh3166027t c pbeh3166027t c phch3166027t c pnyh3166027t c pnxh3166027t c pbth3166027t c ppbh3166027t c pcxh3166027t c pmdc10866443p t cLancet 2000 May 27;355(9218):1869](http://pubmed.ncbi.nlm.nih.gov/10866443?dopt=Abstract)

studySummary

* + - based on pooled analysis of 4 randomized trials Randomized Trial
    - 3,700 pre- and perimenopausal women (including 314 patients < 35 years old) with breast cancer having adjuvant cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy
    - comparing women < 35 years old vs. women ≥ 35 years old
      * 10-year disease-free survival 35% vs. 47% (p < 0.001)
      * overall survival 49% vs. 62% (p < 0.001)
    - PubMed10866443Lancet (London, England)20000527Lancet355921818691869 Reference - [mnh10866443p t caph3166027t c pa9h3166027t c pbyh3166027t c pafh3166027t c pbeh3166027t c phch3166027t c pnyh3166027t c pnxh3166027t c pbth3166027t c ppbh3166027t c pcxh3166027t c pmdc10866443p t cLancet 2000 May 27;355(9218):1869](http://pubmed.ncbi.nlm.nih.gov/10866443?dopt=Abstract) , editorial can be found in [mnh10866433p taph3166011t pa9h3166011t pbyh3166011t pafh3166011t pbeh3166011t phch3166011t pnyh3166011t pnxh3166011t pbth3166011t ppbh3166011t pcxh3166011t pmdc10866433p tLancet 2000 May 27;355(9218):1839](http://pubmed.ncbi.nlm.nih.gov/10866433?dopt=Abstract) , commentary can be found in [mnh11036925p t cmdc11036925p t cLancet 2000 Sep 9;356(9233):944](http://pubmed.ncbi.nlm.nih.gov/11036925?dopt=Abstract) , [mnh11009170p t cmdc11009170p t cLancet 2000 Sep 23;356(9235):1113](http://pubmed.ncbi.nlm.nih.gov/11009170?dopt=Abstract)
  + **women < 40 years old have higher mortality than women aged 40-49 years among women with breast cancer**

Cohort Study[World J Surg Oncol 2004 Jan 22;2:2](http://pubmed.ncbi.nlm.nih.gov/14736343-do-younger-women-with-non-metastatic-and-non-inflammatory-breast-carcinoma-have-poor-prognosis/?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC340386/?tool=pubmed)

studySummary

* + - Cohort Study based on cohort study of 1,701 women in India with nonmetastatic, noninflammatory breast carcinoma, median follow-up 66 months
    - 62% overall survival, estimated 10-year overall survival was 52.6%
      * estimated 10-year overall survival among 437 women < 40 years old 46.5%
        + 62.3% if T1, 58.3% if T2, 36.6% if T3, 10.4% if T4
        + 76.8% if node-negative, 24.2% if node-positive
      * estimated 10-year overall survival among 557 women aged 40-49 years 59.8%
        + 73.2% if T1, 66.3% if T2, 41.9% if T3, 33.5% if T4
        + 73.9% if node-negative, 43.6% if node-positive
      * estimated 10-year overall survival among 433 women aged 50-59 years 58.9%
        + 55.9% if T1, 57.1% if T2, 46.4% if T3, 46.7% if T4
        + 68.8% if node-negative, 41.6% if node-positive
      * estimated 10-year overall survival among 274 women > 60 years old 48%
        + 70% if T1, 55.5% if T2, 47.9% if T3, 18.1% if T4
        + 64.4% if node-negative, 34.5% if node-positive
    - PubMed14736343World journal of surgical oncologyWorld J Surg Oncol20040122222Reference - [World J Surg Oncol 2004 Jan 22;2:2](http://pubmed.ncbi.nlm.nih.gov/14736343-do-younger-women-with-non-metastatic-and-non-inflammatory-breast-carcinoma-have-poor-prognosis/?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC340386/?tool=pubmed)
  + **women < 40 years old at diagnosis appear to have higher mortality in early stage disease compared to women ≥ 40 years old**

Cohort Study[19317994J Am Coll Surg 2009 Mar;208(3):341](http://pubmed.ncbi.nlm.nih.gov/19317994?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/19317994/)

studySummary

* + - based on retrospective cohort study Cohort Study
    - 243,012 women diagnosed with breast cancer from 1988 to 2003 were stratified by age (6.4% < 40 years old vs. 93.6% ≥ 40 years old)
    - comparing women < 40 years old at breast cancer diagnosis vs. women ≥ 40 years old
      * disease-specific mortality 18.3% vs. 12.1% (p < 0.001)
      * disease-specific mortality with stage I diagnosis 6.8% vs. 3.6%(p < 0.05)
      * disease-specific mortality with stage II diagnosis 20.3% vs. 15.2% (p < 0.05)
      * disease-specific mortality with stage IV diagnosis 66.4% vs. 67.8% (p < 0.05)
    - PubMed19317994Journal of the American College of Surgeons20090301J Am Coll Surg2083341341 Reference - [19317994J Am Coll Surg 2009 Mar;208(3):341](http://pubmed.ncbi.nlm.nih.gov/19317994?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/19317994/)
* older age
  + **age ≥ 65 years at diagnosis associated with increased breast cancer mortality in women with hormone receptor-positive early breast cancer**

Randomized Trial[mdc22318280pJAMA 2012 Feb 8;307(6):590](http://pubmed.ncbi.nlm.nih.gov/22318280?dopt=Abstract)[Full Text](http://jama.jamanetwork.com/article.aspx?articleid=1104959)

studySummary

* + - based on post hoc analysis of TEAM trialRandomized Trial
    - 9,766 postmenopausal women with hormone receptor-positive early breast cancer were stratified by age at diagnosis
    - 10.7% mortality during median 5.1 years of follow-up
    - disease-specific mortality defined as time from randomization to breast cancer-related mortality
    - after multivariate analysis age at diagnosis associated with increased risk of (vs. women < 65 years old)
      * breast cancer mortality
        + hazard ratio (HR) 1.25 (95% CI 1.01-1.54) in women aged 65-74 years
        + HR 1.63 (95% CI 1.23-2.16) in women ≥ 75 years old
      * other mortality
        + HR 2.66 (95% CI 1.96-3.63) in women aged 65-74 years
        + HR 7.3 (95% CI 5.29-10.07) in women ≥ 75 years old
    - PubMed22318280JAMA20120208JAMA3076590590Reference - [mdc22318280pJAMA 2012 Feb 8;307(6):590](http://pubmed.ncbi.nlm.nih.gov/22318280?dopt=Abstract) [full-text](http://jama.jamanetwork.com/article.aspx?articleid=1104959)
  + **in women > 70 years old with early breast cancer treated with conservative surgery plus adjuvant tamoxifen, mortality from breast cancer reported in 17%**

Cohort Study[18098268Cancer 2008 Feb 1;112(3):481](http://pubmed.ncbi.nlm.nih.gov/18098268?dopt=Abstract)[Full Text](http://onlinelibrary.wiley.com/doi/10.1002/cncr.23213/full)

studySummary

* + - based on cohort studyCohort Study
    - 354 women ≥ 70 years old with primary, operable breast cancer and no palpable axillary lymph nodes were treated with conservative surgery and adjuvant tamoxifen
    - conservative surgery consisted of breast-conserving surgery (quadrantectomy) without axillary dissection or postoperative radiation therapy
    - median follow-up 15 years
    - breast cancer mortality 17%
    - crude cumulative incidence
      * axillary disease in 4.2%
      * ipsilateral breast tumor recurrence in 8.3%
    - PubMed18098268Cancer20080201Cancer1123481481Reference - [18098268Cancer 2008 Feb 1;112(3):481](http://pubmed.ncbi.nlm.nih.gov/18098268?dopt=Abstract)[full-text](http://onlinelibrary.wiley.com/doi/10.1002/cncr.23213/full)

Race and ethnicity

Weight and body mass

* **obesity associated with poorer survival in women with breast cancer**

Systematic Review[mnh20571870pcxh53704105pmdc20571870pBreast Cancer Res Treat 2010 Oct;123(3):627](http://pubmed.ncbi.nlm.nih.gov/20571870?dopt=Abstract)

studySummary

* + based on systematic review of observational studies Systematic Review
  + systematic review of 45 cohort studies evaluating survival in nonobese and women with obesity and with breast cancer
  + sample size ranged from 100 to 424,168 (median 1,192)
  + women with obesity had poorer survival in analysis of 43 studies
    - poorer overall survival hazard ratio (HR) 1.33 (95% CI 1.21-1.47)
    - poorer breast cancer-specific survival HR 1.33 (95% CI 1.19-1.5)
  + no significant difference in risk between premenopausal and postmenopausal women with obesity
  + PubMed20571870Breast cancer research and treatment20101001Breast Cancer Res Treat1233627627 Reference - [mnh20571870pcxh53704105pmdc20571870pBreast Cancer Res Treat 2010 Oct;123(3):627](http://pubmed.ncbi.nlm.nih.gov/20571870?dopt=Abstract) , editorial can be found in [mnh20711653pcxh53704102pmdc20711653pBreast Cancer Res Treat 2010 Oct;123(3):637](http://pubmed.ncbi.nlm.nih.gov/20711653?dopt=Abstract)
* body mass index (BMI) ≥ 30 kg/m2 associated with increased all-cause mortality in study of 1,254 women aged 20-54 years with invasive breast cancer followed 8-10 years ([17035393Cancer Epidemiol Biomarkers Prev 2006 Oct;15(10):1871](http://pubmed.ncbi.nlm.nih.gov/17035393?dopt=Abstract)[full-text](http://cebp.aacrjournals.org/content/15/10/1871.long))
* elevated waist-to-hip ratio, based on 603 patients with breast cancer followed 4-10 years ([14607804Am J Epidemiol 2003 Nov 15;153(10):963](http://pubmed.ncbi.nlm.nih.gov/14607804?dopt=Abstract))
* increased body weight and negative estrogen receptor each were associated with 2-fold higher risk of death from breast cancer in women with early-stage breast cancer, based on cohort of 1,376 women followed for median 6.8 years after diagnosis ([mdc15381612pArch Surg 2004 Sep;139(9):954](http://pubmed.ncbi.nlm.nih.gov/15381612?dopt=Abstract) )
* **obesity associated with reduced survival in women with hormone receptor-positive breast cancer treated with chemotherapy**

Randomized Trial[22926690Cancer 2012 Dec 1;118(23):5937](http://pubmed.ncbi.nlm.nih.gov/22926690?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3586227/)

studySummary

* + based on cohort analysis of data from 3 randomized trials Randomized Trial
  + 4,770 women with hormone receptor-positive operable breast cancer from 1 randomized trial evaluating chemotherapy regimens were assessed
    - 31% were normal or underweight (BMI < 25 kg/m2)
    - 32% were overweight (BMI 25-29.9 kg/m2)
    - 37% were obese (BMI ≥ 30 kg/m2)
  + compared to lower BMI categories, obesity associated with reduced survival in analysis of women with hormone receptor-positive disease (hazard ratio for death 1.37, 95% CI 1.13-1.67)
  + no significant association between obesity and survival in women with other disease subtypes
  + similar association between obesity and mortality found in 2 additional trials
  + PubMed22926690Cancer20121201Cancer1182359375937 Reference - [22926690Cancer 2012 Dec 1;118(23):5937](http://pubmed.ncbi.nlm.nih.gov/22926690?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3586227/)
* **weight gain > 10% after breast cancer diagnosis associated with increased risk of all-cause mortality**

Systematic Review[26424778J Natl Cancer Inst 2015 Dec;107(12):djv275](http://pubmed.ncbi.nlm.nih.gov/26424778?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4715249/)

studySummary

* + based on systematic review of observational studies Systematic Review
  + systematic review of 12 observational studies (retrospective and prospective cohort studies, and cohort analysis of randomized trials) evaluating association between weight gain and risk of mortality in 23,832 women with stage I-IIIC breast cancer
  + median follow-up time ranged from 2 years to > 10 years
  + compared to maintaining body weight, weight gain > 5% associated with increased overall risk of all-cause mortality (hazard ratio [HR] 1.12, 95% CI 1.03-1.22) in analysis of 8 studies, results limited by statistical heterogeneity
  + in subgroup analysis stratified by level of weight gain
    - weight gain > 10% associated with increased risk of all-cause mortality (HR 1.23, 95% CI 1.09-1.39) in analysis of 4 studies, results limited by significant heterogeneity
    - no significant association between weight gain 5%-10% and risk of all-cause mortality in analysis of 4 studies
  + in subgroup analysis of patients with weight gain > 5% also stratified by prediagnosis body mass index (BMI), no significant association between BMI < 25 kg/m2 or BMI ≥ 25 kg/m2 and risk of all-cause mortality in analysis of 4 studies
  + PubMed26424778Journal of the National Cancer Institute20151201J Natl Cancer Inst10712djv275djv275 Reference - [26424778J Natl Cancer Inst 2015 Dec;107(12):djv275](http://pubmed.ncbi.nlm.nih.gov/26424778?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4715249/)
* **overweight and obesity associated with reduced disease-free survival compared to normal weight after resection plus adjuvant chemotherapy for human epidermal growth factor receptor type 2 (HER2)-positive breast cancer**

Randomized Trial[23585192Cancer 2013 Jul 1;119(13):2447](http://pubmed.ncbi.nlm.nih.gov/23585192?dopt=Abstract)

studySummary

* + based on cohort analysis of data from randomized trial Randomized Trial
  + 3,017 women with resected stage I-III invasive HER2-positive breast cancer with data on BMI were categorized as normal weight (BMI < 25 kg/m2), overweight (BMI 25-29.9 kg/m2), or obese (BMI ≥ 30 kg/m2) and evaluated
  + all women had doxorubicin plus cyclophosphamide followed by paclitaxel or paclitaxel plus concurrent or sequential trastuzumab
  + disease-related events included recurrence, contralateral breast cancer, new primary cancer, or death from any cause
  + 5-year disease-free survival
    - 82.5% with normal weight (p < 0.05 vs. other groups)
    - 78.6% with overweight
    - 78.5% with obesity
  + PubMed23585192Cancer20130701Cancer1191324472447 Reference - [23585192Cancer 2013 Jul 1;119(13):2447](http://pubmed.ncbi.nlm.nih.gov/23585192?dopt=Abstract)
* **overweight associated with increased risk of mortality and disease recurrence in premenopausal women having adjuvant anastrozole for hormone receptor-positive breast cancer**

Randomized Trial[mdc21555684pJ Clin Oncol 2011 Jul 1;29(19):2653](http://pubmed.ncbi.nlm.nih.gov/21555684?dopt=Abstract)

studySummary

* + based on cohort analysis of data from randomized trial Randomized Trial
  + 1,803 premenopausal women with stage IB, IC, or II hormone receptor-positive breast cancer who were randomized to goserelin plus tamoxifen vs. goserelin plus anastrozole were stratified by BMI and followed for mean 5 years
  + comparing women with overweight vs. normal weight women taking anastrozole, overweight associated with increased risk of
    - mortality (hazard ratio [HR] 2.14, 95% CI 1.17-3.92)
    - disease recurrence (HR 1.6, 95% CI 1.06-2.41)
  + anastrozole associated with increased mortality compared to tamoxifen (p = 0.004) in subgroup of women with overweight
  + no significant differences in recurrence or mortality comparing women with overweight vs. normal weight women taking tamoxifen
  + PubMed21555684Journal of clinical oncology : official journal of the American Society of Clinical Oncology20110701J Clin Oncol291926532653 Reference - [mdc21555684pJ Clin Oncol 2011 Jul 1;29(19):2653](http://pubmed.ncbi.nlm.nih.gov/21555684?dopt=Abstract)
* **obesity and overweight not associated with increased mortality risk in postmenopausal women with breast cancer who received adjuvant therapy with letrozole or tamoxifen**

Randomized Trial[cxh83235281pmdc23045588pJ Clin Oncol 2012 Nov 10;30(32):3967](http://pubmed.ncbi.nlm.nih.gov/23045588?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23045588/)

studySummary

* + based on cohort analysis of data from BIG 1-98 randomized trial Randomized Trial
  + 4,760 postmenopausal women with nonmetastatic hormone receptor-positive invasive breast cancer who received monotherapy with [letrozole](https://dpa-pde-oxford.shinyapps.io/drug-monograph/letrozole) or [tamoxifen](https://dpa-pde-oxford.shinyapps.io/drug-monograph/tamoxifen) for 5 years were followed for median 8.7 years
  + baseline BMI was ≥ 30 kg/m2 in 23%, and 25-29 kg/m2 in 36%
  + overall survival 83%
  + mortality risk compared to BMI < 25 kg/m2 (normal weight)
    - nonsignificant increase associated with BMI ≥ 30 kg/m2 (obesity) (hazard ratio 1.19, 95% CI 0.99-1.44)
    - no significant difference compared to BMI 25 to < 30 kg/m2 (overweight)
  + no significant difference in disease-free survival, breast cancer-free survival, or distant recurrence-free survival comparing obesity or overweight status to normal weight
  + PubMed23045588Journal of clinical oncology : official journal of the American Society of Clinical Oncology20121110J Clin Oncol303239673967 Reference - [cxh83235281pmdc23045588pJ Clin Oncol 2012 Nov 10;30(32):3967](http://pubmed.ncbi.nlm.nih.gov/23045588?dopt=Abstract) [full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23045588/)
* **obesity might not be associated with increased mortality in women with node-positive breast cancer who received adjuvant chemotherapy**

Cohort Study[24315625Eur J Cancer 2014 Feb;50(3):506](http://pubmed.ncbi.nlm.nih.gov/24315625?dopt=Abstract)

studySummary

* + based on cohort analysis of pooled patient data from 2 randomized trials Cohort Study
  + 4,996 women in France with node-positive breast cancer who received adjuvant chemotherapy of anthracycline-based treatment plus taxane or taxane alone were analyzed
  + median follow-up 5.9 years
  + no significant differences in overall or disease-free survival comparing women with obesity (BMI ≥ 30kg/m2) vs. women without obesity in adjusted analyses
  + PubMed24315625European journal of cancer20140201Eur J Cancer503506506 Reference - [24315625Eur J Cancer 2014 Feb;50(3):506](http://pubmed.ncbi.nlm.nih.gov/24315625?dopt=Abstract)

Psychosocial factors

* **conflicting data regarding association of psychosocial factors and survival in patients with breast cancer**

Systematic Review[17640330Breast Cancer Res 2007;9(4):R44](http://pubmed.ncbi.nlm.nih.gov/17640330?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2206717/?tool=pubmed)

studySummary

* + based on systematic review Systematic Review
  + systematic review of 37 studies of psychosocial factors and breast cancer in 61,611 female patients with breast cancer
  + 31 studies were descriptive studies and 6 studies evaluated psychologic intervention
  + factors with inconsistent findings across studies
    - fighting spirit
    - stressful events
    - anxiety
    - hopelessness/helplessness
    - joy
    - depression/negative mood
    - perceived social support
    - repressive defensiveness/emotional constraints
    - adjustment
    - fatalism/stoic appearance
    - denial/avoidance
    - anger/hostility
    - expressive activities
    - group participation in religious/nonreligious activities
    - somatization, obsessive-compulsive symptoms, paranoia, psychotic behavior, interpersonal sensitivity
    - marriage
  + factors with no impact on survival or recurrence risk (and no evidence suggesting impact)
    - coping in 4 studies
    - beliefs about cancer incurability in 1 study
    - locus of control in 5 studies
    - vigor/activity in 2 studies
    - fatigue/inertia in 1 study
    - confusion/bewilderment in 1 study
    - self-esteem in 2 studies
  + factors with positive impact on survival or recurrence risk (and no conflicting evidence)
    - cognitive/role functioning in 1 study
    - minimizing in 2 studies
    - guilt in 1 study
    - extroversion in 1 study
    - hobbies in 1 study
    - female child in 1 study
  + only factor with negative impact (and no conflicting evidence) was positive constructing daydreaming in 1 study
  + PubMed17640330Breast cancer research : BCR200701Breast Cancer Res94R44R44 Reference - [17640330Breast Cancer Res 2007;9(4):R44](http://pubmed.ncbi.nlm.nih.gov/17640330?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2206717/?tool=pubmed)
* **psychosocial factors may not be associated with recurrence or survival in women with nonmetastatic breast cancer**

Cohort Study[mdc18824713pJ Clin Oncol 2008 Oct 1;26(28):4666](http://pubmed.ncbi.nlm.nih.gov/18824713?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/18824713/)

studySummary

* + based on population-based prospective cohort study Cohort Study
  + 708 women ≤ 60 years old with nonmetastatic breast cancer had depression, anxiety, coping style, and social support assessed at median 11 months after diagnosis and were followed for median 8.2 years
  + mortality was 24% and distant recurrence occurred in 33% during follow-up
  + no significant associations between any measured psychosocial factor and distant disease-free survival or overall survival
  + PubMed18824713Journal of clinical oncology : official journal of the American Society of Clinical Oncology20081001J Clin Oncol262846664666 Reference - [mdc18824713pJ Clin Oncol 2008 Oct 1;26(28):4666](http://pubmed.ncbi.nlm.nih.gov/18824713?dopt=Abstract) [full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/18824713/)
* **depression and/or anxiety common in first 5 years after diagnosis of breast cancer, especially in first year**

Cohort Study[BMJ 2005 Mar 26;330(7493):702](http://pubmed.ncbi.nlm.nih.gov/15695497-depression-and-anxiety-in-women-with-early-breast-cancer-five-year-observational-cohort-study/?dopt=Abstract)

studySummary

* + Cohort Study based on cohort of 222 women < 60 years old with breast cancer, 170 women (77%) were followed for 5 years or until recurrence
  + clinically important depression and/or anxiety occurred in nearly 50% in first year, 25% in second through fourth years, and 15% in fifth year after diagnosis
  + PubMed15695497BMJ (Clinical research ed.)BMJ200503263307493702702Reference - [BMJ 2005 Mar 26;330(7493):702](http://pubmed.ncbi.nlm.nih.gov/15695497-depression-and-anxiety-in-women-with-early-breast-cancer-five-year-observational-cohort-study/?dopt=Abstract)
* low socioeconomic status
  + **women living in communities with lowest socioeconomic status had increased mortality in United States (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cohort Study[18391595Am J Clin Oncol 2008 Apr;31(2):125](http://pubmed.ncbi.nlm.nih.gov/18391595?dopt=Abstract)

studySummary2

* + - based on retrospective cohort study Cohort Study
    - 35,029 women ≥ 65 years old with stage I-IIIA breast cancer from Surveillance, Epidemiology and End Results (SEER)-medicare linked database and up to 11 years of follow-up were analyzed
    - increased risk for death associated with living in lowest socioeconomic communities (hazard ratio 1.1, 95% CI 1.04-1.16) compared to living in highest socioeconomic communities
    - PubMed18391595American journal of clinical oncology20080401Am J Clin Oncol312125125 Reference - [18391595Am J Clin Oncol 2008 Apr;31(2):125](http://pubmed.ncbi.nlm.nih.gov/18391595?dopt=Abstract)
  + **low socioeconomic status may be associated with differences in treatment received for breast cancer**

Cohort Study[11929949J Natl Cancer Inst 2002 Apr 3;94(7):490](http://pubmed.ncbi.nlm.nih.gov/11929949?dopt=Abstract)

studySummary

* + - based on analysis of data available in Metropolitan Detroit Cancer Surveillance System (MDCSS) database Cohort Study
    - 5,719 women (mean age 61.1 years) diagnosed with in situ or invasive breast cancer from 1996 to 1997 were analyzed for variables associated with late-stage breast cancer at diagnosis, chosen treatment, and mortality within study period
    - socioeconomic status was defined by percentage of residents below federal poverty line within census tract of patient's residence and stratified by < 5%, 5%-12%, and ≥ 13%
    - compared to women living in census tracts with poverty levels < 5%, women living in census tracts with poverty levels ≥ 13% were
      * less likely to have breast-conserving surgery (adjusted odds ratio [OR] 0.68, 95% CI 0.56-0.82)
      * less likely to have adjuvant radiation (OR 0.78, 95% CI 0.6-1)
    - PubMed11929949Journal of the National Cancer Institute20020403J Natl Cancer Inst947490490 Reference - [11929949J Natl Cancer Inst 2002 Apr 3;94(7):490](http://pubmed.ncbi.nlm.nih.gov/11929949?dopt=Abstract), commentary can be found in [12189230J Natl Cancer Inst 2002 Aug 21;94(16):1254](http://pubmed.ncbi.nlm.nih.gov/12189230?dopt=Abstract)

Comorbidities

* **preexisting dementia associated with increased mortality in breast cancer**

Cohort Study[mdc18852406pArch Intern Med 2008 Oct 13;168(18):2033](http://pubmed.ncbi.nlm.nih.gov/18852406?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/18852406/)

studySummary

* + based on retrospective cohort Cohort Study
  + 31,935 women ≥ 65 years old with breast cancer were analyzed for associations between dementia and breast cancer outcomes
  + 7.4% had preexisting dementia diagnosis
  + comparing patients with vs. without dementia
    - 1-year cancer-specific mortality 7.6% vs. 3.8% (p < 0.05)
    - 1-year noncancer mortality 9% vs. 3% (p < 0.05)
    - 5-year cancer-specific mortality 17.9% vs. 13.1% (p < 0.05)
    - 5-year noncancer mortality 31.8% vs. 16.2% (p < 0.05)
  + PubMed18852406Archives of internal medicine20081013Arch Intern Med1681820332033 Reference - [mdc18852406pArch Intern Med 2008 Oct 13;168(18):2033](http://pubmed.ncbi.nlm.nih.gov/18852406?dopt=Abstract) [full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/18852406/), commentary can be found in [mdc19307529pArch Intern Med 2009 Mar 23;169(6):633](http://pubmed.ncbi.nlm.nih.gov/19307529?dopt=Abstract)

Delay in diagnosis or treatment

* **delay in diagnosis associated with decreased survival but not after controlling for stage**

Systematic Review[mnh10209974p t caph1711558t c pa9h1711558t c pbyh1711558t c pafh1711558t c pbeh1711558t c phch1711558t c pnyh1711558t c pnxh1711558t c pbth1711558t c ppbh1711558t c pcxh1711558t c pmdc10209974p t cLancet 1999 Apr 3;353(9159):1119](http://pubmed.ncbi.nlm.nih.gov/10209974?dopt=Abstract)

studySummary

* + based on systematic review of observational studies Systematic Review
  + systematic review of 87 observational studies evaluating duration of symptoms and survival in 101,954 women presenting with symptomatic breast cancer
  + compared to delays (between the onset of symptoms and the start of treatment) < 3 months
    - delays ≥ 3 months associated with higher 5-year mortality (odds ratio (OR) 1.47, 95% CI 1.42-1.53) in analysis of 26 studies with 44, 347 women
    - delays 3-6 months associated with higher 5-year mortality (OR 1.24, 95% CI 1.17-1.3) in analysis of 23 studies with 25,052 women
  + compared to delays < 6 months, delays > 6 months associated with higher 5-year mortality (OR 1.45, 95% CI 1.4-1.5)
  + longer delay was not associated with shorter survival in studies that controlled for stage of disease
  + PubMed10209974Lancet (London, England)19990403Lancet353915911191119 Reference - [mnh10209974p t caph1711558t c pa9h1711558t c pbyh1711558t c pafh1711558t c pbeh1711558t c phch1711558t c pnyh1711558t c pnxh1711558t c pbth1711558t c ppbh1711558t c pcxh1711558t c pmdc10209974p t cLancet 1999 Apr 3;353(9159):1119](http://pubmed.ncbi.nlm.nih.gov/10209974?dopt=Abstract) , commentary can be found in [mnh10382714paph20242065pa9h20242065pbyh20242065pafh20242065pbeh20242065phch20242065pnyh20242065pnxh20242065pbth20242065ppbh20242065pcxh20242065pmdc10382714pLancet 1999 Jun 19;353(9170):2154](http://pubmed.ncbi.nlm.nih.gov/10382714?dopt=Abstract)
* **delays by providers in diagnosis of ≥ 3 months do not appear to decrease survival**

Cohort Study[mnh10209976p t caph1711561t c pa9h1711561t c pbyh1711561t c pafh1711561t c pbeh1711561t c phch1711561t c pnyh1711561t c pnxh1711561t c pbth1711561t c ppbh1711561t c pcxh1711561t c pmdc10209976p t cLancet 1999 Apr 3;353(9159):1132](http://pubmed.ncbi.nlm.nih.gov/10209976?dopt=Abstract)

studySummary

* + based on retrospective analysis of data available in Yorkshire Cancer Registry Cohort Study
  + 36,222 patients diagnosed with breast cancer from 1976 to 1995 were analyzed for associations between delays in referral, hospital visit, or start of treatment and survival
  + median time from family-physician referral to first hospital visit for breast cancer was 10 days in 1976 vs. 12 days in 1995 (no p value reported)
  + median delay between first hospital visit and treatment was 7 days in 1976 vs. 13 days in 1995 (no p value reported)
  + compared to delays < 30 days vs
    - delays 30-59 days associated with decreased mortality (adjusted hazard ratio [HR] 0.75, 95% CI 0.69-0.82)
    - delays ≥ 60 days associated with decreased mortality (HR 0.78, 95% CI 0.69-0.89)
  + PubMed10209976Lancet (London, England)19990403Lancet353915911321132 Reference - [mnh10209976p t caph1711561t c pa9h1711561t c pbyh1711561t c pafh1711561t c pbeh1711561t c phch1711561t c pnyh1711561t c pnxh1711561t c pbth1711561t c ppbh1711561t c pcxh1711561t c pmdc10209976p t cLancet 1999 Apr 3;353(9159):1132](http://pubmed.ncbi.nlm.nih.gov/10209976?dopt=Abstract) , commentary can be found in [mnh10209969p taph1711552t pa9h1711552t pbyh1711552t pafh1711552t pbeh1711552t phch1711552t pnyh1711552t pnxh1711552t pbth1711552t ppbh1711552t pcxh1711552t pmdc10209969p tLancet 1999 Apr 3;353(9159):1112](http://pubmed.ncbi.nlm.nih.gov/10209969?dopt=Abstract) , [mnh10382716paph20242065pa9h20242065pbyh20242065pafh20242065pbeh20242065phch20242065pnyh20242065pnxh20242065pbth20242065ppbh20242065pcxh20242065pmdc10382716pLancet 1999 Jun 19;353(9170):2154](http://pubmed.ncbi.nlm.nih.gov/10382716?dopt=Abstract) , [mnh10543705paph20238594pa9h20238594pbyh20238594pafh20238594pbeh20238594phch20238594pnyh20238594pnxh20238594pbth20238594ppbh20238594pcxh20238594pmdc10543705pLancet 1999 Oct 23;354(9188):1478](http://pubmed.ncbi.nlm.nih.gov/10543705?dopt=Abstract)
* **length of delay in diagnosis not associated with prognostic factors or survival rates**

Cohort Study[16978961Am J Surg 2006 Oct;192(4):506](http://pubmed.ncbi.nlm.nih.gov/16978961?dopt=Abstract)

studySummary

* + based on retrospective analysis Cohort Study
  + 40 patients with delay in breast cancer diagnosis of 3-36 months were analyzed for associations between delay in diagnosis and prognostic factors such as tumor size, nodal status, and stage at diagnosis
  + higher stage at diagnosis associated with decreased survival (p = 0.03)
  + no significant associations found between delay of diagnosis and primary tumor diameter, number of positive lymph nodes, tumor grade, or pathologic stage
  + PubMed16978961American journal of surgery20061001Am J Surg1924506506 Reference - [16978961Am J Surg 2006 Oct;192(4):506](http://pubmed.ncbi.nlm.nih.gov/16978961?dopt=Abstract)
* **delay in surgery and in adjuvant and neoadjuvant systemic therapy each associated with increased mortality in patients with breast cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[BMJ 2020 Nov 4 early online](http://pubmed.ncbi.nlm.nih.gov/33148535)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7610021/)

Family\_Medicine Internal\_Medicine Oncologic\_Disease Primary\_Care Surgery\_and\_Proceduresdelay in surgery and in adjuvant and neoadjuvant systemic therapy each associated with increased mortality in patients with breast cancer (BMJ 2020 Nov 4 early online)12/01/2020 10:42:32 AMstudySummary

* + Systematic Review based on systematic review of observational studies
  + systematic review of 34 retrospective cohort studies evaluating delay in cancer treatment in 1,272,681 patients
    - treatments included surgery (curative, neoadjuvant, and adjuvant indications), systemic treatment, or radiation therapy
    - patients had cancers of bladder, breast, colon, rectum, lung, cervix, or head and neck
  + treatment delay was assessed from diagnosis to first treatment, or from completion of 1 treatment to start of next, and ranged from 3 to 16 weeks across studies
  + in patients with breast cancer, increased mortality associated with (hazard ratio [HR] for each 4-week delay)
    - delay in surgery (HR 1.08, 95% CI 1.03-1.13) in analysis of 6 studies
    - delay in adjuvant systemic therapy (HR 1.09, 95% CI 1.07-1.11) in analysis of 3 studies
    - delay in neoadjuvant systemic therapy (HR 1.28, 95% CI 1.05-1.56) in 1 study with 1,101 patients
  + no significant differences in mortality with delay in adjuvant radiation therapy in patients with breast cancer in 1 study with 1,062 patients
  + PubMed33148535BMJ (Clinical research ed.)BMJ20201104371m4087m4087Reference - [BMJ 2020 Nov 4 early online](http://pubmed.ncbi.nlm.nih.gov/33148535)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7610021/)

Smoking

* **smoking associated with increased mortality in women with breast cancer**

Systematic Review[23053660Breast Cancer Res Treat 2012 Nov;136(2):521](http://pubmed.ncbi.nlm.nih.gov/23053660?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23053660/)

studySummary

* + based on systematic review of observational studies Systematic Review
  + systematic review of 7 cohort studies examined association between smoking and breast cancer mortality in women with breast cancer
  + compared to never smoking, smoking significantly associated with significant increased breast cancer mortality in 4 studies
  + 2,265 women diagnosed with breast cancer were followed for median 12 years
    - compared with never smoking, current smoking associated with increased risk of
      * breast cancer mortality (hazard ratio 2.01, 95% CI 1.27-3.18)
      * nonbreast cancer mortality (hazard ratio 3.84, 95% CI 2.5-5.89)
    - no significant association between former smoking and breast cancer mortality
  + PubMed23053660Breast cancer research and treatment20121101Breast Cancer Res Treat1362521521 Reference - [23053660Breast Cancer Res Treat 2012 Nov;136(2):521](http://pubmed.ncbi.nlm.nih.gov/23053660?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23053660/)
* **current smoking and former smoking of ≥ 20 pack-years each associated with increased risk of breast cancer recurrence and mortality**

Cohort Study[24317179J Natl Cancer Inst 2014 Jan;106(1):djt359](http://pubmed.ncbi.nlm.nih.gov/24317179?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3906992/)

studySummary

* + based on cohort study Cohort Study
  + 9,975 women (mean age at diagnosis 59 years) who survived invasive primary early stage breast cancer from 3 cohorts in After Breast Cancer Pooling Project were assessed
  + 7% were current smokers, 45% were former smokers, and 48% were never smokers
  + rate of breast cancer recurrence 17.3%, breast cancer mortality 10.6%, and all-cause mortality 18.1% at median follow-up of 11 years
  + compared to never smoking
    - current smoking associated with increased risk of breast cancer recurrence, breast cancer mortality, and all-cause mortality (p < 0.001 for each)
    - former smoking of ≥ 35 pack-years associated with increased risk of breast cancer recurrence (p = 0.001), breast cancer mortality (p < 0.001), and all-cause mortality (p < 0.001)
    - former smoking of 20-34.9 pack-years associated with increased risk of breast cancer recurrence (p = 0.04) and all-cause mortality (p = 0.01), but no significant difference in risk of breast cancer mortality
  + no significant differences in breast cancer recurrence, breast cancer mortality, or all-cause mortality comparing former smoking of < 20 pack-years to never smoking
  + PubMed24317179Journal of the National Cancer Institute20140101J Natl Cancer Inst1061djt359djt359 Reference - [24317179J Natl Cancer Inst 2014 Jan;106(1):djt359](http://pubmed.ncbi.nlm.nih.gov/24317179?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3906992/)

Additional factors affecting survival

* **cosmetic breast augmentation prior to cancer detection associated with increased risk of breast cancer-specific mortality**

Systematic Review[23637132BMJ 2013 Apr 29;346:f2399](http://pubmed.ncbi.nlm.nih.gov/23637132?dopt=Abstract)[Full Text](http://www.bmj.com/content/346/bmj.f2399?view=long&pmid=23637132)

studySummary

* + based on systematic review of observational studies Systematic Review
  + systematic review of 29 observational studies with data to assess effects of cosmetic breast augmentation prior to cancer detection in women with breast cancer
  + comparing women with implants who had breast cancer to women without implants who had breast cancer, cosmetic breast implants associated with
    - increased risk of breast cancer-specific mortality (hazard ratio 1.38, 95% CI 1.08-1.75) in analysis of 5 studies with > 18,000 women
    - nonsignificant increase in risk of nonlocalized stage of breast cancer at diagnosis (p = 0.058) in analysis of 12 studies
  + PubMed23637132BMJ (Clinical research ed.)20130429BMJ346f2399f2399 Reference - [23637132BMJ 2013 Apr 29;346:f2399](http://pubmed.ncbi.nlm.nih.gov/23637132?dopt=Abstract)[full-text](http://www.bmj.com/content/346/bmj.f2399?view=long&pmid=23637132)
* **pathologic complete response after neoadjuvant chemotherapy associated with increased survival in women with large operable or locally advanced breast cancer**

Randomized Trial[24618153Ann Oncol 2014 Jun;25(6):1128](http://pubmed.ncbi.nlm.nih.gov/24618153?dopt=Abstract)

studySummary

* + based on prespecified cohort analysis of data from randomized trial without blinding Randomized Trial
  + 1,856 women with large operable or locally advanced breast cancer who were randomized to 6 cycles of neoadjuvant chemotherapy with anthracycline-based regimen vs. docetaxel-based regimen were assessed
  + 1,212 patients (65%) had evaluable pathologic response data and were included in analyses
  + 18% had pathologic complete response
  + event-free survival defined as freedom from progression, locoregional relapse, first distant metastasis, or all-cause death
  + compared to no or incomplete response, pathologic complete response associated with increased
    - event-free survival (adjusted hazard ratio for event 0.4, 95% CI 0.25-0.64)
    - overall survival (adjusted hazard ratio for death 0.4, 95% CI 0.24-0.65)
  + pathologic complete response associated with improvements in survival regardless of intrinsic subtype
  + PubMed24618153Annals of oncology : official journal of the European Society for Medical Oncology20140601Ann Oncol25611281128 Reference - [24618153Ann Oncol 2014 Jun;25(6):1128](http://pubmed.ncbi.nlm.nih.gov/24618153?dopt=Abstract)
* **higher serum 25-hydroxyvitamin D levels associated with reduced mortality in patients with breast cancer**

Systematic Review[24582912Eur J Cancer 2014 May;50(8):1510](http://pubmed.ncbi.nlm.nih.gov/24582912?dopt=Abstract)

studySummary

* + based on systematic review of observational studies Systematic Review
  + systematic review of 9 prospective cohort studies evaluating association between serum 25-hydroxyvitamin D levels and survival in 6,743 patients with colorectal or breast cancer
  + 5 studies evaluated patients with breast cancer
    - mean age was 50-56 years
    - follow-up ranged from 4.7 to 24 years
  + comparing highest (weighted mean 88 nmol/L) to lowest (weighted mean 41 nmol/L) category of serum 25-hydroxyvitamin D levels, highest category of serum 25-hydroxyvitamin D levels associated with
    - decreased overall mortality (hazard ratio [HR] 0.62, 95% CI 0.49-0.78) in analysis of 5 studies with 4,413 patients
    - decreased breast cancer-related mortality (HR 0.57, 95% CI 0.38-0.84) in analysis of 3 studies with 2,636 patients
  + PubMed24582912European journal of cancer20140501Eur J Cancer50815101510 Reference - [24582912Eur J Cancer 2014 May;50(8):1510](http://pubmed.ncbi.nlm.nih.gov/24582912?dopt=Abstract)
* aspirin associated with decreased breast cancer-specific mortality
  + **aspirin use after breast cancer diagnosis associated with decreased risk of breast cancer-specific mortality (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[mnh25677744pcxh101228872pmdc25677744pBreast Cancer Res Treat 2015 Feb;150(1):199](http://pubmed.ncbi.nlm.nih.gov/25677744?dopt=Abstract)

studySummary2

* + - based on systematic review of observational studies Systematic Review
    - systematic review of 10 observational studies (8 cohort, 2 nested case-control) evaluating association between aspirin use and risk of mortality in breast cancer in 685,829 women
    - duration of follow-up ranged from 2.6 to 30 years
    - postdiagnostic aspirin use
      * associated with decrease in breast cancer-specific mortality (risk ratio [RR] 0.73, 95% CI 0.54-0.98) in analysis of 7 studies with 26,931 women, results limited by significant heterogeneity
      * not significantly associated with all-cause mortality in analysis of 7 studies with 26,931 women, results limited by significant heterogeneity
    - prediagnostic aspirin use not significantly associated with
      * breast cancer-specific mortality in analysis of 6 studies with 673,453 women, results limited by significant heterogeneity
      * all-cause mortality in analysis of 2 studies with 8,447 women, results limited by significant heterogeneity
    - PubMed25677744Breast cancer research and treatment20150201Breast Cancer Res Treat1501199199 Reference - [mnh25677744pcxh101228872pmdc25677744pBreast Cancer Res Treat 2015 Feb;150(1):199](http://pubmed.ncbi.nlm.nih.gov/25677744?dopt=Abstract)
  + **aspirin associated with reduced risk of breast cancer mortality in women with early or locally advanced breast cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cohort Study[J Clin Oncol 2010 Mar 20;28(9):1467](http://pubmed.ncbi.nlm.nih.gov/20159825-aspirin-intake-and-survival-after-breast-cancer/?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2849768/)Cohort Study[Br J Cancer 2014 Jul 29;111(3):623](http://pubmed.ncbi.nlm.nih.gov/24945997-aspirin-use-and-survival-after-the-diagnosis-of-breast-cancer-a-population-based-cohort-study/?dopt=Abstract)

studySummary

* + - Cohort StudyCohort Study based on 2 cohort studies
    - 4,164 women in Nurses' Health Study diagnosed with breast cancer stage I, II, or III between 1976 and 2002 were followed up to 2006
      * breast cancer-related death in 8.2%
      * decreased risk of breast cancer-related death with aspirin use (p < 0.001 for trend)
        + adjusted relative risk (RR) 1.07 (95% CI 0.7-1.63) for aspirin use 1 day weekly vs. no use
        + adjusted RR 0.29 (95% CI 0.16-0.52) for aspirin use 2-5 days weekly vs. no use
        + adjusted RR 0.36 (95% CI 0.24-0.54) for aspirin use 6-7 days weekly vs. no use
      * decreased risk of distant recurrence with aspirin use (p = 0.03 for trend)
        + adjusted RR 0.91 (95% CI 0.62-1.33) for aspirin use 1 day weekly vs. no use
        + adjusted RR 0.4 (95% CI 0.24-0.65) for aspirin use 2-5 days weekly vs. no use
        + adjusted RR 0.57 (95% CI 0.39-0.82) for aspirin use 6-7 days weekly vs. no use
      * decreased risk of all-cause mortality with aspirin use (p = 0.004 for trend)
        + adjusted RR 0.94 (95% CI 0.67-1.32) for aspirin use 1 day weekly vs. no use
        + adjusted RR 0.53 (95% CI 0.37-0.76) for aspirin use 2-5 days weekly vs. no use
        + adjusted RR 0.54 (95% CI 0.41-0.7) for aspirin use 6-7 days weekly vs. no use
      * PubMed20159825Journal of clinical oncology : official journal of the American Society of Clinical OncologyJ Clin Oncol201003202891467-721467Reference - [J Clin Oncol 2010 Mar 20;28(9):1467](http://pubmed.ncbi.nlm.nih.gov/20159825-aspirin-intake-and-survival-after-breast-cancer/?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2849768/)
    - 4,627 women diagnosed with breast cancer between 1998 and 2008 were followed up to 2010
      * breast cancer-related death in 18%, aspirin prescribed post diagnosis in 22%
      * aspirin use post diagnosis associated with lower risk of
        + all-cause mortality (hazard ratio 0.53, 95% CI 0.45-0.63)
        + breast cancer-specific mortality (hazard ratio 0.42, 95% CI 0.31-0.55)
      * PubMed24945997British journal of cancerBr J Cancer201407291113623-7623Reference - [Br J Cancer 2014 Jul 29;111(3):623](http://pubmed.ncbi.nlm.nih.gov/24945997-aspirin-use-and-survival-after-the-diagnosis-of-breast-cancer-a-population-based-cohort-study/?dopt=Abstract)

Recurrence risk

Tumor size and lymph node status

* **higher number of positive lymph nodes and lower number of uninvolved lymph nodes associated with high rates of 10-year locoregional recurrence after mastectomy**

Cohort Study[22776708Ann Oncol 2012 Nov;23(11):2852](http://pubmed.ncbi.nlm.nih.gov/22776708?dopt=Abstract)

studySummary

* + based on retrospective cohort study Cohort Study
  + 8,109 patients from 13 International Breast Cancer Study Group randomized trials who had total mastectomy plus chemotherapy and/or endocrine therapy but not radiation therapy were evaluated for local, axillary, and supraclavicular cancer recurrences and associated risk factors
  + median follow-up 15.2 years
  + 10-year cumulative incidence of chest wall recurrence was highest in patients
    - with ≥ 4 positive lymph nodes (16.5%)
    - with 0-7 uninvolved lymph nodes (15.1%)
    - aged < 40 years (16.1%)
  + 10-year incidence of supraclavicular recurrence was highest in patients with ≥ 4 positive lymph nodes (10.2%)
  + 10-year incidence of axillary recurrence was below 10% for all risk factors examined
  + PubMed22776708Annals of oncology : official journal of the European Society for Medical Oncology20121101Ann Oncol231128522852 Reference - [22776708Ann Oncol 2012 Nov;23(11):2852](http://pubmed.ncbi.nlm.nih.gov/22776708?dopt=Abstract)
* **tumor size > 2 cm may have decreased disease-free survival and time to recurrence in women with node-negative breast cancer**

Cohort Study[mdc7738620pJ Clin Oncol 1995 May;13(5):1144](http://pubmed.ncbi.nlm.nih.gov/7738620?dopt=Abstract)

studySummary

* + based on retrospective cohort study Cohort Study
  + 826 women with node-negative breast cancer treated with mastectomy and axillary dissection from 1927 to 1984 and followed for mean 13.5 years
  + comparing tumors < 2 cm vs. tumors > 2 cm
    - 20-year disease-free survival 79% vs. 64% (p < 0.001)
    - median time to recurrence 48 months vs. 37 months (p = 0.01)
  + PubMed7738620Journal of clinical oncology : official journal of the American Society of Clinical Oncology19950501J Clin Oncol13511441144 Reference - [mdc7738620pJ Clin Oncol 1995 May;13(5):1144](http://pubmed.ncbi.nlm.nih.gov/7738620?dopt=Abstract) , commentary can be found in [mdc8558214pJ Clin Oncol 1996 Jan;14(1):321](http://pubmed.ncbi.nlm.nih.gov/8558214?dopt=Abstract)
* **larger tumor size correlated with lower breast cancer-specific survival, except in women with basal-like breast cancer (BLBC)**

Cohort Study[mnh18600446pcxh43707079pmdc18600446pBreast Cancer Res Treat 2009 Sep;117(1):199](http://pubmed.ncbi.nlm.nih.gov/18600446?dopt=Abstract)

studySummary

* + based on retrospective analysis of data available in Nottingham Breast Cancer Series Cohort Study
  + 1,520 women with breast cancer (196 of whom had basal-like breast cancer) were evaluated for tumor size, nodal status, and survival and followed for median 136 months
  + increasing tumor size associated with worsening breast cancer-specific survival in non-BLBC cases (p < 0.001) but not in BLBC cases (not significant)
  + PubMed18600446Breast cancer research and treatment20090901Breast Cancer Res Treat1171199199 Reference - [mnh18600446pcxh43707079pmdc18600446pBreast Cancer Res Treat 2009 Sep;117(1):199](http://pubmed.ncbi.nlm.nih.gov/18600446?dopt=Abstract)
* **≥ 4 positive lymph nodes and primary tumor > 2 cm may be associated with decreased 20-year disease-free survival**

Cohort Study[mdc8955655pJ Clin Oncol 1996 Dec;14(12):3105](http://pubmed.ncbi.nlm.nih.gov/8955655?dopt=Abstract)

studySummary

* + based on retrospective cohort study Cohort Study
  + 501 women diagnosed with node-positive breast cancer from 1927 to 1987 were treated with radical, extended radical, or modified radical mastectomy and followed for mean 10 years
  + comparing tumors < 2 cm vs. tumors > 2 cm, 20-year disease-free survival 73% vs. 47% (p < 0.001)
  + comparing 1-3 positive lymph nodes vs. ≥ 4 positive lymph nodes, 20-year disease-free survival 63% vs. 36% (p < 0.001)
  + comparing tumors < 1.1 cm vs. 1.1-2 cm vs. > 2 cm in patients with
    - 0 positive nodes, 20-year disease-free survival 79% vs. 79% vs. 64% (p < 0.001)
    - 1 positive node, 20-year disease-free survival 95% vs. 78% vs. 59% (p = 0.003)
    - 2-3 positive nodes, 20-year disease-free survival 73% vs. 73% vs. 53% (p = 0.01)
  + PubMed8955655Journal of clinical oncology : official journal of the American Society of Clinical Oncology19961201J Clin Oncol141231053105 Reference - [mdc8955655pJ Clin Oncol 1996 Dec;14(12):3105](http://pubmed.ncbi.nlm.nih.gov/8955655?dopt=Abstract)
* **metastatic lymph node ratio (MLNR) associated with breast cancer recurrence**

Cohort Study[mnh19488815pcxh43265289pmdc19488815pWorld J Surg 2009 Aug;33(8):1659](http://pubmed.ncbi.nlm.nih.gov/19488815?dopt=Abstract)

studySummary

* + based on retrospective cohort study Cohort Study
  + 441 women (median age 59 years) with T1-2, N1-3 breast cancer included in Castellon (Spain) Cancer Registry
  + recurrence occurred in 26%
  + MLNR is number of metastatic lymph nodes over total number of resected lymph nodes
  + MLNR associated with increased risk of recurrence (hazard ratio 5.2, 95% CI 1.5-17.8), although not after 60 months of follow-up (hazard ratio 1.38, 95% CI 0.02-85.9)
  + comparing MLNR < 20% vs. 20%-60% vs. > 60%, disease-free survival (extrapolated from graph) in 20% vs. 25% vs. 50% (no p value reported)
  + PubMed19488815World journal of surgery20090801World J Surg33816591659 Reference - [mnh19488815pcxh43265289pmdc19488815pWorld J Surg 2009 Aug;33(8):1659](http://pubmed.ncbi.nlm.nih.gov/19488815?dopt=Abstract)
* **primary breast cancer with ≥ 10 involved lymph nodes associated with increased risk of metachronous contralateral breast cancer**

Cohort Study[cxh82203233pmdc22927521pJ Clin Oncol 2012 Oct 1;30(28):3478](http://pubmed.ncbi.nlm.nih.gov/22927521?dopt=Abstract)

studySummary

* + based on prospective cohort study Cohort Study
  + from a cohort of 42,670 women with breast cancer in Sweden from 1992 to 2008, 35,897 women with data available for initial tumor size and nodal status were assessed for risk factors for metachronous contralateral breast cancer
  + 2.5% developed metachronous contralateral breast cancer in median follow-up 9.9 years
  + increased risk of contralateral breast cancer associated with
    - primary breast cancer with ≥ 10 involved lymph nodes compared to node-negative breast cancer (adjusted hazard ratio 1.8, 95% CI 1.2-2.7)
    - tumor of any size with extension to chest wall and/or skin compared to tumor < 2 cm (adjusted hazard ratio 2.2, 95% CI 1.3-3.6)
  + PubMed22927521Journal of clinical oncology : official journal of the American Society of Clinical Oncology20121001J Clin Oncol302834783478 Reference - [cxh82203233pmdc22927521pJ Clin Oncol 2012 Oct 1;30(28):3478](http://pubmed.ncbi.nlm.nih.gov/22927521?dopt=Abstract)
* **larger tumor size and positive nodal status associated with increased risk of locoregional recurrence after neoadjuvant chemotherapy**

Cohort Study[cxh83235280pmdc23032615pJ Clin Oncol 2012 Nov 10;30(32):3960](http://pubmed.ncbi.nlm.nih.gov/23032615?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3488269/)

studySummary

* + based on prospective cohort study Cohort Study
  + 3,088 women with breast cancer from 2 neoadjuvant trials (doxorubicin/cyclophosphamide alone or doxorubicin/cyclophosphamide followed by neoadjuvant/adjuvant docetaxel) were followed for 10 years
  + 10-year incidence of locoregional recurrence was 11.1% overall
  + factors associated with increased risk of locoregional recurrence in overall analysis were
    - tumor size > 5 cm vs. ≤ 5 cm (hazard ratio [HR] 1.51, 95% CI 1.19-1.91)
    - positive vs. negative clinical nodal status (HR 1.61, 95% CI 1.28-2.02)
    - absence of vs. presence of pathologic complete response in patients with negative pathologic nodal status (HR 1.55, 95% CI 1.01-2.39)
    - positive vs. negative pathologic nodal status in patients with pathologic complete response (HR 2.71, 95% CI 1.79-4.09)
  + PubMed23032615Journal of clinical oncology : official journal of the American Society of Clinical Oncology20121110J Clin Oncol303239603960 Reference - [cxh83235280pmdc23032615pJ Clin Oncol 2012 Nov 10;30(32):3960](http://pubmed.ncbi.nlm.nih.gov/23032615?dopt=Abstract) [full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3488269/), editorials can be found at [cxh83235272pmdc23032624pJ Clin Oncol 2012 Nov 10;30(32):3913](http://pubmed.ncbi.nlm.nih.gov/23032624?dopt=Abstract)

Risk for axillary recurrence

* **5-year incidence of isolated axillary recurrence 1%**

Cohort Study[mdc16983030pArch Surg 2006 Sep;141(9):867](http://pubmed.ncbi.nlm.nih.gov/16983030?dopt=Abstract)

studySummary

* + based on 19,789 women with stage 0- III breast cancer from 1989 to 2003 Cohort Study
  + 220 had isolated axillary recurrence, with median survival 4.9 years after recurrence (range 2 months to 15 years)
  + PubMed16983030Archives of surgery (Chicago, Ill. : 1920)20060901Arch Surg1419867867 Reference - [mdc16983030pArch Surg 2006 Sep;141(9):867](http://pubmed.ncbi.nlm.nih.gov/16983030?dopt=Abstract)
* **isolated axillary node recurrence after negative sentinel lymph node biopsy (SLNB) is rare (< 1%)**

Systematic Review[21254004Br J Surg 2011 Mar;98(3):326](http://pubmed.ncbi.nlm.nih.gov/21254004?dopt=Abstract)

studySummary

* + based on systematic review of cohort studies Systematic Review
  + systematic review of 45 cohort studies evaluating reporting isolated axillary recurrence after negative SLNB in 23,357 patients with breast cancer followed for median 39 months
  + 127 patients (0.5%) had isolated axillary recurrence
  + PubMed21254004The British journal of surgery20110301Br J Surg983326326 Reference - [21254004Br J Surg 2011 Mar;98(3):326](http://pubmed.ncbi.nlm.nih.gov/21254004?dopt=Abstract)

Risk for late recurrence

* **risk for late recurrence (after being disease-free for ≥ 5 years) is 7%-13%**

Cohort Study[18695137J Natl Cancer Inst 2008 Aug 20;100(16):1179](http://pubmed.ncbi.nlm.nih.gov/18695137?dopt=Abstract)[Full Text](http://jnci.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=18695137)

studySummary

* + based on retrospective cohort study Cohort Study
  + 2,838 patients with stage I-III breast cancer who were disease-free for ≥ 5 years after adjuvant or neoadjuvant systemic therapy evaluated
  + among 216 patients (8%) with late recurrence, 5-year residual risk for recurrence was
    - 7% for stage I (95% CI 3%-15%)
    - 11% for stage II (95% CI 9%-13%)
    - 13% for stage III (95% CI 10%-17%)
  + late recurrence was associated with stage, grade, hormone receptor status, and endocrine therapy
  + PubMed18695137Journal of the National Cancer Institute20080820J Natl Cancer Inst1001611791179 Reference - [18695137J Natl Cancer Inst 2008 Aug 20;100(16):1179](http://pubmed.ncbi.nlm.nih.gov/18695137?dopt=Abstract)[full-text](http://jnci.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=18695137)

Other risk factors for recurrence

* **women < 35 years old with operable breast cancer have higher recurrence rate than older women**

Cohort Study[mnh15546499paph29336656pa9h29336656pafh29336656pcxh29336656pmdc15546499pBMC Cancer 2004 Nov 17;4:82](http://pubmed.ncbi.nlm.nih.gov/15546499?dopt=Abstract)[Full Text](http://www.biomedcentral.com/1471-2407/4/82)

studySummary

* + based on retrospective cohort study Cohort Study
  + 2,040 women who had surgery for primary invasive breast cancer from 1990 to 1999 followed for median 74 months
  + 12.5% were < 35 years old
  + compared to age > 35 years, age < 35 years associated with increased risk of recurrence (adjusted hazard ratio 1.7, 95% CI 1.1-2.6)
  + comparing age < 35 years vs. > 35 years, 5-year recurrence rate 30.4% vs. 18.7% (p < 0.001)
  + PubMed15546499BMC cancer20041117BMC Cancer48282 Reference - [mnh15546499paph29336656pa9h29336656pafh29336656pcxh29336656pmdc15546499pBMC Cancer 2004 Nov 17;4:82](http://pubmed.ncbi.nlm.nih.gov/15546499?dopt=Abstract) [full-text](http://www.biomedcentral.com/1471-2407/4/82)
* women < 35 years old may have increased risk for occurrence of metachronous contralateral breast cancer
  + 45,229 women with operable stage I-IIIA breast cancer evaluated
  + median follow-up 5.8 years
  + 1,477 developed new cancer in contralateral breast (metachronous contralateral breast cancer)
  + standardized incidence ratios for metachronous contralateral breast cancers
    - 11.4 for women < 35 years old (95% CI 8.6-14.8)
    - 4.9 for women aged 35-39 years (95% CI 3.9-6.1)
    - 2.4 for women aged 40-49 years (95% CI 2.1-2.7)
    - 1.8 for women aged 50-59 years (95% CI 1.5-2)
    - 1.5 for women aged 60-69 years (95% CI 1.3-1.8)
    - 1.7 for women aged 70-79 years (95% CI 1.5-2)
    - 1.2 for women ≥ 80 years old (95% CI 0.9-1.6)
  + Reference - [mnh17687645pcxh33052959pmdc17687645pBreast Cancer Res Treat 2008 Jul;110(1):189](http://pubmed.ncbi.nlm.nih.gov/17687645?dopt=Abstract) [full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/17687645/)
* **anemia developing during chemotherapy may be associated with risk for local recurrence in premenopausal women with primary breast cancer**

Cohort Study[18381948Clin Cancer Res 2008 Apr 1;14(7):2082](http://pubmed.ncbi.nlm.nih.gov/18381948?dopt=Abstract)[Full Text](http://clincancerres.aacrjournals.org/content/14/7/2082.long)

studySummary

* + based on retrospective cohort study Cohort Study
  + 424 premenopausal women with early-stage primary breast cancer and hormone receptor-expressing tumors had adjuvant cyclophosphamide/methotrexate/5-fluorouracil (CMF) and were followed for median 5 years
  + patients with < 3 cycles of CMF or without serum hemoglobin levels at between cycles 3 and 6 of CMF were excluded
  + 18.2% developed anemia (hemoglobin < 12 g/dL [120 g/L]) while on CMF therapy
  + local relapse occurred in 19.6% anemic vs. 8.9% nonanemic patients (p = 0.0006)
  + PubMed18381948Clinical cancer research : an official journal of the American Association for Cancer Research20080401Clin Cancer Res14720822082 Reference - [18381948Clin Cancer Res 2008 Apr 1;14(7):2082](http://pubmed.ncbi.nlm.nih.gov/18381948?dopt=Abstract)[full-text](http://clincancerres.aacrjournals.org/content/14/7/2082.long)
  + Whether patients with and without anemia had similar chemotherapy durations was not reported. Anemia as a prognostic factor could be confounded by interruptions or earlier termination of chemotherapy.
* **beta-blockers may be associated with increased risk of breast cancer recurrence**

Cohort Study[cxh88102092pmdc23650417pJ Clin Oncol 2013 Jun 20;31(18):2265](http://pubmed.ncbi.nlm.nih.gov/23650417?dopt=Abstract)

studySummary

* + based on cohort study Cohort Study
  + 18,733 women with nonmetastatic breast cancer were analyzed
  + median follow-up 6.8 years, 19.5% were ever users of any beta-blocker
  + compared with never use, 10-year risk of breast cancer recurrence
    - increased with any beta-blocker in adjusted analysis (adjusted hazard ratio [HR] 1.3, 95% CI 1.1-1.5), but not increased in unadjusted analysis
    - not significantly increased with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers
  + PubMed23650417Journal of clinical oncology : official journal of the American Society of Clinical Oncology20130620J Clin Oncol311822652265 Reference - [cxh88102092pmdc23650417pJ Clin Oncol 2013 Jun 20;31(18):2265](http://pubmed.ncbi.nlm.nih.gov/23650417?dopt=Abstract)
* **higher serum estrogen levels may be associated with increased risk for recurrence or new primary breast cancer**

Case-Control Study[18323413Cancer Epidemiol Biomarkers Prev 2008 Mar;17(3):614](http://pubmed.ncbi.nlm.nih.gov/18323413?dopt=Abstract)[Full Text](http://cebp.aacrjournals.org/content/17/3/614.long)

studySummary

* + based on nested case-control study Case-Control Study
  + Women's Healthy Eating and Living Study (WHEL) was randomized diet trial with breast cancer patients followed for mean 7.3 years
  + 153 peri- or postmenopausal women with recurrent or new primary early-stage breast cancer were matched to 153 recurrence-free controls from WHEL
  + risk of recurrence or new cancer increased with increasing baseline concentrations of total estradiol, bioavailable estradiol, and free estradiol
  + PubMed18323413Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology20080301Cancer Epidemiol Biomarkers Prev173614614 Reference - [18323413Cancer Epidemiol Biomarkers Prev 2008 Mar;17(3):614](http://pubmed.ncbi.nlm.nih.gov/18323413?dopt=Abstract)[full-text](http://cebp.aacrjournals.org/content/17/3/614.long)
* **stressful life experiences do not increase recurrence risk**

Cohort Study[12065263BMJ 2002 Jun 15;324(7351):1420](http://pubmed.ncbi.nlm.nih.gov/12065263?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC115851/)

studySummary

* + based on prospective cohort study Cohort Study
  + 170 women < 60 years old and newly diagnosed with operable breast cancer from 1991 to 1994 were interviewed about stressful life experiences and depression every 18 months, beginning 1 year before diagnosis and continuing up to 5 years after diagnosis or to recurrence
  + 76% overall 5-year relapse-free survival
  + recurrence confirmed in 31.6%
  + compared to 0 severely stressful life experiences before or after diagnosis, ≥ 1 severely stressful life experiences after diagnosis associated with decreased risk of recurrence (hazard ratio 0.52, 95% CI 0.29-0.95), but no association before diagnosis
  + PubMed12065263BMJ (Clinical research ed.)20020615BMJ324735114201420 Reference - [12065263BMJ 2002 Jun 15;324(7351):1420](http://pubmed.ncbi.nlm.nih.gov/12065263?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC115851/), commentary can be found in [12218002BMJ 2002 Sep 7;325(7363):548](http://pubmed.ncbi.nlm.nih.gov/12218002?dopt=Abstract)

BRCA mutations

* ***BRCA1* and *BRCA2* (breast cancer susceptibility genes) mutation carriers have similar prognosis (survival and distant recurrences) as patients with sporadic breast cancer**

Cohort Study[J Clin Oncol 2012 Jan 1;30(1):19](http://pubmed.ncbi.nlm.nih.gov/22147742-breast-cancer-prognosis-in-brca1-and-brca2-mutation-carriers-an-international-prospective-breast-cancer-family-registry-population-based-cohort-study/?dopt=Abstract)

studySummary

* + Cohort Study based on cohort study
  + prospective cohort study of 3,220 women (mean age 45.3 years) with incident breast cancer in Canada, United States, and Australia from 1995 to 2000
    - mean follow-up 7.9 years
    - 93 women had BRCA1 mutations, 71 had BRCA2 mutations, 1 had both mutations
    - 1,550 had sporadic breast cancer
    - 1,505 had familial breast cancer (without known BRCA1 or BRCA2 mutations)
    - no significant differences in mortality or distant recurrence in multivariate analyses comparing carriers of BRCA1 or BRCA2 mutations and patients with sporadic breast cancer
    - BRCA2 carriers had higher mortality and risk for distant recurrence in univariate analysis but no significant difference after adjusting for age, tumor stage and grade, nodal status, hormonal receptors, and year of diagnosis
    - Reference - [cxh70106115pmdc22147742pJ Clin Oncol 2012 Jan 1;30(1):19](http://pubmed.ncbi.nlm.nih.gov/22147742?dopt=Abstract) , editorial can be found in [cxh70106110pmdc22147741pJ Clin Oncol 2012 Jan 1;30(1):2](http://pubmed.ncbi.nlm.nih.gov/22147741?dopt=Abstract)
  + PubMed22147742Journal of clinical oncology : official journal of the American Society of Clinical OncologyJ Clin Oncol2012010130119-2619Reference - [J Clin Oncol 2012 Jan 1;30(1):19](http://pubmed.ncbi.nlm.nih.gov/22147742-breast-cancer-prognosis-in-brca1-and-brca2-mutation-carriers-an-international-prospective-breast-cancer-family-registry-population-based-cohort-study/?dopt=Abstract), editorial can be found in
  + breast cancer-specific mortality not significantly different in carriers of BRCA1 and BRCA2 mutations in medical record review of 1,545 women with breast cancer ([17625123N Engl J Med 2007 Jul 12;357(2):115](http://pubmed.ncbi.nlm.nih.gov/17625123?dopt=Abstract)[full-text](http://www.nejm.org/doi/full/10.1056/NEJMoa070608#t=article)), editorial can be found in [17625130N Engl J Med 2007 Jul 12;357(2):175](http://pubmed.ncbi.nlm.nih.gov/17625130?dopt=Abstract), commentary can be found in [17928608N Engl J Med 2007 Oct 11;357(15):1555](http://pubmed.ncbi.nlm.nih.gov/17928608?dopt=Abstract)
* ***BRCA* mutation carriers have similar rates of recurrence after breast-conserving surgery and radiation therapy compared to nonmutation carriers**

Cohort Study[16140006Eur J Cancer 2005 Oct;41(15):2304](http://pubmed.ncbi.nlm.nih.gov/16140006?dopt=Abstract)

studySummary

* + based on retrospective cohort study Cohort Study
  + 131 patients (median age 43 years) with family history of breast and/or ovarian cancer treated with breast-conserving surgery and radiation therapy screened for BRCA1 and BRCA2 gene mutations and 261 women with breast cancer and without family history of breast cancer were evaluated
  + median follow-up 8.75 years
  + BRCA1/2 mutations found in 20.6% with family history
  + decreasing age associated with breast cancer recurrence (p < 0.05)
  + no significant differences in breast cancer recurrence as first event

| Comparing Recurrence by Tumor Type | | | |
| --- | --- | --- | --- |
|  | **Women with BRCA Mutations** | **Women with Family History but no Mutations** | **Women without Family History** |
| Median time to breast cancer recurrence | 80 months | 39 months | 46 months |
| Breast cancer recurrence | 24% | 22% | 19% |
| Contralateral breast cancer | 37% | 18.3%\* | 7.3%\* |
| Abbreviation: BRCA, breast cancer                                              susceptibility gene.  \* p < 0.001 vs.                                              BRCA mutations. | | | |

* + PubMed16140006European journal of cancer20051001Eur J Cancer411523042304 Reference - [16140006Eur J Cancer 2005 Oct;41(15):2304](http://pubmed.ncbi.nlm.nih.gov/16140006?dopt=Abstract)

Pregnancy-associated breast cancer

* there is mixed evidence regarding outcomes in women with pregnancy-associated breast cancer, which may be attributed to
  + the years in which the study was conducted (in older studies there may have been further delays in treatment or substandard treatment offered)
  + timing of diagnosis (during pregnancy vs. postpartum vs. lactation)
  + PubMed28232597The oncologistOncologist20170301223324-334324Reference - [Oncologist 2017 Mar;22(3):324](http://pubmed.ncbi.nlm.nih.gov/28232597)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5344634/)
* **women with pregnancy-associated breast cancer have similar number of hospitalizations and similar length of stay as women with history of breast cancer**

Cohort Study[Gynecol Obstet Invest 2019;84(1):79](http://pubmed.ncbi.nlm.nih.gov/30219806)[Full Text](https://www.karger.com/Article/FullText/493128)

studySummary

* + Cohort Study based on retrospective cohort study
  + 69 pregnant women with either current (pregnancy-associated) breast cancer or history of breast cancer between 2004 and 2015 were included
  + 22 (32%, mean age 35 years) had pregnancy-associated breast cancer and 47 women (68%, mean age 37 years) had history of breast cancer
  + 13 women (59%) with pregnancy-associated breast cancer received antepartum chemotherapy
  + comparing women with pregnancy-associated breast cancer vs. those with history of breast cancer
    - labor induction in 50% vs. 32.6% (p = 0.045)
    - preterm birth in 63.6% vs. 8.7% (p < 0.0001)
  + no significant difference in number of antepartum or postpartum hospitalizations or length of hospital stay
  + PubMed30219806Gynecologic and obstetric investigationGynecol Obstet Invest2019010184179-8579Reference - [Gynecol Obstet Invest 2019;84(1):79](http://pubmed.ncbi.nlm.nih.gov/30219806)[full-text](https://www.karger.com/Article/FullText/493128)
* **women with pregnancy-associated breast cancer who electively terminate their pregnancy do not appear to have increased survival compared to those who continue pregnancy through to a live birth (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cohort Study[Cancer J 2010 Jan;16(1):76](http://pubmed.ncbi.nlm.nih.gov/20164696)

studySummary

* + Cohort Study based on cohort study
  + 130 women (mean age at diagnosis 34 years) with pregnancy-associated breast cancer from the international Cancer and Pregnancy Registry were included
    - included women diagnosed with breast cancer while pregnant or up to 6 weeks postpartum
    - 99 women (76%) were prospectively enrolled and 31 women (24%) were retrospectively enrolled
  + 120 women (92%) were diagnosed with a primary breast tumor, 8 (6%) with recurrence of breast cancer, and 2 (1.5%) with a new primary cancer
  + 10 women (8%) electively terminated their pregnancy and 6 (5%) had spontaneous abortions prior to 13 weeks gestational age
  + 113 women (87%) were followed for mean 3.14 years
    - 30 women (26.5%) had recurrence occurring at a mean 16 months after delivery; 20 (67% of those with recurrence) had stage IV disease at time of recurrence
    - 1 woman (0.9%) had a new primary
    - overall survival for 103 women with a primary breast tumor who continued pregnancy to birth was
      * 100% in women with stage I disease
      * 86% in women with stage II disease
      * 86% in women with stage III disease
      * 0% in women with stage IV disease
    - comparing women who electively terminated the pregnancy vs. those who continued pregnancy through to a live birth, survival was 83% vs. 85% (not significant)
  + PubMed20164696Cancer journal (Sudbury, Mass.)Cancer J2010010116176-8276Reference - [Cancer J 2010 Jan;16(1):76](http://pubmed.ncbi.nlm.nih.gov/20164696)
* **pregnancy-associated breast cancer (PABC) may be associated with poorer survival**

Case-Control Study[18591310Obstet Gynecol 2008 Jul;112(1):71](http://pubmed.ncbi.nlm.nih.gov/18591310?dopt=Abstract)

studySummary

* + based on case-control study Case-Control Study
  + 797 women with PABC compared to 4,177 age-matched controls with breast cancer
  + PABC defined as occurring within 9 months before to 1 year after delivery
  + comparing PABC cases vs. controls
    - mortality 39.2% vs. 33.4% (p = 0.002)
    - pregnancy-associated cases presented with more advanced disease, larger tumors, and increased percentage of hormone receptor-negative tumors
  + other factors associated with significantly increased mortality included advanced stage, race (African American patients > non-Hispanic White patients), hormone receptor negative tumors, and pregnancy
  + PubMed18591310Obstetrics and gynecology20080701Obstet Gynecol11217171 Reference - [18591310Obstet Gynecol 2008 Jul;112(1):71](http://pubmed.ncbi.nlm.nih.gov/18591310?dopt=Abstract)
* **women < 35 years old with PABC may have similar rates of survival, recurrence, and distant metastases compared to other young women with breast cancer**

Cohort Study[19204903Cancer 2009 Mar 15;115(6):1174](http://pubmed.ncbi.nlm.nih.gov/19204903?dopt=Abstract)[Full Text](http://onlinelibrary.wiley.com/doi/10.1002/cncr.24165/full)

studySummary

* + based on retrospective cohort study Cohort Study
  + 652 women ≤ 35 years old with breast cancer evaluated
  + 104 breast cancers were pregnancy-associated
  + median follow-up for living patients 114 months
  + comparing patients with PABC vs. non-PABC
    - overall survival 64.6% vs. 64.8% (not significant)
    - 10-year locoregional recurrence rate 23.4% vs. 19.2% (not significant)
    - distant metastases in 45.1% vs. 38.9% (not significant)
  + PABC had significantly more advanced T classification, N classification, and stage group (p < 0.04)
  + PubMed19204903Cancer20090315Cancer115611741174 Reference - [19204903Cancer 2009 Mar 15;115(6):1174](http://pubmed.ncbi.nlm.nih.gov/19204903?dopt=Abstract)[full-text](http://onlinelibrary.wiley.com/doi/10.1002/cncr.24165/full)
* **diagnosis during lactation associated with increased risk of cause-specific death**

Cohort Study[mdc19029418pJ Clin Oncol 2009 Jan 1;27(1):45](http://pubmed.ncbi.nlm.nih.gov/19029418?dopt=Abstract)

studySummary

* + based on cohort study Cohort Study
  + 42,511 women aged 16-49 years, diagnosed with cancer from 1967 to 2002
  + cohort classified as not pregnant, pregnant, or lactating at time of cancer diagnosis
  + increased risk of cause-specific death if lactating at time of diagnosis of ovarian cancer (hazard ratio 1.95, p < 0.05)
  + PubMed19029418Journal of clinical oncology : official journal of the American Society of Clinical Oncology20090101J Clin Oncol2714545 Reference - [mdc19029418pJ Clin Oncol 2009 Jan 1;27(1):45](http://pubmed.ncbi.nlm.nih.gov/19029418?dopt=Abstract)
* **recent pregnancy (within 2 years of diagnosis) may be a negative prognostic factor**

Cohort Study[Obstet Gynecol 2008 May;111(5):1167](http://pubmed.ncbi.nlm.nih.gov/18448751-relationship-of-time-since-childbirth-and-other-pregnancy-factors-to-premenopausal-breast-cancer-prognosis/?dopt=Abstract)Cohort Study[BMJ 1997 Oct 4;315(7112):851](http://pubmed.ncbi.nlm.nih.gov/9353505-time-since-childbirth-and-prognosis-in-primary-breast-cancer-population-based-study/?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2127579/)

studySummary

* + Cohort StudyCohort Study based on 2 cohort studies
  + cohort study of women in Nova Scotia giving birth from 1980 to 2001
    - among 123,323 women giving birth, 716 were diagnosed with invasive breast cancer
    - women with < 2 years between childbirth and diagnosis of breast cancer had significantly increased risk for having later-stage disease and poorer survival than women with interval ≥ 5 years
    - PubMed18448751Obstetrics and gynecologyObstet Gynecol2008050111151167-731167Reference - [Obstet Gynecol 2008 May;111(5):1167](http://pubmed.ncbi.nlm.nih.gov/18448751-relationship-of-time-since-childbirth-and-other-pregnancy-factors-to-premenopausal-breast-cancer-prognosis/?dopt=Abstract)
  + retrospective study of 5,652 women < 46 years old at time of diagnosis of primary breast cancer
    - women diagnosed within 2 years after last childbirth had 58.7% five-year survival and 46.1% ten-year survival
    - women whose last childbirth was > 2 years before diagnosis had 78.4% five-year survival and 66% ten-year survival
    - PubMed9353505BMJ (Clinical research ed.)BMJ199710043157112851-5851Reference - [BMJ 1997 Oct 4;315(7112):851](http://pubmed.ncbi.nlm.nih.gov/9353505-time-since-childbirth-and-prognosis-in-primary-breast-cancer-population-based-study/?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2127579/)

Pregnancy after breast cancer

* **pregnancy after breast cancer does not appear to increase risk for mortality**

Systematic Review[20943370Eur J Cancer 2011 Jan;47(1):74](http://pubmed.ncbi.nlm.nih.gov/20943370?dopt=Abstract)

studySummary

* + based on systematic review Systematic Review
  + systematic review of 7 case-control studies and 7 cohort studies evaluating effect of pregnancy on overall survival of women with history of breast cancer
  + meta-analysis included 1,244 women who got pregnant and 18,145 women with no pregnancy after history of breast cancer
  + pregnancy following breast cancer diagnosis associated with reduced risk of death (relative risk [RR] 0.59, 90% CI 0.5-0.7)
  + no significant association in subgroup analysis in women known to be free of relapse (RR 0.85, 95% CI 0.53-1.35)
  + PubMed20943370European journal of cancer20110101Eur J Cancer4717474 Reference - [20943370Eur J Cancer 2011 Jan;47(1):74](http://pubmed.ncbi.nlm.nih.gov/20943370?dopt=Abstract)

Quality of life

* **suboptimal health-related quality of life after diagnosis reported in young Black female breast cancer survivors**

Systematic Review[mnh27601138pcxh118527374pmdc27601138pBreast Cancer Res Treat 2016 Nov;160(1):1](http://pubmed.ncbi.nlm.nih.gov/27601138?dopt=Abstract)

studySummary

* + based on systematic review with limited evidence Systematic Review
  + systematic review of 6 cross-sectional studies evaluating health-related quality of life in 3,805 female breast cancer survivors
    - 2 studies included only young women (< 50 years old at diagnosis), 3 studies included only Black women, and 1 study included only young Black women
    - time since breast cancer diagnosis varied across studies (≤ 12 months in 1 study, ≥ 12 months in 2 studies, and no specific timing in 3 studies)
  + meta-analyses not performed due to heterogeneity in health-related quality of life assessment tools among studies
  + after diagnosis, young Black breast cancer survivors reported
    - worse psychological well-being (including fear, anxiety, or depression) compared to older Black survivors or young Black women without breast cancer in 5 studies
    - substantial decline in physical well-being and functioning compared to older Black breast cancer survivors in 2 studies
    - higher levels of financial distress compared to young White breast cancer survivors in 1 study
    - higher levels of emotional support compared to older Black survivors in 1 study
  + PubMed27601138Breast cancer research and treatment20161101Breast Cancer Res Treat160111 Reference - [mnh27601138pcxh118527374pmdc27601138pBreast Cancer Res Treat 2016 Nov;160(1):1](http://pubmed.ncbi.nlm.nih.gov/27601138?dopt=Abstract)

Prognosis

Survival and Mortality

* **estimated global breast cancer mortality 626,679 in 2018**

Population-based Surveillance[CA Cancer J Clin 2018 Nov;68(6):394](http://pubmed.ncbi.nlm.nih.gov/30207593?dopt=Abstract)

studySummary

* + based on population-based cancer registries, vital registration data, and mortality data from 185 countries or territories with total population > 150,000 during 2018Population-based Surveillance
  + mortality
    - estimated global breast cancer mortality 626,679
    - age-standardized rate (ASR) 13 per 100,000 women
    - cumulative global lifetime risk of death (ages 0-74 years) 1.41%

| Estimated Global Breast Cancer Mortality by Gl obal Region, 2018 | |
| --- | --- |
| **Region** | **Age-Standardized Rates per 100,000** |
| **Americas** | |
| North America | 12.6 |
| Central America | 10.1 |
| Caribbean | 18.1 |
| South America | 13.4 |
| **Africa** |  |
| Northern Africa | 18.4 |
| Western Africa | 17.8 |
| Middle Africa | 15.8 |
| Eastern Africa | 15.4 |
| Southern Africa | 15.6 |
| **Europe** | |
| Western Europe | 15.5 |
| Northern Europe | 14.1 |
| Southern Europe | 13.3 |
| Eastern Europe | 15.5 |
| **Asia** | |
| Western Asia | 13.6 |
| South Central Asia | 13.6 |
| Eastern Asia | 8.6 |
| South-Eastern Asia | 14.1 |
| **Oceana** | |
| Australia/New Zealand | 12.6 |
| Melanesia | 25.5 |
| Micronesia/Polynesia | 19.1 |

* + CA: a cancer journal for clinicians20181101CA Cancer J Clin686394394 Reference - GLOBOCAN 2018 ([CA Cancer J Clin 2018 Nov;68(6):394](http://pubmed.ncbi.nlm.nih.gov/30207593?dopt=Abstract))
* unique\_1307423588\_\_LI\_WKP\_WFQ\_DVBEU10112210/11/2022 12:43:15 PMevidenceUpdatestandardOncologic\_Disease5-year age-adjusted breast cancer mortality 128.3 per 100,000 female persons in United States during 2016-2020; highest breast cancer mortality in Black persons compared to persons with other races or ethnicities (CA Cancer J Clin 2022 Nov)

**5-year age-adjusted breast cancer mortality 128.3 per 100,000 person-years for female persons in United States during 2016-2020; highest breast cancer mortality in Black persons compared to persons of other races or ethnicities**

Population-based Surveillance[5-year age-adjusted incidence stratified by race](https://seer.cancer.gov/statistics-network/explorer/application.html?site=55&data_type=1&graph_type=10&compareBy=race&chk_race_1=1&chk_race_6=6&chk_race_5=5&chk_race_4=4&chk_race_9=9&chk_race_8=8&series=9&sex=3&age_range=1&stage=101&advopt_precision=1&advopt_show_ci=on&hdn_view=1#tableWrap)Population-based Surveillance[CA Cancer J Clin 2022 Nov;72(6):524](https://pubmed.ncbi.nlm.nih.gov/36190501)[Full Text](https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21754)

studySummary

* + Population-based SurveillancePopulation-based Surveillance based on population-based surveillance
  + annual population-based surveillance information on incidence (during 2015-2019) and mortality (during 2016-2020) of breast cancer in female persons in the United States from Surveillance, Epidemiology, and End Results (SEER) database was evaluated
    - incidence and mortality rates were age-adjusted to standard population of United States in 2000
    - 5-year age-adjusted incidence and mortality of breast cancer

| 5-Year Age-Adjusted Incidence (in 2015-2019) and Mortality Rates (in 2016-2020) by Race and Ethnicity | | |
| --- | --- | --- |
| **Race/Ethnicity** | **Incidence (per 100,000 Person-years)** | **Mortality (per 100,000 Person-years)** |
| All races | 128.3 | 19.6 |
| American Indian and Alaska Native (non-Hispanic) | 111.3 | 17.6 |
| Asian and Pacific Islander (non-Hispanic) | 106.9 | 11.7 |
| Black (non-Hispanic) | 129.6 | 27.6 |
| Hispanic (any race) | 99.9 | 13.7 |
| White (non-Hispanic) | 137.6 | 19.7 |

* + - PubMed36190501CA: a cancer journal for cliniciansCA Cancer J Clin20221003Reference - SEER Cancer Statistics Review (accessed 2022-10-11) on
      * [5-year age-adjusted incidence stratified by race](https://seer.cancer.gov/statistics-network/explorer/application.html?site=55&data_type=1&graph_type=10&compareBy=race&chk_race_1=1&chk_race_6=6&chk_race_5=5&chk_race_4=4&chk_race_9=9&chk_race_8=8&series=9&sex=3&age_range=1&stage=101&advopt_precision=1&advopt_show_ci=on&hdn_view=1#tableWrap)
      * [5-year age-adjusted mortality stratified by race](https://seer.cancer.gov/statistics-network/explorer/application.html?site=55&data_type=2&graph_type=10&compareBy=race&chk_race_1=1&chk_race_6=6&chk_race_5=5&chk_race_4=4&chk_race_9=9&chk_race_8=8&series=9&sex=3&age_range=1&advopt_precision=1&advopt_show_ci=on&hdn_view=1#tableWrap)
  + during 2016-2020, compared to White persons (non-Hispanic), higher mortality in Black persons (non-Hispanic)
    - for ages 20-29 years (mortality rate ratio [MRR] 2.36, 95% CI not reported, p < 0.05)
    - for ages 30-39 years (MRR 1.86, 95% CI not reported, p < 0.05)
    - for ages 40-49 years (MRR 1.84, 95% CI not reported, p < 0.05)
    - for ages 50-59 years (MRR 1.67, 95% CI not reported, p < 0.05)
    - for ages 60-69 years (MRR 1.45, 95% CI not reported, p < 0.05)
    - for ages 70-79 years (MRR 1.23, 95% CI not reported, p < 0.05)
    - age ages ≥ 80 years (MRR 1.1, 95% CI not reported, p < 0.05)
    - PubMed36190501CA: a cancer journal for cliniciansCA Cancer J Clin20221003Reference - [CA Cancer J Clin 2022 Nov;72(6):524](https://pubmed.ncbi.nlm.nih.gov/36190501)[full-text](https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21754)
* **5-year relative survival rates by stage and race in United States from 2008 to 2014**

| Table 8: 5-Year Relative Survival Rates by Stage and Race in United States From 2008 to 2014 | | | |
| --- | --- | --- | --- |
|  | **Localized Disease\*** | **Regional Disease\*\*** | **Metastatic Disease\*\*\*** |
| All women | 99% | 85% | 27% |
| White women | 99% | 86% | 28% |
| Black women | 95% | 77% | 20% |
| \* Localized disease is stage I and II if negative lymph node(s).  \*\* Regional disease is stage II and III if positive lymph node(s).  \*\*\* Metastatic disease is stage IV. | | | |

* + Reference - [CA Cancer J Clin 2019 Jan;69(1);7](http://pubmed.ncbi.nlm.nih.gov/30620402?dopt=Abstract)[full-text](https://onlinelibrary.wiley.com/doi/full/10.3322/caac.21551)
* age-standardized mortality 20.9 per 100,000 person-years for breast cancer in women in Australia in 2014 ([a9h108929809t pcxh108929809t pmdc26264473pAsia Pac J Clin Oncol 2015 Sep;11(3):208](http://pubmed.ncbi.nlm.nih.gov/26264473?dopt=Abstract) )
* 5-year relative survival rates from CONCORD study (1.9 million adults with first primary invasive cancer from 101 cancer registries in 31 countries) can be found in [18639491Lancet Oncol 2008 Aug;9(8):730](http://pubmed.ncbi.nlm.nih.gov/18639491?dopt=Abstract)
* 20-year cause-specific survival with inflammatory breast cancer increased from 9% of 134 patients from 1975 to 1977 to 20% of 416 patients from 1993 to 1995 ([mnh16242046paph31614021pa9h31614021pafh31614021pcxh31614021pmdc16242046pBMC Cancer 2005 Oct 22;5:137](http://pubmed.ncbi.nlm.nih.gov/16242046?dopt=Abstract) [full-text](http://www.biomedcentral.com/1471-2407/5/137))
* **estimated progression-free survival 7.6 months and overall survival 21.7 months in women starting first-line chemotherapy for metastatic breast cancer**

Systematic Review[mdc21189397pJ Clin Oncol 2011 Feb 1;29(4):456](http://pubmed.ncbi.nlm.nih.gov/21189397?dopt=Abstract)

studySummary

* + based on systematic review without assessment of trial quality Systematic Review
  + systematic review of 36 randomized trials evaluating survival outcomes in 13,083 women having first-line chemotherapy for metastatic breast cancer
  + survival in women with metastatic breast cancer having first-line chemotherapy in analysis of 36 trials with 13,083 women
    - mean of median progression-free survival 7.6 months (interquartile range 6 months-9 months)
    - mean of median overall survival 21.7 months (interquartile range 18.2 months-24 months)
  + overall survival significantly longer in trials with higher proportions of women with estrogen-receptor positive tumors (p = 0.001) and in trials of trastuzumab-treated HER2-positive tumors (p = 0.001)
  + PubMed21189397Journal of clinical oncology : official journal of the American Society of Clinical Oncology20110201J Clin Oncol294456456 Reference - [mdc21189397pJ Clin Oncol 2011 Feb 1;29(4):456](http://pubmed.ncbi.nlm.nih.gov/21189397?dopt=Abstract) , editorial can be found in [mdc21189394pJ Clin Oncol 2011 Feb 1;29(4):347](http://pubmed.ncbi.nlm.nih.gov/21189394?dopt=Abstract)

Prognostic Tools

* [Adjuvant! clinical prognostic tool](http://www.adjuvantonline.com/index.jsp)
  + requires online registration by medical professional
  + accurately predicts 10-year overall survival, breast cancer-specific survival, and event-free survival
  + predicts recurrence rates (based on standard efficacy) after adjuvant chemotherapy, endocrine therapy, or both to predict amount of absolute benefit of therapy
  + validated in study with 4,083 women with stage I and II breast cancer
  + References
    - [mdc15837986pJ Clin Oncol 2005 Apr 20;23(12):2716](http://pubmed.ncbi.nlm.nih.gov/15837986?dopt=Abstract) , commentary can be found in Evidence-Based Medicine 2005 Nov-Dec;10(6):186
    - [19801202Lancet Oncol 2009 Nov;10(11):1070](http://pubmed.ncbi.nlm.nih.gov/19801202?dopt=Abstract)
  + Adjuvant! clinical prognostic tool does not provide risk predictions based on human epidermal growth factor receptor type 2 (HER2/neu) status.
* **Adjuvant! may not accurately predict survival in elderly women with breast cancer**

Cohort Study[24836274Lancet Oncol 2014 Jun;15(7):722](http://pubmed.ncbi.nlm.nih.gov/24836274?dopt=Abstract)

studySummary

* + based on validation cohort study with 2,012 women ≥ 65 years old with breast cancer fulfilling Adjuvant! criteria Cohort Study
  + 2,012 women ≥ 65 years old with breast cancer fulfilling Adjuvant! criteria
  + 45% died and 16% had recurrence during follow-up
  + Adjuvant! overestimated 10-year survival when using comorbidity status "average for age" and underestimated survival when using individualized comorbidity status
  + PubMed24836274The Lancet. Oncology20140601Lancet Oncol157722722 Reference - [24836274Lancet Oncol 2014 Jun;15(7):722](http://pubmed.ncbi.nlm.nih.gov/24836274?dopt=Abstract), editorial can be found in [24872094Lancet Oncol 2014 Jun;15(7):672](http://pubmed.ncbi.nlm.nih.gov/24872094?dopt=Abstract)
* **in women < 55 years old with lymph node-negative breast cancer and Adjuvant!-predicted 10-year breast cancer-specific survival ≥ 95%, mitotic activity index may further stratify high-risk and low-risk patients (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Diagnostic Cohort Study[mdc21189388pJ Clin Oncol 2011 Mar 1;29(7):852](http://pubmed.ncbi.nlm.nih.gov/21189388?dopt=Abstract)

studySummary2

* + based on derivation cohort study without validation Diagnostic Cohort Study
  + 516 women < 55 years old with lymph node-negative breast cancer were assessed using mitotic activity index (MAI) and Adjuvant! prognostic tool
  + median follow-up 118 months
  + 122 women had Adjuvant!-predicted 10-year breast cancer-specific survival ≥ 95%
    - observed breast cancer-specific survival 91%
    - breast cancer-specific survival stratified by MAI (p < 0.001)
      * 99% in 74 women with MAI < 3
      * 79% in 48 women with MAI ≥ 3
  + 394 women had Adjuvant!-predicted 10-year breast cancer-specific survival < 95%
    - observed breast cancer-specific survival 74%
    - breast cancer-specific survival stratified by MAI (p < 0.001)
      * 92% in 86 women with MAI < 3
      * 70% in 308 women with MAI ≥ 3
  + PubMed21189388Journal of clinical oncology : official journal of the American Society of Clinical Oncology20110301J Clin Oncol297852852 Reference - [mdc21189388pJ Clin Oncol 2011 Mar 1;29(7):852](http://pubmed.ncbi.nlm.nih.gov/21189388?dopt=Abstract)
* [Finprog](http://www.finprog.org/) is an online system to enter individual patient data and predict overall survival based on data from 2,032 breast cancer patients in Finland followed for 8-11 years ([12511459BMJ 2003 Jan 4;326(7379):29](http://pubmed.ncbi.nlm.nih.gov/12511459?dopt=Abstract)[full-text](http://www.bmj.com/content/326/7379/29.full)), editorial can be found in [12511432BMJ 2003 Jan 4;326(7379):2](http://pubmed.ncbi.nlm.nih.gov/12511432?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/12511432/), commentary can be found in [12689987BMJ 2003 Apr 12;326(7393):822](http://pubmed.ncbi.nlm.nih.gov/12689987?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/12689987/)
* **prognostic score predicts 5-year disease-specific survival after surgery as first intervention for stage I-IIIA breast cancer (**[**level 1 [likely reliable] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Diagnostic Cohort Study[mdc22084362pJ Clin Oncol 2011 Dec 10;29(35):4654](http://pubmed.ncbi.nlm.nih.gov/22084362?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/22084362/)

studySummary1

* + based on derivation and validation cohort study Diagnostic Cohort Study
  + derivation cohort included 3,728 patients with stage I-IIIA breast cancer who had surgery as first intervention and who were followed for mean of 6.6 years
  + validation cohort included 26,711 similar patients who were followed for mean of 5.9 years
  + 5-year disease-specific survival
    - 97.4% for derivation cohort
    - 93.2% for validation cohort
  + 6 prognostic scores based on 6 risk factors were evaluated in derivation cohort
  + risk factors associated with 5-year disease-specific survival in derivation cohort and points assigned to derive prognostic score (total score 0-4 points)
    - pathologic stage - 0 points if stage I, 1 point if stage IIA-IIB, 2 points if stage IIIA
    - nuclear grade - 0 points if grade I-II, 1 point if grade III
    - estrogen receptor status - 0 points if positive, 1 point if negative
  + 5-year disease-specific survival by prognostic score in derivation and validation cohorts

| Results | | |
| --- | --- | --- |
| **Score** | **Derivation Cohort** | **Validation Cohort** |
| 0 points | 99.5% | 98.5% |
| 1 point | 98.9% | 95.2% |
| 2 points | 96.1% | 86.3% |
| 3 points | 86.2% | 72.2% |
| 4 points | 65.2% | 54.2% |

* + PubMed22084362Journal of clinical oncology : official journal of the American Society of Clinical Oncology20111210J Clin Oncol293546544654 Reference - [mdc22084362pJ Clin Oncol 2011 Dec 10;29(35):4654](http://pubmed.ncbi.nlm.nih.gov/22084362?dopt=Abstract) [full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/22084362/)
* **lymph vascular space invasion tumor burden ≥ 60 has high specificity but low sensitivity for prediction of disease relapse in women with node-negative breast cancer (**[**level 1 [likely reliable] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Diagnostic Cohort Study[24114856Ann Oncol 2013 Dec;24(12):2994](http://pubmed.ncbi.nlm.nih.gov/24114856?dopt=Abstract)

studySummary1

* + based on derivation and validation cohort study Diagnostic Cohort Study
  + derivation cohort included 120 women with node-negative breast cancer who had immunohistochemical stained breast cancer tissue samples assessed for lymph vascular space invasion tumor burden (number of lymph vascular space invasion foci × number of tumor cells in largest tumor embolus)
  + validation cohort included 238 similar women
  + prevalence of disease relapse was 38.3% overall
  + lymph vascular space invasion tumor burden ≥ 60 was optimal cutoff for prediction of disease relapse in comparative analysis
  + for prediction of disease relapse, lymph vascular space invasion tumor burden with cutoff ≥ 60 had sensitivity 23.9% and specificity 94.6%
  + lymph vascular space invasion tumor burden ≥ 60 associated with reduced survival compared to lymph vascular space invasion tumor burden < 60 in analysis of validation cohort (hazard ratio for mortality 2.4, 95% CI 1.37-4.09)
  + PubMed24114856Annals of oncology : official journal of the European Society for Medical Oncology20131201Ann Oncol241229942994 Reference - [24114856Ann Oncol 2013 Dec;24(12):2994](http://pubmed.ncbi.nlm.nih.gov/24114856?dopt=Abstract)

Prognostic Factors

Race and Ethnicity

* **breast cancer mortality generally highest among non-Hispanic Black women and lowest among Asian/Pacific Islander women in the United States**

Population-based Surveillance[CA Cancer J Clin 2019 Jan;69(1);7](http://pubmed.ncbi.nlm.nih.gov/30620402?dopt=Abstract)[Full Text](https://onlinelibrary.wiley.com/doi/full/10.3322/caac.21551)

studySummary

* + based on annual report of cancer status in United States with data 2012-2016 for death ratesPopulation-based Surveillance
  + age-adjusted breast cancer death rates per 100,000 women by race/ethnicities
    - all women 20.6
    - non-Hispanic Black women 28.9
    - non-Hispanic White women 20.6
    - American Indian/Alaska Native women 14.5
    - Hispanic women 14.3
    - Asian/Pacific Islander women 11.3
  + CA: a cancer journal for clinicians20190101CA Cancer J Clin7 Reference - [CA Cancer J Clin 2019 Jan;69(1);7](http://pubmed.ncbi.nlm.nih.gov/30620402?dopt=Abstract)[full-text](https://onlinelibrary.wiley.com/doi/full/10.3322/caac.21551)
* **mortality of breast cancer may be highest in African American women in United States**
  + female breast cancer mortality by ethnicity in United States

| Table 9: Incidence and Mortality in United States | |
| --- | --- |
| **Ethnic Group** | **Mortality Rates per 100,000 (2010-2014)** |
| Non-Hispanic White women | 21.1 |
| African American women | 30 |
| Hispanic/Latina women | 14.4 |
| American Indian/Alaska Native women | 14.1 |
| Asian American/Pacific Islander women | 11.3 |

* + Reference - [mnh28055103pcxh120669112t pmdc28055103pCA Cancer J Clin 2017 Jan;67(1):7](http://pubmed.ncbi.nlm.nih.gov/28055103?dopt=Abstract) [full-text](http://onlinelibrary.wiley.com/doi/10.3322/caac.21387/full)
* **breast cancer mortality higher among Black women than White women < 65 years old in the United States**

Cohort Study[19084242J Surg Res 2009 May 1;153(1):105](http://pubmed.ncbi.nlm.nih.gov/19084242?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/19084242/)

studySummary

* + based on retrospective cohort study Cohort Study
  + 20,424 Black women and 204,506 White women diagnosed with first primary breast cancer from 1988 to 2003 were analyzed
  + hazard ratios comparing Black women vs. White women
    - for breast cancer mortality 1.9 (95% CI 1.83-1.96)
    - all-cause mortality 1.52 (95% CI 1.48-1.55)
  + Black women had increased risk of breast cancer mortality for each stage 0-IV and unstaged cancer and for each age group < 40 years old, aged 40-49 years, and aged 50-64 years
  + increased risk not found for Black women ≥ 65 years old
  + PubMed19084242The Journal of surgical research20090501J Surg Res1531105105 Reference - [19084242J Surg Res 2009 May 1;153(1):105](http://pubmed.ncbi.nlm.nih.gov/19084242?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/19084242/)
* **breast cancer mortality at 7 years after diagnosis with stage I breast cancer appears higher in Black women than in non-Hispanic White women in the United States**

Population-based Surveillance[cxh100436460pmdc25585328pJAMA 2015 Jan 13;313(2):165](http://pubmed.ncbi.nlm.nih.gov/25585328?dopt=Abstract)

studySummary

* + based on analysis of 373,563 women (mean age 61 years) with invasive breast cancer diagnosed from 2004 to 2011 in Surveillance, Epidemiology, and End Results (SEER) database in United States Population-based Surveillance
  + median follow-up 38 months
  + stage I breast cancer at diagnosis in 48%
  + actuarial 7-year mortality due to stage I breast cancer 6.2% in Black women vs. 3% in non-Hispanic White women (adjusted hazard ratio [HR] 1.57, 95% CI 1.4-1.75)
  + no significant differences in mortality comparing non-Hispanic White women vs. Hispanic women, or women of Japanese or South Asian descent
  + mortality significantly lower in women of Chinese descent vs. non-Hispanic White women
  + presence of nodal metastases and distant metastases more common with breast cancer tumors ≤ 2 cm in African American women compared to non-Hispanic White women (p < 0.001 for each)
  + PubMed25585328JAMA20150113JAMA3132165165 Reference - [cxh100436460pmdc25585328pJAMA 2015 Jan 13;313(2):165](http://pubmed.ncbi.nlm.nih.gov/25585328?dopt=Abstract) , editorial can be found in [cxh100436455pmdc25585323pJAMA 2015 Jan 13;313(2):141](http://pubmed.ncbi.nlm.nih.gov/25585323?dopt=Abstract)
* **differences in survival between Black and White older women with breast cancer may be associated with differences in presentation factors (comorbidities and tumor characteristics) and differences in treatment**

Cohort Study[mdc23917289pJAMA 2013 Jul 24;310(4):389](http://pubmed.ncbi.nlm.nih.gov/23917289?dopt=Abstract)

studySummary

* + based on cohort studyCohort Study
  + 7,375 Black women ≥ 65 years old with breast cancer diagnosed from 1991 to 2005 were compared to 22,125 matched White women with breast cancer from the United States SEER database
    - mean age at diagnosis 76 years
    - matching was based on
      * demographic factors (including age and year of diagnosis)
      * presentation factors at diagnosis (including comorbidities and tumor characteristics) plus demographics
      * treatment received plus presentation factors plus demographics
  + 5-year overall survival in Black women was 55.9%
  + difference in 5-year survival in White women compared to Black women (p < 0.001 for each)
    - +12.9% in White women matched for demographics alone
    - +4.4% in White women matched for presentation factors plus demographics
    - +3.6% in White women matched for treatment received plus presentation factors plus demographics
  + PubMed23917289JAMA20130724JAMA3104389389 Reference - [mdc23917289pJAMA 2013 Jul 24;310(4):389](http://pubmed.ncbi.nlm.nih.gov/23917289?dopt=Abstract) , editorial can be found in [mdc23917286pJAMA 2013 Jul 24;310(4):376](http://pubmed.ncbi.nlm.nih.gov/23917286?dopt=Abstract)
* **British women of Black race with breast cancer may present at a younger age and have more aggressive tumors than British women of White race**

Cohort Study[mnh18182985paph28611088pa9h28611088pbyh28611088pafh28611088pcxh28611088pmdc18182985pBr J Cancer 2008 Jan 29;98(2):277](http://pubmed.ncbi.nlm.nih.gov/18182985?dopt=Abstract)[Full Text](http://dx.doi.org/10.1038/sj.bjc.6604174)

studySummary

* + based on retrospective cohort study Cohort Study
  + 445 women with invasive breast cancer presenting to 1 clinic in London from 1994 to 2005
  + comparing Black women vs. White women
    - median age at presentation 46 years vs. 67 years presentation at younger age (p = 0.001)
    - presence of grade 3 tumors in 62% vs. 42% (p = 0.02)
    - proportion of women < 60 years old who have
      * estrogen receptor (ER)-negative tumors 39% vs. 21% (p = 0.03)
      * triple-negative tumors 25% vs. 12% (p = 0.09)
    - Black women had poorer survival with tumors ≤ 2 cm (hazard ratio 2.9, 95% CI 0.98-8.6, p = 0.05)
  + PubMed18182985British journal of cancer20080129Br J Cancer982277277 Reference - [mnh18182985paph28611088pa9h28611088pbyh28611088pafh28611088pcxh28611088pmdc18182985pBr J Cancer 2008 Jan 29;98(2):277](http://pubmed.ncbi.nlm.nih.gov/18182985?dopt=Abstract) [full-text](http://dx.doi.org/10.1038/sj.bjc.6604174)
* **breast cancer diagnosed without screening or during screening interval associated with 80% 10-year survival (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cohort Study[23160783BMJ 2012 Nov 16;345:e7536](http://pubmed.ncbi.nlm.nih.gov/23160783?dopt=Abstract)[Full Text](http://www.bmj.com/content/345/bmj.e7536?view=long&pmid=23160783)

studySummary2

* + based on retrospective cohort study Cohort Study
  + 7,116 women aged 50-72 years with diagnosis of invasive breast cancer in Norway from 1996 to 2006 were evaluated
    - 26% had diagnosis between 1 of 2 mammography screenings or ≤ 2 years and 2 months after last normal screening (interval group)
    - 74% had diagnosis prior to invitation for mammography screening (nonscreened group)
  + at baseline, interval group had slightly more lobular cancers, large tumors (diameter > 20 mm), negative axillary lymph nodes, and stage II (vs. stage I) disease (p < 0.001 for each)
  + mean follow-up of 3.6 years in interval group and 6.3 years in nonscreened group
  + 10-year survival rate 79.1% for women with interval cancers vs. 76.8% for women who did not receive screening (hazard ratio 0.98, 95% CI 0.84-1.15, p = 0.53)
  + PubMed23160783BMJ (Clinical research ed.)20121116BMJ345e7536e7536 Reference - [23160783BMJ 2012 Nov 16;345:e7536](http://pubmed.ncbi.nlm.nih.gov/23160783?dopt=Abstract)[full-text](http://www.bmj.com/content/345/bmj.e7536?view=long&pmid=23160783)

Tumor Characteristics and Extent

* **larger tumor diameter and greater number of positive nodes at diagnosis each associated with increasing risk of distant recurrence 5-20 years after diagnosis in women with estrogen receptor-positive early stage breast cancer who were disease-free after 5 years of endocrine therapy**

Randomized Trial[29117498N Engl J Med 2017 Nov 9;377(19):1836](http://pubmed.ncbi.nlm.nih.gov/29117498?dopt=Abstract)

studySummary

* + based on meta-analysis of observational data from randomized trials Randomized Trial
  + individual patient data meta-analysis of 88 randomized trials with data to assess risk factors for distant recurrence in 62,923 women with estrogen receptor-positive early stage breast cancer who were disease-free after scheduled endocrine therapy (tamoxifen or aromatase inhibitors)
  + all women were scheduled to receive 5-year endocrine therapy, but authors state that "substantial minority" did not complete treatment
  + rates of distant recurrence 5-20 years after diagnosis
    - stage T1 (tumor diameter ≤ 2 cm)
      * with no nodes involved, 13%
      * with 1-3 nodes involved, 20%
      * with 4-9 nodes involved, 34%
    - stage T2 (tumor diameter 2-5 cm)
      * with no nodes involved, 19%
      * with 1-3 nodes involved, 26%
      * with 4-9 nodes involved, 41%
  + increasing tumor diameter and increasing number of positive nodes at diagnosis each significantly associated with increasing risk of distant recurrence and breast cancer-related death at 5-20 years after diagnosis
  + no significant association between progesterone receptor status or HER2 status and risk of distant recurrence in analysis controlling for tumor diameter and number of nodes
  + PubMed29117498The New England journal of medicine20171109N Engl J Med3771918361836 Reference - [29117498N Engl J Med 2017 Nov 9;377(19):1836](http://pubmed.ncbi.nlm.nih.gov/29117498?dopt=Abstract)
* **risk factors for breast cancer mortality include higher histologic grade, larger tumor size, ipsilateral breast tumor recurrence, and lymphatic invasion**

Cohort Study[16859523Breast Cancer Res 2006 Jul 19;8(4):R44](http://pubmed.ncbi.nlm.nih.gov/16859523?dopt=Abstract)[Full Text](http://breast-cancer-research.com/content/8/4/R44)

studySummary

* + based on prospective cohort study of 1,540 consecutive women aged 18-75 years with node-negative breast cancer followed for up to 12 years Cohort Study
  + 98 ipsilateral breast tumor recurrences (6.4%) and 117 deaths (7.4%) occurred
  + risk factors for ipsilateral breast cancer recurrence included
    - age < 40 years (relative risk [RR] 1.89, 95% CI 1-3.58)
    - presence of intraductal disease (RR 1.81, 95% CI 1.15-2.85)
    - histological grade (G2 or G3 vs. G1) (RR 1.59, 95% CI 0.87-2.94)
  + risk factors for disease-specific mortality included
    - histologic grade (G2 or G3 vs. G1) (RR 8.59, 95% CI 2.09-35.36)
    - tumor size > 2 cm (vs. < 1 cm) (RR 2.94, 95% CI 1.56-5.56)
    - ipsilateral breast tumor recurrence (RR 2.58, 95% CI 1.05-3.64)
    - progesterone receptor status (negative or equivocal vs. positive or unknown) (RR 2.15, 95% CI 1.36-3.39)
    - lymphatic invasion (RR 1.78, 95% CI 1.17-2.72)
  + PubMed16859523Breast cancer research : BCR20060719Breast Cancer Res84R44R44 Reference - [16859523Breast Cancer Res 2006 Jul 19;8(4):R44](http://pubmed.ncbi.nlm.nih.gov/16859523?dopt=Abstract)[full-text](http://breast-cancer-research.com/content/8/4/R44)
* **survival varies with histologic type**

Cohort Study[Arch Intern Med 2003 Oct 13;163(18):2149](http://pubmed.ncbi.nlm.nih.gov/14557212-risk-of-mortality-by-histologic-type-of-breast-cancer-among-women-aged-50-to-79-years/?dopt=Abstract)

studySummary

* + Cohort Study based on retrospective cohort study of 164,958 women aged 50-79 years with 1 of 7 histologic types of invasive breast cancer in 9 cancer registries from 1974 to 1998
  + 80.2% women had invasive ductal carcinoma, 41.3% overall mortality
  + 11.8% had invasive lobular carcinoma, 33% mortality
  + 2.4% had mucinous carcinoma, 34.7% mortality
  + 1.9% had comedocarcinoma, 29.7% mortality
  + 1.8% had medullary carcinoma, 44.8% mortality
  + 1.4% had tubular carcinoma, 18.5% mortality
  + 0.6% had papillary carcinoma, 37.2% mortality
  + PubMed14557212Archives of internal medicineArch Intern Med20031013163182149-532149 Reference - [Arch Intern Med 2003 Oct 13;163(18):2149](http://pubmed.ncbi.nlm.nih.gov/14557212-risk-of-mortality-by-histologic-type-of-breast-cancer-among-women-aged-50-to-79-years/?dopt=Abstract)
* **5-year overall survival 94% with breast cancer immunohistochemical subtype luminal A**

Cohort Study[mnh23892409pcxh89702728pmdc23892409pJ Cancer Res Clin Oncol 2013 Sep;139(9):1569](http://pubmed.ncbi.nlm.nih.gov/23892409?dopt=Abstract)

studySummary

* + based on retrospective cohort study of 3,381 women diagnosed from 2003 through 2005 with 1 of 5 breast cancer immunohistochemical subtypes Cohort Study
  + 5-year overall survival (per subtype)
    - 94.4% with luminal A
    - 89% with luminal B
    - 87% with luminal-HER2
    - 74.8% with HER2-enriched
    - 74.7% with triple-negative
  + luminal A subtype associated with significantly improved overall survival compared to other subtypes in adjusted analyses
  + PubMed23892409Journal of cancer research and clinical oncology20130901J Cancer Res Clin Oncol139915691569 Reference - [mnh23892409pcxh89702728pmdc23892409pJ Cancer Res Clin Oncol 2013 Sep;139(9):1569](http://pubmed.ncbi.nlm.nih.gov/23892409?dopt=Abstract)
  + This time period preceded the use of HER2 targeted therapy in women with early and locally advanced breast cancer. Survival in women with HER2 positive breast cancer and access to HER2 targeted therapy is improving.
* **clinical outcome with infiltrating lobular carcinoma similar to infiltrating ductal carcinoma**

Cohort Study[15084238Breast Cancer Res 2004 Feb 17;6(3):R149](http://pubmed.ncbi.nlm.nih.gov/15084238?dopt=Abstract)[Full Text](http://breast-cancer-research.com/content/6/3/R149)

studySummary

* + based on study of 4,140 patients with infiltrating lobular carcinoma compared to 45,169 patients with infiltrating ductal carcinoma Cohort Study
  + median follow-up of 87 months
  + comparing patients with infiltrating lobular carcinoma vs. patients with infiltrating ductal carcinoma
    - 5-year overall survival 85.6% vs. 84.1%
    - recurrence rate over 5 years 14.3% vs. 16.5% ("disease-free survival" rates did not account for deaths)
    - contralateral breast cancer in 20.9% vs. 11.2% (p < 0.0001)
    - after first recurrence
      * median survival 22 months vs. 19 months (p = 0.002)
      * 5-year overall survival 32.8% vs. 26.7% (p = 0.002)
  + PubMed15084238Breast cancer research : BCR20040217Breast Cancer Res63R149R149 Reference - [15084238Breast Cancer Res 2004 Feb 17;6(3):R149](http://pubmed.ncbi.nlm.nih.gov/15084238?dopt=Abstract)[full-text](http://breast-cancer-research.com/content/6/3/R149)
* **invasive medullary breast tumors associated with higher overall survival than invasive ductal breast tumors**

Cohort Study[22707751Ann Oncol 2012 Nov;23(11):2843](http://pubmed.ncbi.nlm.nih.gov/22707751?dopt=Abstract)[Full Text](http://annonc.oxfordjournals.org/content/23/11/2843.long)

studySummary

* + based on prognostic cohort study Cohort Study
  + 127 women with invasive medullary tumors and 8,096 women with invasive ductal tumors were assessed for recurrence and survival
    - all women were previously included in 1 of 13 trials assessing timing and duration of chemoendocrine therapies in women with early breast cancer
    - 47 women with medullary tumors and 1,407 women with ductal tumors had estrogen-receptor negative grade 3 tumors
    - median duration of follow-up of 14 years
  + comparing medullary tumors to ductal tumors in overall cohort
    - 14-year overall survival 66% vs. 57% (p = 0.03)
    - 14-year distant recurrence-free survival in 76% vs. 64% (p = 0.0005)
  + comparing medullary tumors to ductal tumors in women with estrogen-receptor negative grade 3 tumors
    - 14-year overall survival 74% vs. 54% (p = 0.01)
    - 14-year distant recurrence-free survival in 89% vs. 63% (p = 0.002)
  + PubMed22707751Annals of oncology : official journal of the European Society for Medical Oncology20121101Ann Oncol231128432843 Reference - [22707751Ann Oncol 2012 Nov;23(11):2843](http://pubmed.ncbi.nlm.nih.gov/22707751?dopt=Abstract)[full-text](http://annonc.oxfordjournals.org/content/23/11/2843.long)
* **asymptomatic second tumors associated with improved survival compared to symptomatic tumors in breast cancer survivors (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cohort Study[19297316Ann Oncol 2009 Sep;20(9):1505](http://pubmed.ncbi.nlm.nih.gov/19297316?dopt=Abstract)[Full Text](http://annonc.oxfordjournals.org/content/20/9/1505.long)

studySummary2

* + based on retrospective cohort study Cohort Study
  + 1,044 breast cancer survivors who had second invasive tumor ≥ 6 months after initial diagnosis were followed for median 13.7 years after first diagnosis
  + 67% of women with second cancers were asymptomatic
  + asymptomatic tumors were (compared to symptomatic)
    - smaller (p < 0.001)
    - more likely to be early-stage tumors (p < 0.0001)
    - less likely to be cancer stage pT2 or larger (p < 0.001)
    - fewer node metastases in contralateral cancer (p = 0.0001)
    - associated with increased disease-specific survival from first cancer diagnosis (p < 0.0001)
  + despite mammography being more sensitive than clinical examination (86% vs. 57%, p < 0.0001), 13.8% of second cancer cases were only identified clinically
  + PubMed19297316Annals of oncology : official journal of the European Society for Medical Oncology20090901Ann Oncol20915051505 Reference - [19297316Ann Oncol 2009 Sep;20(9):1505](http://pubmed.ncbi.nlm.nih.gov/19297316?dopt=Abstract)[full-text](http://annonc.oxfordjournals.org/content/20/9/1505.long)
* **in women with metachronous contralateral breast cancer, increased risk of breast cancer-related death with larger tumor size, positive nodal status, and short time interval to development of contralateral cancer**

Cohort Study[cxh82203233pmdc22927521pJ Clin Oncol 2012 Oct 1;30(28):3478](http://pubmed.ncbi.nlm.nih.gov/22927521?dopt=Abstract)

studySummary

* + based on prospective cohort study Cohort Study
  + from a cohort of 42,670 women with breast cancer in Sweden from 1992 to 2008, 803 women who developed metachronous contralateral breast cancer were assessed for factors associated with breast cancer-related mortality
  + 13.4% died from breast cancer in median follow-up of 9.9 years
  + in women with metachronous contralateral breast cancer, risk of breast cancer-related mortality increased with
    - larger tumor size compared to tumors ≤ 2 cm
      * for tumors 2-5 cm, hazard ratio (HR) 2.2 (95% CI 1.3-3.6)
      * for > 5 cm, HR 6.3 (95% CI 3-13)
      * for tumor of any size with extension to chest wall and/or skin, HR 4.1 (95% CI 1.5-12)
    - positive nodal status compared to negative status (HR 2.4, 95% CI 1.5-3.9)
    - contralateral breast cancer ≤ 5 years after primary tumor compared to longer latency (HR 1.7, 95% CI 1.1-2.6)
    - negative estrogen receptor status compared to positive status (HR 2.6, 95% CI 1-4.8)
    - negative progesterone receptor status compared to positive status (HR 2.4, 95% CI 1-5.9)
  + PubMed22927521Journal of clinical oncology : official journal of the American Society of Clinical Oncology20121001J Clin Oncol302834783478 Reference - [cxh82203233pmdc22927521pJ Clin Oncol 2012 Oct 1;30(28):3478](http://pubmed.ncbi.nlm.nih.gov/22927521?dopt=Abstract)
* lymph node metastases
  + **metastases ≤ 2 mm diameter in axillary lymph nodes associated with poorer survival compared with absence of metastases**

Systematic Review[20190185J Natl Cancer Inst 2010 Mar 17;102(6):410](http://pubmed.ncbi.nlm.nih.gov/20190185?dopt=Abstract)[Full Text](http://jnci.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=20190185)

studySummary

* + - based on systematic review of 58 studies evaluating prognosis of occult lymph node metastases, isolated tumor cells, and micrometastases in 297,533 persons with breast cancer Systematic Review
    - axillary lymph node metastases of ≤ 2 mm diameter associated with poorer overall survival compared with absence of metastases (pooled hazard ratio 1.44, 95% CI 1.29-1.62)
    - PubMed20190185Journal of the National Cancer Institute20100317J Natl Cancer Inst1026410410 Reference - [20190185J Natl Cancer Inst 2010 Mar 17;102(6):410](http://pubmed.ncbi.nlm.nih.gov/20190185?dopt=Abstract)[full-text](http://jnci.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=20190185)
  + **isolated tumor cells or micrometastases in regional lymph nodes associated with reduced 5-year disease-free survival in women with early-stage breast cancer not receiving adjuvant therapy**

Cohort Study[19675329N Engl J Med 2009 Aug 13;361(7):653](http://pubmed.ncbi.nlm.nih.gov/19675329?dopt=Abstract)

studySummary

* + - based on cohort study in Netherlands Cohort Study
    - all women having sentinel-node biopsy for breast cancer before 2006 for breast cancer with favorable primary-tumor characteristics and isolated tumor cells or micrometastases in regional lymph nodes were compared to women with node-negative disease from 2000 to 2001
      * 856 women with isolated tumor cells or micrometastases did not receive systemic adjuvant therapy
      * 995 women with isolated tumor cells or micrometastases received systemic adjuvant therapy
      * 856 women with node-negative disease did not receive systemic adjuvant therapy
    - women followed for median of 5.1 years
    - adjusted hazard ratio (HR) for disease events in women not receiving adjuvant therapy
      * 1.5 (95% CI 1.15-1.94) in women with isolated tumor cells vs. node-negative disease
      * 1.56 (95% CI 1.15-2.13) in women with micrometastases vs. node-negative disease
    - unadjusted 5-year disease-free survival in women not receiving adjuvant therapy
      * 85.7% with node-negative disease
      * 75.9% with micrometastases without adjuvant therapy (p = 0.002 vs. node-negative disease)
      * 77.2% with isolated tumor cells without adjuvant therapy (p < 0.001 vs. node-negative disease, not significant vs. micrometastases)
    - adjusted HR for disease events 0.57 (95% CI 0.45-0.73) in women with isolated tumor cells or micrometastases with adjuvant therapy vs. no adjuvant therapy
    - PubMed19675329The New England journal of medicine20090813N Engl J Med3617653653 Reference - [19675329N Engl J Med 2009 Aug 13;361(7):653](http://pubmed.ncbi.nlm.nih.gov/19675329?dopt=Abstract), commentary can be found in [19907048N Engl J Med 2009 Nov 12;361(20):1994](http://pubmed.ncbi.nlm.nih.gov/19907048?dopt=Abstract)
  + **axillary lymph node macrometastasis on pathology associated with small reduction in survival compared to no macrometastasis in women with clinically node-negative breast cancer**

Cohort Study[21247310N Engl J Med 2011 Feb 3;364(5):412](http://pubmed.ncbi.nlm.nih.gov/21247310?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/21247310/)

studySummary

* + - based on cohort analysis of data from NSABP-32 randomized trial Cohort Study
    - 3,887 women with invasive breast cancer and clinically negative nodes were evaluated for macrometastases ≥ 2 mm
    - 15.9% had occult metastases
    - comparing patients with detectable occult metastases vs. no detectable occult metastases at 5 years
      * overall survival 94.6% vs. 95.8% (p = 0.03)
      * cancer-free survival 86.4% vs. 89.2% (p = 0.02)
      * distant cancer-free 89.7% vs. 92.5% (p = 0.04)
    - PubMed21247310The New England journal of medicine20110203N Engl J Med3645412412 Reference - [21247310N Engl J Med 2011 Feb 3;364(5):412](http://pubmed.ncbi.nlm.nih.gov/21247310?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/21247310/)
  + **increased number of involved lymph nodes associated with decreased survival in women with endocrine-responsive breast cancer**

Cohort Study[cxh75345721pmdc22207051pAnn Surg Oncol 2012 Jun;19(6):1808](http://pubmed.ncbi.nlm.nih.gov/22207051?dopt=Abstract)

studySummary

* + - based on retrospective prognostic cohort study Cohort Study
    - 7,052 women with endocrine-responsive breast cancer from 4 randomized trials having axillary lymph node dissection were included in analysis
    - 2718 patients (39%) had node-positive disease
    - decreased overall survival in patients with
      * increased number of involved lymph nodes (p < 0.0001)
      * increased lymph node ratio (p < 0.0001), but significant association confined to women with 1-3 lymph nodes and treated with mastectomy in subgroup analysis
    - consistent results for recurrence-free survival
    - no significant association between number of removed nodes and either recurrence-free survival or overall survival
    - PubMed22207051Annals of surgical oncology20120601Ann Surg Oncol19618081808 Reference - [cxh75345721pmdc22207051pAnn Surg Oncol 2012 Jun;19(6):1808](http://pubmed.ncbi.nlm.nih.gov/22207051?dopt=Abstract)
* distant metastases
  + **bone marrow micrometastasis at time of breast cancer diagnosis associated with poor prognosis**

Meta-analysis[16120859N Engl J Med 2005 Aug 25;353(8):793](http://pubmed.ncbi.nlm.nih.gov/16120859?dopt=Abstract)[Full Text](http://www.nejm.org/doi/full/10.1056/NEJMoa050434#t=article)

studySummary

* + - based on meta-analysis of individual patient data from 9 studies with 4,703 patients with stages I-III breast cancer followed for median of 5.2 years Meta-analysis
    - 1,438 patients (30.6%) had micrometastasis
    - compared to those without micrometastases, patients with bone marrow micrometastasis had (p < 0.01 for all variables)
      * larger tumors
      * tumors with a higher histologic grade
      * more frequent lymph node metastasis
      * more hormone receptor-negative tumors
    - micrometastasis associated with reduced overall survival, breast cancer-specific survival, disease-free survival, and distant disease-free survival
    - PubMed16120859The New England journal of medicine20050825N Engl J Med3538793793 Reference - [16120859N Engl J Med 2005 Aug 25;353(8):793](http://pubmed.ncbi.nlm.nih.gov/16120859?dopt=Abstract)[full-text](http://www.nejm.org/doi/full/10.1056/NEJMoa050434#t=article), commentary can be found in [16291991N Engl J Med 2005 Nov 17;353(20):2191](http://pubmed.ncbi.nlm.nih.gov/16291991?dopt=Abstract)
  + **occult bone marrow metastases not independently associated with reduced survival in women with early stage invasive breast cancer having chemotherapy**

Cohort Study[mdc21791687pJAMA 2011 Jul 27;306(4):385](http://pubmed.ncbi.nlm.nih.gov/21791687?dopt=Abstract)[Full Text](http://jama.jamanetwork.com/article.aspx?articleid=1104148)

studySummary

* + - based on analysis of data from prospective cohort from American College of Surgeons Oncology Group (ACOSOG) Z0010 trial Cohort Study
    - 5,210 women with early stage invasive breast cancer had breast-conserving surgery and sentinel lymph node (SLN) dissection followed for median of 6.3 years
      * bone marrow aspiration at time of operation was initially optional but became mandatory midtrial
      * SLN specimens (hematoxylin-eosin negative) and bone marrow specimens were sent for immunochemical staining
      * 86.2% received systemic chemotherapy
      * 65.5% had bone marrow specimens examined by immunocytochemistry
    - bone marrow positive for tumor in 2%
    - mortality in 8.3%
    - disease progression in 7.2%
    - comparing immunohistochemical evidence of bone marrow metastases vs. no evidence of bone marrow metastases
      * overall survival at 5 years 90.1% vs. 95% (p = 0.01) in univariate analysis
      * no significant difference in overall survival at 5 years in multivariate analysis
    - PubMed21791687JAMA20110727JAMA3064385385 Reference - [mdc21791687pJAMA 2011 Jul 27;306(4):385](http://pubmed.ncbi.nlm.nih.gov/21791687?dopt=Abstract) [full-text](http://jama.jamanetwork.com/article.aspx?articleid=1104148), editorial can be found in [mdc21791695pJAMA 2011 Jul 27;306(4):436](http://pubmed.ncbi.nlm.nih.gov/21791695?dopt=Abstract)
  + **women with metastases in unusual sites and women with metastases in usual sites appear to have similar 5-year survival**

Cohort Study[18613072Cancer 2008 Aug 15;113(4):677](http://pubmed.ncbi.nlm.nih.gov/18613072?dopt=Abstract)[Full Text](http://dx.doi.org/10.1002/cncr.23612)

studySummary

* + - based on retrospective cohort study Cohort Study
    - 3,783 patients evaluated with median follow-up of 5 years
    - 85 (2.2%) had unusual metastases (defined as systemic failures occurring with frequency ≤ 1%)
    - among 764 patients with distant metastases, 5-year cumulative overall survival was 53.5% for women with unusual metastases vs. 53.4% for women without unusual metastases
    - PubMed18613072Cancer20080815Cancer1134677677 Reference - [18613072Cancer 2008 Aug 15;113(4):677](http://pubmed.ncbi.nlm.nih.gov/18613072?dopt=Abstract)[full-text](http://dx.doi.org/10.1002/cncr.23612)
  + **increasing numbers of bony metastases associated with decreased survival in women with breast cancer**

Cohort Study[11148555Cancer 2001 Jan 1;91(1):17](http://pubmed.ncbi.nlm.nih.gov/11148555?dopt=Abstract)

studySummary

* + - based on retrospective cohort of 641 women with stage I-III breast cancer Cohort Study
    - 116 women had bone metastases as sole initial site of metastatic disease
    - median survival from time of recurrence in women with bony metastases
      * 53 months with 1 lesion (p < 0.0001 vs. ≥ 3 lesions)
      * 38 months with 2 lesions (p < 0.005 vs. ≥ 3 lesions)
      * 22 months with ≥ 3 lesions
    - PubMed11148555Cancer20010101Cancer9111717 Reference - [11148555Cancer 2001 Jan 1;91(1):17](http://pubmed.ncbi.nlm.nih.gov/11148555?dopt=Abstract)
* circulating tumor cells (CTCs)
  + **increased numbers of CTCs may be associated with worse overall survival**

Cohort Study[Cancer 2008 Nov 1;113(9):2422](http://pubmed.ncbi.nlm.nih.gov/18785255-circulating-tumor-cells-in-metastatic-breast-cancer-from-prognostic-stratification-to-modification-of-the-staging-system/?dopt=Abstract)[Full Text](http://onlinelibrary.wiley.com/doi/10.1002/cncr.23852/full)

studySummary

* + - Cohort Study based on retrospective cohort study
    - 185 patients (median age 49 years) with metastatic or recurrent breast cancer evaluated
    - median survival 15 months for patients with ≥ 5 CTCs per 750 mL of whole blood vs. 28.3 months for patients with < 5 CTCs per 750 mL of whole blood (p < 0.001)
    - Reference - [18785255Cancer 2008 Nov 1;113(9):2422](http://pubmed.ncbi.nlm.nih.gov/18785255?dopt=Abstract)[full-text](http://onlinelibrary.wiley.com/doi/10.1002/cncr.23852/full)
    - PubMed18785255CancerCancer2008110111392422-302422Reference - [Cancer 2008 Nov 1;113(9):2422](http://pubmed.ncbi.nlm.nih.gov/18785255-circulating-tumor-cells-in-metastatic-breast-cancer-from-prognostic-stratification-to-modification-of-the-staging-system/?dopt=Abstract)[full-text](http://onlinelibrary.wiley.com/doi/10.1002/cncr.23852/full)
  + number of CTCs before treatment and at first follow-up significantly predicted disease progression and overall survival in prospective study of 177 patients with measurable metastatic breast cancer ([15317891N Engl J Med 2004 Aug 19;351(8):781](http://pubmed.ncbi.nlm.nih.gov/15317891?dopt=Abstract)), editorial can be found in [15317898N Engl J Med 2004 Aug 19;351(8):824](http://pubmed.ncbi.nlm.nih.gov/15317898?dopt=Abstract), commentary can be found in [15580681N Engl J Med 2004 Dec 2;351(23):2452](http://pubmed.ncbi.nlm.nih.gov/15580681?dopt=Abstract)
* **residual breast cancer following neoadjuvant chemotherapy associated with reduced distant relapse-free survival**

Cohort Study[mdc17785706pJ Clin Oncol 2007 Oct 1;25(28):4414](http://pubmed.ncbi.nlm.nih.gov/17785706?dopt=Abstract)[Full Text](http://jco.ascopubs.org/content/25/28/4414.long)

studySummary

* + based on retrospective analysis of 382 patients treated with fluorouracil, doxorubicin, and cyclophosphamide (preceded by paclitaxel in 241 patients) Cohort Study
  + residual breast cancer determined by pathologic measurement of primary tumor and nodal metastases
  + PubMed17785706Journal of clinical oncology : official journal of the American Society of Clinical Oncology20071001J Clin Oncol252844144414 Reference - [mdc17785706pJ Clin Oncol 2007 Oct 1;25(28):4414](http://pubmed.ncbi.nlm.nih.gov/17785706?dopt=Abstract) [full-text](http://jco.ascopubs.org/content/25/28/4414.long), commentary can be found in [mdc18565900pJ Clin Oncol 2008 Jun 20;26(18):3094](http://pubmed.ncbi.nlm.nih.gov/18565900?dopt=Abstract)
* in mammographic lesions < 14 mm, casting-type calcifications associated with lower long-term survival in prospective study of 343 mammograms of invasive breast cancers of size 1-14 mm ([mnh10841122p t caph2753270t c pa9h2753270t c pbyh2753270t c pafh2753270t c pbeh2753270t c phch2753270t c pnyh2753270t c pnxh2753270t c pbth2753270t c ppbh2753270t c pcxh2753270t c pmdc10841122p t cLancet 2000 Feb 5;355(9202):429](http://pubmed.ncbi.nlm.nih.gov/10841122?dopt=Abstract) ), correction can be found in Lancet 2000 Apr 15;355(9212):1372, commentary can be found in [mnh10801193p t cmdc10801193p t cLancet 2000 Apr 29;355(9214):1551](http://pubmed.ncbi.nlm.nih.gov/10801193?dopt=Abstract)

Age

* young age
  + **young age at presentation (≤ 25 years old) associated with poorer survival in women with invasive breast cancer**

Nested case-control study[23812457Obstet Gynecol 2013 Jun;121(6):1235](http://pubmed.ncbi.nlm.nih.gov/23812457?dopt=Abstract)

studySummary

* + - based on 2-phase, retrospective, nested, within-cases matched study Nested case-control study
    - 28 women ≤ 25 years old with invasive breast cancer compared with 685 older (> 25 years old) premenopausal women with invasive breast cancer
      * age ≤ 25 years at diagnosis associated with
        + more advanced stage (p = 0.012, pairwise comparisons not reported)
        + higher grade (p = 0.018, pairwise comparisons not reported)
      * no significant difference in histologic subtype, estrogen receptor status, and progesterone receptor status
    - 23 women ≤ 25 years old with invasive breast cancer compared with 23 older (> 25 years old) premenopausal women with invasive breast cancer from above study population
      * age ≤ 25 years at diagnosis associated with
        + reduced overall survival (adjusted hazard ratio [HR] for death 4.3, 95% CI 1.09-17.03)
        + reduced relapse-free survival (adjusted HR for recurrence 8.28, 95% CI 2.24-30.6)
    - PubMed23812457Obstetrics and gynecology20130601Obstet Gynecol121612351235 Reference - [23812457Obstet Gynecol 2013 Jun;121(6):1235](http://pubmed.ncbi.nlm.nih.gov/23812457?dopt=Abstract)
  + **young age not associated with increased risk of early recurrence or survival in women with early stage human epidermal growth factor receptor 2 (HER2)-positive breast cancer**

Randomized Trial[cxh88999352pmdc23752109pJ Clin Oncol 2013 Jul 20;31(21):2692](http://pubmed.ncbi.nlm.nih.gov/23752109?dopt=Abstract)

studySummary

* + - based on cohort analysis of data from randomized trial Randomized Trial
    - 3,401 women with early stage HER2- positive breast cancer from HERA trial were randomized to trastuzumab vs. observation and evaluated after median 2 years of follow-up
    - all women received surgery and/or adjuvant or neoadjuvant chemotherapy, with or without radiation therapy
    - compared to women > 40 years old, no significant differences for disease-free survival or overall survival in women ≤ 40 years old for either group
    - PubMed23752109Journal of clinical oncology : official journal of the American Society of Clinical Oncology20130720J Clin Oncol312126922692 Reference - [cxh88999352pmdc23752109pJ Clin Oncol 2013 Jul 20;31(21):2692](http://pubmed.ncbi.nlm.nih.gov/23752109?dopt=Abstract) , commentary can be found in [cxh93375658pmdc24323029pJ Clin Oncol 2014 Jan 10;32(2):161](http://pubmed.ncbi.nlm.nih.gov/24323029?dopt=Abstract)
  + **young age at presentation (< 35 years old) of breast cancer may be associated with higher mortality**

Cohort Study[mnh16857060paph29336839pa9h29336839pafh29336839pcxh29336839pmdc16857060pBMC Cancer 2006 Jul 20;6:194](http://pubmed.ncbi.nlm.nih.gov/16857060?dopt=Abstract)[Full Text](http://www.biomedcentral.com/1471-2407/6/194)

studySummary

* + - based on retrospective cohort study Cohort Study
    - 1,320 consecutive patients (mean age at presentation 50.8 years) diagnosed with breast cancer from 1990 to 2001 and followed for median of 2.9 years
    - 8.1% were aged < 35 years
    - comparing patients < 35 years old vs. patients aged 35-50 years vs. patients > 50 years old
      * development of metastasis in 32.4% vs. 22.9% vs. 22.8% (not significant)
      * 5-year survival (extrapolated from graph) 70% vs. 85% vs. 90% (p = 0.03)
    - PubMed16857060BMC cancer20060720BMC Cancer6194194 Reference - [mnh16857060paph29336839pa9h29336839pafh29336839pcxh29336839pmdc16857060pBMC Cancer 2006 Jul 20;6:194](http://pubmed.ncbi.nlm.nih.gov/16857060?dopt=Abstract) [full-text](http://www.biomedcentral.com/1471-2407/6/194)
  + **increased mortality in women < 40 years old compared to women aged 45-49 years at diagnosis of breast cancer among women not receiving adjuvant cytotoxic chemotherapy**

Cohort Study[10678859BMJ 2000 Feb 19;320(7233):474](http://pubmed.ncbi.nlm.nih.gov/10678859?dopt=Abstract)[Full Text](http://www.bmj.com/content/320/7233/474.full)

studySummary

* + - based on retrospective cohort study Cohort Study
    - 10,356 women with primary breast cancer who were aged < 50 years old at diagnosis
    - compared to women diagnosed age 45-49 years, increased risk of mortality in
      * women diagnosed age 35-39 years (adjusted relative risk [RR] 1.4, 95% CI 1.1-1.8)
      * women diagnosed at < 35 years old (RR 2.18, 95% CI 1.64-2.89)
    - association of younger age and mortality not found for women who received adjuvant cytotoxic chemotherapy
    - PubMed10678859BMJ (Clinical research ed.)20000219BMJ3207233474474 Reference - [10678859BMJ 2000 Feb 19;320(7233):474](http://pubmed.ncbi.nlm.nih.gov/10678859?dopt=Abstract)[full-text](http://www.bmj.com/content/320/7233/474.full), editorial can be found in [10678839BMJ 2000 Feb 19;320(7233):457](http://pubmed.ncbi.nlm.nih.gov/10678839?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/10678839/) (correction can be found in BMJ 2000 Apr 29;320(7243):1173), commentary can be found in [10939831BMJ 2000 Jul 1;321(7252):53](http://pubmed.ncbi.nlm.nih.gov/10939831?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/10939831/)
  + **higher risk of relapse and death in younger premenopausal women than older premenopausal women, especially if estrogen receptor-positive tumors**

Randomized Trial[mnh10866443p t caph3166027t c pa9h3166027t c pbyh3166027t c pafh3166027t c pbeh3166027t c phch3166027t c pnyh3166027t c pnxh3166027t c pbth3166027t c ppbh3166027t c pcxh3166027t c pmdc10866443p t cLancet 2000 May 27;355(9218):1869](http://pubmed.ncbi.nlm.nih.gov/10866443?dopt=Abstract)

studySummary

* + - based on pooled analysis of 4 randomized trials Randomized Trial
    - 3,700 pre- and perimenopausal women (including 314 patients < 35 years old) with breast cancer having adjuvant cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy
    - comparing women < 35 years old vs. women ≥ 35 years old
      * 10-year disease-free survival 35% vs. 47% (p < 0.001)
      * overall survival 49% vs. 62% (p < 0.001)
    - PubMed10866443Lancet (London, England)20000527Lancet355921818691869 Reference - [mnh10866443p t caph3166027t c pa9h3166027t c pbyh3166027t c pafh3166027t c pbeh3166027t c phch3166027t c pnyh3166027t c pnxh3166027t c pbth3166027t c ppbh3166027t c pcxh3166027t c pmdc10866443p t cLancet 2000 May 27;355(9218):1869](http://pubmed.ncbi.nlm.nih.gov/10866443?dopt=Abstract) , editorial can be found in [mnh10866433p taph3166011t pa9h3166011t pbyh3166011t pafh3166011t pbeh3166011t phch3166011t pnyh3166011t pnxh3166011t pbth3166011t ppbh3166011t pcxh3166011t pmdc10866433p tLancet 2000 May 27;355(9218):1839](http://pubmed.ncbi.nlm.nih.gov/10866433?dopt=Abstract) , commentary can be found in [mnh11036925p t cmdc11036925p t cLancet 2000 Sep 9;356(9233):944](http://pubmed.ncbi.nlm.nih.gov/11036925?dopt=Abstract) , [mnh11009170p t cmdc11009170p t cLancet 2000 Sep 23;356(9235):1113](http://pubmed.ncbi.nlm.nih.gov/11009170?dopt=Abstract)
  + **women < 40 years old have higher mortality than women aged 40-49 years among women with breast cancer**

Cohort Study[World J Surg Oncol 2004 Jan 22;2:2](http://pubmed.ncbi.nlm.nih.gov/14736343-do-younger-women-with-non-metastatic-and-non-inflammatory-breast-carcinoma-have-poor-prognosis/?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC340386/?tool=pubmed)

studySummary

* + - Cohort Study based on cohort study of 1,701 women in India with nonmetastatic, noninflammatory breast carcinoma, median follow-up 66 months
    - 62% overall survival, estimated 10-year overall survival was 52.6%
      * estimated 10-year overall survival among 437 women < 40 years old 46.5%
        + 62.3% if T1, 58.3% if T2, 36.6% if T3, 10.4% if T4
        + 76.8% if node-negative, 24.2% if node-positive
      * estimated 10-year overall survival among 557 women aged 40-49 years 59.8%
        + 73.2% if T1, 66.3% if T2, 41.9% if T3, 33.5% if T4
        + 73.9% if node-negative, 43.6% if node-positive
      * estimated 10-year overall survival among 433 women aged 50-59 years 58.9%
        + 55.9% if T1, 57.1% if T2, 46.4% if T3, 46.7% if T4
        + 68.8% if node-negative, 41.6% if node-positive
      * estimated 10-year overall survival among 274 women > 60 years old 48%
        + 70% if T1, 55.5% if T2, 47.9% if T3, 18.1% if T4
        + 64.4% if node-negative, 34.5% if node-positive
    - PubMed14736343World journal of surgical oncologyWorld J Surg Oncol20040122222Reference - [World J Surg Oncol 2004 Jan 22;2:2](http://pubmed.ncbi.nlm.nih.gov/14736343-do-younger-women-with-non-metastatic-and-non-inflammatory-breast-carcinoma-have-poor-prognosis/?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC340386/?tool=pubmed)
  + **women < 40 years old at diagnosis appear to have higher mortality in early stage disease compared to women ≥ 40 years old**

Cohort Study[19317994J Am Coll Surg 2009 Mar;208(3):341](http://pubmed.ncbi.nlm.nih.gov/19317994?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/19317994/)

studySummary

* + - based on retrospective cohort study Cohort Study
    - 243,012 women diagnosed with breast cancer from 1988 to 2003 were stratified by age (6.4% < 40 years old vs. 93.6% ≥ 40 years old)
    - comparing women < 40 years old at breast cancer diagnosis vs. women ≥ 40 years old
      * disease-specific mortality 18.3% vs. 12.1% (p < 0.001)
      * disease-specific mortality with stage I diagnosis 6.8% vs. 3.6%(p < 0.05)
      * disease-specific mortality with stage II diagnosis 20.3% vs. 15.2% (p < 0.05)
      * disease-specific mortality with stage IV diagnosis 66.4% vs. 67.8% (p < 0.05)
    - PubMed19317994Journal of the American College of Surgeons20090301J Am Coll Surg2083341341 Reference - [19317994J Am Coll Surg 2009 Mar;208(3):341](http://pubmed.ncbi.nlm.nih.gov/19317994?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/19317994/)
* older age
  + **age ≥ 65 years at diagnosis associated with increased breast cancer mortality in women with hormone receptor-positive early breast cancer**

Randomized Trial[mdc22318280pJAMA 2012 Feb 8;307(6):590](http://pubmed.ncbi.nlm.nih.gov/22318280?dopt=Abstract)[Full Text](http://jama.jamanetwork.com/article.aspx?articleid=1104959)

studySummary

* + - based on post hoc analysis of TEAM trialRandomized Trial
    - 9,766 postmenopausal women with hormone receptor-positive early breast cancer were stratified by age at diagnosis
    - 10.7% mortality during median 5.1 years of follow-up
    - disease-specific mortality defined as time from randomization to breast cancer-related mortality
    - after multivariate analysis age at diagnosis associated with increased risk of (vs. women < 65 years old)
      * breast cancer mortality
        + hazard ratio (HR) 1.25 (95% CI 1.01-1.54) in women aged 65-74 years
        + HR 1.63 (95% CI 1.23-2.16) in women ≥ 75 years old
      * other mortality
        + HR 2.66 (95% CI 1.96-3.63) in women aged 65-74 years
        + HR 7.3 (95% CI 5.29-10.07) in women ≥ 75 years old
    - PubMed22318280JAMA20120208JAMA3076590590Reference - [mdc22318280pJAMA 2012 Feb 8;307(6):590](http://pubmed.ncbi.nlm.nih.gov/22318280?dopt=Abstract) [full-text](http://jama.jamanetwork.com/article.aspx?articleid=1104959)
  + **in women > 70 years old with early breast cancer treated with conservative surgery plus adjuvant tamoxifen, mortality from breast cancer reported in 17%**

Cohort Study[18098268Cancer 2008 Feb 1;112(3):481](http://pubmed.ncbi.nlm.nih.gov/18098268?dopt=Abstract)[Full Text](http://onlinelibrary.wiley.com/doi/10.1002/cncr.23213/full)

studySummary

* + - based on cohort studyCohort Study
    - 354 women ≥ 70 years old with primary, operable breast cancer and no palpable axillary lymph nodes were treated with conservative surgery and adjuvant tamoxifen
    - conservative surgery consisted of breast-conserving surgery (quadrantectomy) without axillary dissection or postoperative radiation therapy
    - median follow-up 15 years
    - breast cancer mortality 17%
    - crude cumulative incidence
      * axillary disease in 4.2%
      * ipsilateral breast tumor recurrence in 8.3%
    - PubMed18098268Cancer20080201Cancer1123481481Reference - [18098268Cancer 2008 Feb 1;112(3):481](http://pubmed.ncbi.nlm.nih.gov/18098268?dopt=Abstract)[full-text](http://onlinelibrary.wiley.com/doi/10.1002/cncr.23213/full)

Weight and Body Mass

* **obesity associated with poorer survival in women with breast cancer**

Systematic Review[mnh20571870pcxh53704105pmdc20571870pBreast Cancer Res Treat 2010 Oct;123(3):627](http://pubmed.ncbi.nlm.nih.gov/20571870?dopt=Abstract)

studySummary

* + based on systematic review of observational studies Systematic Review
  + systematic review of 45 cohort studies evaluating survival in nonobese and women with obesity and with breast cancer
  + sample size ranged from 100 to 424,168 (median 1,192)
  + women with obesity had poorer survival in analysis of 43 studies
    - poorer overall survival hazard ratio (HR) 1.33 (95% CI 1.21-1.47)
    - poorer breast cancer-specific survival HR 1.33 (95% CI 1.19-1.5)
  + no significant difference in risk between premenopausal and postmenopausal women with obesity
  + PubMed20571870Breast cancer research and treatment20101001Breast Cancer Res Treat1233627627 Reference - [mnh20571870pcxh53704105pmdc20571870pBreast Cancer Res Treat 2010 Oct;123(3):627](http://pubmed.ncbi.nlm.nih.gov/20571870?dopt=Abstract) , editorial can be found in [mnh20711653pcxh53704102pmdc20711653pBreast Cancer Res Treat 2010 Oct;123(3):637](http://pubmed.ncbi.nlm.nih.gov/20711653?dopt=Abstract)
* body mass index (BMI) ≥ 30 kg/m2 associated with increased all-cause mortality in study of 1,254 women aged 20-54 years with invasive breast cancer followed 8-10 years ([17035393Cancer Epidemiol Biomarkers Prev 2006 Oct;15(10):1871](http://pubmed.ncbi.nlm.nih.gov/17035393?dopt=Abstract)[full-text](http://cebp.aacrjournals.org/content/15/10/1871.long))
* elevated waist-to-hip ratio, based on 603 patients with breast cancer followed 4-10 years ([14607804Am J Epidemiol 2003 Nov 15;153(10):963](http://pubmed.ncbi.nlm.nih.gov/14607804?dopt=Abstract))
* increased body weight and negative estrogen receptor each were associated with 2-fold higher risk of death from breast cancer in women with early-stage breast cancer, based on cohort of 1,376 women followed for median 6.8 years after diagnosis ([mdc15381612pArch Surg 2004 Sep;139(9):954](http://pubmed.ncbi.nlm.nih.gov/15381612?dopt=Abstract) )
* **obesity associated with reduced survival in women with hormone receptor-positive breast cancer treated with chemotherapy**

Randomized Trial[22926690Cancer 2012 Dec 1;118(23):5937](http://pubmed.ncbi.nlm.nih.gov/22926690?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3586227/)

studySummary

* + based on cohort analysis of data from 3 randomized trials Randomized Trial
  + 4,770 women with hormone receptor-positive operable breast cancer from 1 randomized trial evaluating chemotherapy regimens were assessed
    - 31% were normal or underweight (BMI < 25 kg/m2)
    - 32% were overweight (BMI 25-29.9 kg/m2)
    - 37% were obese (BMI ≥ 30 kg/m2)
  + compared to lower BMI categories, obesity associated with reduced survival in analysis of women with hormone receptor-positive disease (hazard ratio for death 1.37, 95% CI 1.13-1.67)
  + no significant association between obesity and survival in women with other disease subtypes
  + similar association between obesity and mortality found in 2 additional trials
  + PubMed22926690Cancer20121201Cancer1182359375937 Reference - [22926690Cancer 2012 Dec 1;118(23):5937](http://pubmed.ncbi.nlm.nih.gov/22926690?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3586227/)
* **weight gain > 10% after breast cancer diagnosis associated with increased risk of all-cause mortality**

Systematic Review[26424778J Natl Cancer Inst 2015 Dec;107(12):djv275](http://pubmed.ncbi.nlm.nih.gov/26424778?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4715249/)

studySummary

* + based on systematic review of observational studies Systematic Review
  + systematic review of 12 observational studies (retrospective and prospective cohort studies, and cohort analysis of randomized trials) evaluating association between weight gain and risk of mortality in 23,832 women with stage I-IIIC breast cancer
  + median follow-up time ranged from 2 years to > 10 years
  + compared to maintaining body weight, weight gain > 5% associated with increased overall risk of all-cause mortality (hazard ratio [HR] 1.12, 95% CI 1.03-1.22) in analysis of 8 studies, results limited by statistical heterogeneity
  + in subgroup analysis stratified by level of weight gain
    - weight gain > 10% associated with increased risk of all-cause mortality (HR 1.23, 95% CI 1.09-1.39) in analysis of 4 studies, results limited by significant heterogeneity
    - no significant association between weight gain 5%-10% and risk of all-cause mortality in analysis of 4 studies
  + in subgroup analysis of patients with weight gain > 5% also stratified by prediagnosis body mass index (BMI), no significant association between BMI < 25 kg/m2 or BMI ≥ 25 kg/m2 and risk of all-cause mortality in analysis of 4 studies
  + PubMed26424778Journal of the National Cancer Institute20151201J Natl Cancer Inst10712djv275djv275 Reference - [26424778J Natl Cancer Inst 2015 Dec;107(12):djv275](http://pubmed.ncbi.nlm.nih.gov/26424778?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4715249/)
* **overweight and obesity associated with reduced disease-free survival compared to normal weight after resection plus adjuvant chemotherapy for human epidermal growth factor receptor type 2 (HER2)-positive breast cancer**

Randomized Trial[23585192Cancer 2013 Jul 1;119(13):2447](http://pubmed.ncbi.nlm.nih.gov/23585192?dopt=Abstract)

studySummary

* + based on cohort analysis of data from randomized trial Randomized Trial
  + 3,017 women with resected stage I-III invasive HER2-positive breast cancer with data on BMI were categorized as normal weight (BMI < 25 kg/m2), overweight (BMI 25-29.9 kg/m2), or obese (BMI ≥ 30 kg/m2) and evaluated
  + all women had doxorubicin plus cyclophosphamide followed by paclitaxel or paclitaxel plus concurrent or sequential trastuzumab
  + disease-related events included recurrence, contralateral breast cancer, new primary cancer, or death from any cause
  + 5-year disease-free survival
    - 82.5% with normal weight (p < 0.05 vs. other groups)
    - 78.6% with overweight
    - 78.5% with obesity
  + PubMed23585192Cancer20130701Cancer1191324472447 Reference - [23585192Cancer 2013 Jul 1;119(13):2447](http://pubmed.ncbi.nlm.nih.gov/23585192?dopt=Abstract)
* **overweight associated with increased risk of mortality and disease recurrence in premenopausal women having adjuvant anastrozole for hormone receptor-positive breast cancer**

Randomized Trial[mdc21555684pJ Clin Oncol 2011 Jul 1;29(19):2653](http://pubmed.ncbi.nlm.nih.gov/21555684?dopt=Abstract)

studySummary

* + based on cohort analysis of data from randomized trial Randomized Trial
  + 1,803 premenopausal women with stage IB, IC, or II hormone receptor-positive breast cancer who were randomized to goserelin plus tamoxifen vs. goserelin plus anastrozole were stratified by BMI and followed for mean 5 years
  + comparing women with overweight vs. normal weight women taking anastrozole, overweight associated with increased risk of
    - mortality (hazard ratio [HR] 2.14, 95% CI 1.17-3.92)
    - disease recurrence (HR 1.6, 95% CI 1.06-2.41)
  + anastrozole associated with increased mortality compared to tamoxifen (p = 0.004) in subgroup of women with overweight
  + no significant differences in recurrence or mortality comparing women with overweight vs. normal weight women taking tamoxifen
  + PubMed21555684Journal of clinical oncology : official journal of the American Society of Clinical Oncology20110701J Clin Oncol291926532653 Reference - [mdc21555684pJ Clin Oncol 2011 Jul 1;29(19):2653](http://pubmed.ncbi.nlm.nih.gov/21555684?dopt=Abstract)
* **obesity and overweight not associated with increased mortality risk in postmenopausal women with breast cancer who received adjuvant therapy with letrozole or tamoxifen**

Randomized Trial[cxh83235281pmdc23045588pJ Clin Oncol 2012 Nov 10;30(32):3967](http://pubmed.ncbi.nlm.nih.gov/23045588?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23045588/)

studySummary

* + based on cohort analysis of data from BIG 1-98 randomized trial Randomized Trial
  + 4,760 postmenopausal women with nonmetastatic hormone receptor-positive invasive breast cancer who received monotherapy with [letrozole](https://dpa-pde-oxford.shinyapps.io/drug-monograph/letrozole) or [tamoxifen](https://dpa-pde-oxford.shinyapps.io/drug-monograph/tamoxifen) for 5 years were followed for median 8.7 years
  + baseline BMI was ≥ 30 kg/m2 in 23%, and 25-29 kg/m2 in 36%
  + overall survival 83%
  + mortality risk compared to BMI < 25 kg/m2 (normal weight)
    - nonsignificant increase associated with BMI ≥ 30 kg/m2 (obesity) (hazard ratio 1.19, 95% CI 0.99-1.44)
    - no significant difference compared to BMI 25 to < 30 kg/m2 (overweight)
  + no significant difference in disease-free survival, breast cancer-free survival, or distant recurrence-free survival comparing obesity or overweight status to normal weight
  + PubMed23045588Journal of clinical oncology : official journal of the American Society of Clinical Oncology20121110J Clin Oncol303239673967 Reference - [cxh83235281pmdc23045588pJ Clin Oncol 2012 Nov 10;30(32):3967](http://pubmed.ncbi.nlm.nih.gov/23045588?dopt=Abstract) [full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23045588/)
* **obesity might not be associated with increased mortality in women with node-positive breast cancer who received adjuvant chemotherapy**

Cohort Study[24315625Eur J Cancer 2014 Feb;50(3):506](http://pubmed.ncbi.nlm.nih.gov/24315625?dopt=Abstract)

studySummary

* + based on cohort analysis of pooled patient data from 2 randomized trials Cohort Study
  + 4,996 women in France with node-positive breast cancer who received adjuvant chemotherapy of anthracycline-based treatment plus taxane or taxane alone were analyzed
  + median follow-up 5.9 years
  + no significant differences in overall or disease-free survival comparing women with obesity (BMI ≥ 30kg/m2) vs. women without obesity in adjusted analyses
  + PubMed24315625European journal of cancer20140201Eur J Cancer503506506 Reference - [24315625Eur J Cancer 2014 Feb;50(3):506](http://pubmed.ncbi.nlm.nih.gov/24315625?dopt=Abstract)

Psychosocial Factors

* **conflicting data regarding association of psychosocial factors and survival in patients with breast cancer**

Systematic Review[17640330Breast Cancer Res 2007;9(4):R44](http://pubmed.ncbi.nlm.nih.gov/17640330?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2206717/?tool=pubmed)

studySummary

* + based on systematic review Systematic Review
  + systematic review of 37 studies of psychosocial factors and breast cancer in 61,611 female patients with breast cancer
  + 31 studies were descriptive studies and 6 studies evaluated psychologic intervention
  + factors with inconsistent findings across studies
    - fighting spirit
    - stressful events
    - anxiety
    - hopelessness/helplessness
    - joy
    - depression/negative mood
    - perceived social support
    - repressive defensiveness/emotional constraints
    - adjustment
    - fatalism/stoic appearance
    - denial/avoidance
    - anger/hostility
    - expressive activities
    - group participation in religious/nonreligious activities
    - somatization, obsessive-compulsive symptoms, paranoia, psychotic behavior, interpersonal sensitivity
    - marriage
  + factors with no impact on survival or recurrence risk (and no evidence suggesting impact)
    - coping in 4 studies
    - beliefs about cancer incurability in 1 study
    - locus of control in 5 studies
    - vigor/activity in 2 studies
    - fatigue/inertia in 1 study
    - confusion/bewilderment in 1 study
    - self-esteem in 2 studies
  + factors with positive impact on survival or recurrence risk (and no conflicting evidence)
    - cognitive/role functioning in 1 study
    - minimizing in 2 studies
    - guilt in 1 study
    - extroversion in 1 study
    - hobbies in 1 study
    - female child in 1 study
  + only factor with negative impact (and no conflicting evidence) was positive constructing daydreaming in 1 study
  + PubMed17640330Breast cancer research : BCR200701Breast Cancer Res94R44R44 Reference - [17640330Breast Cancer Res 2007;9(4):R44](http://pubmed.ncbi.nlm.nih.gov/17640330?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2206717/?tool=pubmed)
* **psychosocial factors may not be associated with recurrence or survival in women with nonmetastatic breast cancer**

Cohort Study[mdc18824713pJ Clin Oncol 2008 Oct 1;26(28):4666](http://pubmed.ncbi.nlm.nih.gov/18824713?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/18824713/)

studySummary

* + based on population-based prospective cohort study Cohort Study
  + 708 women ≤ 60 years old with nonmetastatic breast cancer had depression, anxiety, coping style, and social support assessed at median 11 months after diagnosis and were followed for median 8.2 years
  + mortality was 24% and distant recurrence occurred in 33% during follow-up
  + no significant associations between any measured psychosocial factor and distant disease-free survival or overall survival
  + PubMed18824713Journal of clinical oncology : official journal of the American Society of Clinical Oncology20081001J Clin Oncol262846664666 Reference - [mdc18824713pJ Clin Oncol 2008 Oct 1;26(28):4666](http://pubmed.ncbi.nlm.nih.gov/18824713?dopt=Abstract) [full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/18824713/)
* **depression and/or anxiety common in first 5 years after diagnosis of breast cancer, especially in first year**

Cohort Study[BMJ 2005 Mar 26;330(7493):702](http://pubmed.ncbi.nlm.nih.gov/15695497-depression-and-anxiety-in-women-with-early-breast-cancer-five-year-observational-cohort-study/?dopt=Abstract)

studySummary

* + Cohort Study based on cohort of 222 women < 60 years old with breast cancer, 170 women (77%) were followed for 5 years or until recurrence
  + clinically important depression and/or anxiety occurred in nearly 50% in first year, 25% in second through fourth years, and 15% in fifth year after diagnosis
  + PubMed15695497BMJ (Clinical research ed.)BMJ200503263307493702702Reference - [BMJ 2005 Mar 26;330(7493):702](http://pubmed.ncbi.nlm.nih.gov/15695497-depression-and-anxiety-in-women-with-early-breast-cancer-five-year-observational-cohort-study/?dopt=Abstract)
* low socioeconomic status
  + **women living in communities with lowest socioeconomic status had increased mortality in United States (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cohort Study[18391595Am J Clin Oncol 2008 Apr;31(2):125](http://pubmed.ncbi.nlm.nih.gov/18391595?dopt=Abstract)

studySummary2

* + - based on retrospective cohort study Cohort Study
    - 35,029 women ≥ 65 years old with stage I-IIIA breast cancer from Surveillance, Epidemiology and End Results (SEER)-medicare linked database and up to 11 years of follow-up were analyzed
    - increased risk for death associated with living in lowest socioeconomic communities (hazard ratio 1.1, 95% CI 1.04-1.16) compared to living in highest socioeconomic communities
    - PubMed18391595American journal of clinical oncology20080401Am J Clin Oncol312125125 Reference - [18391595Am J Clin Oncol 2008 Apr;31(2):125](http://pubmed.ncbi.nlm.nih.gov/18391595?dopt=Abstract)
  + **low socioeconomic status may be associated with differences in treatment received for breast cancer**

Cohort Study[11929949J Natl Cancer Inst 2002 Apr 3;94(7):490](http://pubmed.ncbi.nlm.nih.gov/11929949?dopt=Abstract)

studySummary

* + - based on analysis of data available in Metropolitan Detroit Cancer Surveillance System (MDCSS) database Cohort Study
    - 5,719 women (mean age 61.1 years) diagnosed with in situ or invasive breast cancer from 1996 to 1997 were analyzed for variables associated with late-stage breast cancer at diagnosis, chosen treatment, and mortality within study period
    - socioeconomic status was defined by percentage of residents below federal poverty line within census tract of patient's residence and stratified by < 5%, 5%-12%, and ≥ 13%
    - compared to women living in census tracts with poverty levels < 5%, women living in census tracts with poverty levels ≥ 13% were
      * less likely to have breast-conserving surgery (adjusted odds ratio [OR] 0.68, 95% CI 0.56-0.82)
      * less likely to have adjuvant radiation (OR 0.78, 95% CI 0.6-1)
    - PubMed11929949Journal of the National Cancer Institute20020403J Natl Cancer Inst947490490 Reference - [11929949J Natl Cancer Inst 2002 Apr 3;94(7):490](http://pubmed.ncbi.nlm.nih.gov/11929949?dopt=Abstract), commentary can be found in [12189230J Natl Cancer Inst 2002 Aug 21;94(16):1254](http://pubmed.ncbi.nlm.nih.gov/12189230?dopt=Abstract)

Comorbidities

* **preexisting dementia associated with increased mortality in breast cancer**

Cohort Study[mdc18852406pArch Intern Med 2008 Oct 13;168(18):2033](http://pubmed.ncbi.nlm.nih.gov/18852406?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/18852406/)

studySummary

* + based on retrospective cohort Cohort Study
  + 31,935 women ≥ 65 years old with breast cancer were analyzed for associations between dementia and breast cancer outcomes
  + 7.4% had preexisting dementia diagnosis
  + comparing patients with vs. without dementia
    - 1-year cancer-specific mortality 7.6% vs. 3.8% (p < 0.05)
    - 1-year noncancer mortality 9% vs. 3% (p < 0.05)
    - 5-year cancer-specific mortality 17.9% vs. 13.1% (p < 0.05)
    - 5-year noncancer mortality 31.8% vs. 16.2% (p < 0.05)
  + PubMed18852406Archives of internal medicine20081013Arch Intern Med1681820332033 Reference - [mdc18852406pArch Intern Med 2008 Oct 13;168(18):2033](http://pubmed.ncbi.nlm.nih.gov/18852406?dopt=Abstract) [full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/18852406/), commentary can be found in [mdc19307529pArch Intern Med 2009 Mar 23;169(6):633](http://pubmed.ncbi.nlm.nih.gov/19307529?dopt=Abstract)

Delay in Diagnosis or Treatment

* **delay in diagnosis associated with decreased survival but not after controlling for stage**

Systematic Review[mnh10209974p t caph1711558t c pa9h1711558t c pbyh1711558t c pafh1711558t c pbeh1711558t c phch1711558t c pnyh1711558t c pnxh1711558t c pbth1711558t c ppbh1711558t c pcxh1711558t c pmdc10209974p t cLancet 1999 Apr 3;353(9159):1119](http://pubmed.ncbi.nlm.nih.gov/10209974?dopt=Abstract)

studySummary

* + based on systematic review of observational studies Systematic Review
  + systematic review of 87 observational studies evaluating duration of symptoms and survival in 101,954 women presenting with symptomatic breast cancer
  + compared to delays (between the onset of symptoms and the start of treatment) < 3 months
    - delays ≥ 3 months associated with higher 5-year mortality (odds ratio (OR) 1.47, 95% CI 1.42-1.53) in analysis of 26 studies with 44, 347 women
    - delays 3-6 months associated with higher 5-year mortality (OR 1.24, 95% CI 1.17-1.3) in analysis of 23 studies with 25,052 women
  + compared to delays < 6 months, delays > 6 months associated with higher 5-year mortality (OR 1.45, 95% CI 1.4-1.5)
  + longer delay was not associated with shorter survival in studies that controlled for stage of disease
  + PubMed10209974Lancet (London, England)19990403Lancet353915911191119 Reference - [mnh10209974p t caph1711558t c pa9h1711558t c pbyh1711558t c pafh1711558t c pbeh1711558t c phch1711558t c pnyh1711558t c pnxh1711558t c pbth1711558t c ppbh1711558t c pcxh1711558t c pmdc10209974p t cLancet 1999 Apr 3;353(9159):1119](http://pubmed.ncbi.nlm.nih.gov/10209974?dopt=Abstract) , commentary can be found in [mnh10382714paph20242065pa9h20242065pbyh20242065pafh20242065pbeh20242065phch20242065pnyh20242065pnxh20242065pbth20242065ppbh20242065pcxh20242065pmdc10382714pLancet 1999 Jun 19;353(9170):2154](http://pubmed.ncbi.nlm.nih.gov/10382714?dopt=Abstract)
* **delays by providers in diagnosis of ≥ 3 months do not appear to decrease survival**

Cohort Study[mnh10209976p t caph1711561t c pa9h1711561t c pbyh1711561t c pafh1711561t c pbeh1711561t c phch1711561t c pnyh1711561t c pnxh1711561t c pbth1711561t c ppbh1711561t c pcxh1711561t c pmdc10209976p t cLancet 1999 Apr 3;353(9159):1132](http://pubmed.ncbi.nlm.nih.gov/10209976?dopt=Abstract)

studySummary

* + based on retrospective analysis of data available in Yorkshire Cancer Registry Cohort Study
  + 36,222 patients diagnosed with breast cancer from 1976 to 1995 were analyzed for associations between delays in referral, hospital visit, or start of treatment and survival
  + median time from family-physician referral to first hospital visit for breast cancer was 10 days in 1976 vs. 12 days in 1995 (no p value reported)
  + median delay between first hospital visit and treatment was 7 days in 1976 vs. 13 days in 1995 (no p value reported)
  + compared to delays < 30 days vs
    - delays 30-59 days associated with decreased mortality (adjusted hazard ratio [HR] 0.75, 95% CI 0.69-0.82)
    - delays ≥ 60 days associated with decreased mortality (HR 0.78, 95% CI 0.69-0.89)
  + PubMed10209976Lancet (London, England)19990403Lancet353915911321132 Reference - [mnh10209976p t caph1711561t c pa9h1711561t c pbyh1711561t c pafh1711561t c pbeh1711561t c phch1711561t c pnyh1711561t c pnxh1711561t c pbth1711561t c ppbh1711561t c pcxh1711561t c pmdc10209976p t cLancet 1999 Apr 3;353(9159):1132](http://pubmed.ncbi.nlm.nih.gov/10209976?dopt=Abstract) , commentary can be found in [mnh10209969p taph1711552t pa9h1711552t pbyh1711552t pafh1711552t pbeh1711552t phch1711552t pnyh1711552t pnxh1711552t pbth1711552t ppbh1711552t pcxh1711552t pmdc10209969p tLancet 1999 Apr 3;353(9159):1112](http://pubmed.ncbi.nlm.nih.gov/10209969?dopt=Abstract) , [mnh10382716paph20242065pa9h20242065pbyh20242065pafh20242065pbeh20242065phch20242065pnyh20242065pnxh20242065pbth20242065ppbh20242065pcxh20242065pmdc10382716pLancet 1999 Jun 19;353(9170):2154](http://pubmed.ncbi.nlm.nih.gov/10382716?dopt=Abstract) , [mnh10543705paph20238594pa9h20238594pbyh20238594pafh20238594pbeh20238594phch20238594pnyh20238594pnxh20238594pbth20238594ppbh20238594pcxh20238594pmdc10543705pLancet 1999 Oct 23;354(9188):1478](http://pubmed.ncbi.nlm.nih.gov/10543705?dopt=Abstract)
* **length of delay in diagnosis not associated with prognostic factors or survival rates**

Cohort Study[16978961Am J Surg 2006 Oct;192(4):506](http://pubmed.ncbi.nlm.nih.gov/16978961?dopt=Abstract)

studySummary

* + based on retrospective analysis Cohort Study
  + 40 patients with delay in breast cancer diagnosis of 3-36 months were analyzed for associations between delay in diagnosis and prognostic factors such as tumor size, nodal status, and stage at diagnosis
  + higher stage at diagnosis associated with decreased survival (p = 0.03)
  + no significant associations found between delay of diagnosis and primary tumor diameter, number of positive lymph nodes, tumor grade, or pathologic stage
  + PubMed16978961American journal of surgery20061001Am J Surg1924506506 Reference - [16978961Am J Surg 2006 Oct;192(4):506](http://pubmed.ncbi.nlm.nih.gov/16978961?dopt=Abstract)
* **delay in surgery and in adjuvant and neoadjuvant systemic therapy each associated with increased mortality in patients with breast cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[BMJ 2020 Nov 4.doi: 10.1136/bmj.m4087](http://pubmed.ncbi.nlm.nih.gov/33148535)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7610021/)

Family\_Medicine Internal\_Medicine Oncologic\_Disease Primary\_Care Surgery\_and\_Proceduresdelay in surgery and in adjuvant and neoadjuvant systemic therapy each associated with increased mortality in patients with breast cancer (BMJ 2020 Nov 4)12/01/2020 10:42:32 AMstudySummary

* + Systematic Review based on systematic review of observational studies
  + systematic review of 34 retrospective cohort studies evaluating delay in cancer treatment in 1,272,681 patients
    - treatments included surgery (curative, neoadjuvant, and adjuvant indications), systemic treatment, or radiation therapy
    - patients had cancers of bladder, breast, colon, rectum, lung, cervix, or head and neck
  + treatment delay was assessed from diagnosis to first treatment, or from completion of 1 treatment to start of next, and ranged from 3 to 16 weeks across studies
  + in patients with breast cancer, increased mortality associated with (hazard ratio [HR] for each 4-week delay)
    - delay in surgery (HR 1.08, 95% CI 1.03-1.13) in analysis of 6 studies
    - delay in adjuvant systemic therapy (HR 1.09, 95% CI 1.07-1.11) in analysis of 3 studies
    - delay in neoadjuvant systemic therapy (HR 1.28, 95% CI 1.05-1.56) in 1 study with 1,101 patients
  + no significant differences in mortality with delay in adjuvant radiation therapy in patients with breast cancer in 1 study with 1,062 patients
  + PubMed33148535BMJ (Clinical research ed.)BMJ20201104371m4087m4087Reference - [BMJ 2020 Nov 4.doi: 10.1136/bmj.m4087](http://pubmed.ncbi.nlm.nih.gov/33148535)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7610021/)

Smoking

* **smoking associated with increased mortality in women with breast cancer**

Systematic Review[23053660Breast Cancer Res Treat 2012 Nov;136(2):521](http://pubmed.ncbi.nlm.nih.gov/23053660?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23053660/)

studySummary

* + based on systematic review of observational studies Systematic Review
  + systematic review of 7 cohort studies examined association between smoking and breast cancer mortality in women with breast cancer
  + compared to never smoking, smoking significantly associated with significant increased breast cancer mortality in 4 studies
  + 2,265 women diagnosed with breast cancer were followed for median 12 years
    - compared with never smoking, current smoking associated with increased risk of
      * breast cancer mortality (hazard ratio 2.01, 95% CI 1.27-3.18)
      * nonbreast cancer mortality (hazard ratio 3.84, 95% CI 2.5-5.89)
    - no significant association between former smoking and breast cancer mortality
  + PubMed23053660Breast cancer research and treatment20121101Breast Cancer Res Treat1362521521 Reference - [23053660Breast Cancer Res Treat 2012 Nov;136(2):521](http://pubmed.ncbi.nlm.nih.gov/23053660?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23053660/)
* **current smoking and former smoking of ≥ 20 pack-years each associated with increased risk of breast cancer recurrence and mortality**

Cohort Study[24317179J Natl Cancer Inst 2014 Jan;106(1):djt359](http://pubmed.ncbi.nlm.nih.gov/24317179?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3906992/)

studySummary

* + based on cohort study Cohort Study
  + 9,975 women (mean age at diagnosis 59 years) who survived invasive primary early stage breast cancer from 3 cohorts in After Breast Cancer Pooling Project were assessed
  + 7% were current smokers, 45% were former smokers, and 48% were never smokers
  + rate of breast cancer recurrence 17.3%, breast cancer mortality 10.6%, and all-cause mortality 18.1% at median follow-up of 11 years
  + compared to never smoking
    - current smoking associated with increased risk of breast cancer recurrence, breast cancer mortality, and all-cause mortality (p < 0.001 for each)
    - former smoking of ≥ 35 pack-years associated with increased risk of breast cancer recurrence (p = 0.001), breast cancer mortality (p < 0.001), and all-cause mortality (p < 0.001)
    - former smoking of 20-34.9 pack-years associated with increased risk of breast cancer recurrence (p = 0.04) and all-cause mortality (p = 0.01), but no significant difference in risk of breast cancer mortality
  + no significant differences in breast cancer recurrence, breast cancer mortality, or all-cause mortality comparing former smoking of < 20 pack-years to never smoking
  + PubMed24317179Journal of the National Cancer Institute20140101J Natl Cancer Inst1061djt359djt359 Reference - [24317179J Natl Cancer Inst 2014 Jan;106(1):djt359](http://pubmed.ncbi.nlm.nih.gov/24317179?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3906992/)

Additional Factors Affecting Survival

* **cosmetic breast augmentation prior to cancer detection associated with increased risk of breast cancer-specific mortality**

Systematic Review[23637132BMJ 2013 Apr 29;346:f2399](http://pubmed.ncbi.nlm.nih.gov/23637132?dopt=Abstract)[Full Text](http://www.bmj.com/content/346/bmj.f2399?view=long&pmid=23637132)

studySummary

* + based on systematic review of observational studies Systematic Review
  + systematic review of 29 observational studies with data to assess effects of cosmetic breast augmentation prior to cancer detection in women with breast cancer
  + comparing women with implants who had breast cancer to women without implants who had breast cancer, cosmetic breast implants associated with
    - increased risk of breast cancer-specific mortality (hazard ratio 1.38, 95% CI 1.08-1.75) in analysis of 5 studies with > 18,000 women
    - nonsignificant increase in risk of nonlocalized stage of breast cancer at diagnosis (p = 0.058) in analysis of 12 studies
  + PubMed23637132BMJ (Clinical research ed.)20130429BMJ346f2399f2399 Reference - [23637132BMJ 2013 Apr 29;346:f2399](http://pubmed.ncbi.nlm.nih.gov/23637132?dopt=Abstract)[full-text](http://www.bmj.com/content/346/bmj.f2399?view=long&pmid=23637132)
* **pathologic complete response after neoadjuvant chemotherapy associated with increased survival in women with large operable or locally advanced breast cancer**

Randomized Trial[24618153Ann Oncol 2014 Jun;25(6):1128](http://pubmed.ncbi.nlm.nih.gov/24618153?dopt=Abstract)

studySummary

* + based on prespecified cohort analysis of data from randomized trial without blinding Randomized Trial
  + 1,856 women with large operable or locally advanced breast cancer who were randomized to 6 cycles of neoadjuvant chemotherapy with anthracycline-based regimen vs. docetaxel-based regimen were assessed
  + 1,212 patients (65%) had evaluable pathologic response data and were included in analyses
  + 18% had pathologic complete response
  + event-free survival defined as freedom from progression, locoregional relapse, first distant metastasis, or all-cause death
  + compared to no or incomplete response, pathologic complete response associated with increased
    - event-free survival (adjusted hazard ratio for event 0.4, 95% CI 0.25-0.64)
    - overall survival (adjusted hazard ratio for death 0.4, 95% CI 0.24-0.65)
  + pathologic complete response associated with improvements in survival regardless of intrinsic subtype
  + PubMed24618153Annals of oncology : official journal of the European Society for Medical Oncology20140601Ann Oncol25611281128 Reference - [24618153Ann Oncol 2014 Jun;25(6):1128](http://pubmed.ncbi.nlm.nih.gov/24618153?dopt=Abstract)
* **higher serum 25-hydroxyvitamin D levels associated with reduced mortality in patients with breast cancer**

Systematic Review[24582912Eur J Cancer 2014 May;50(8):1510](http://pubmed.ncbi.nlm.nih.gov/24582912?dopt=Abstract)

studySummary

* + based on systematic review of observational studies Systematic Review
  + systematic review of 9 prospective cohort studies evaluating association between serum 25-hydroxyvitamin D levels and survival in 6,743 patients with colorectal or breast cancer
  + 5 studies evaluated patients with breast cancer
    - mean age was 50-56 years
    - follow-up ranged from 4.7 to 24 years
  + comparing highest (weighted mean 88 nmol/L) to lowest (weighted mean 41 nmol/L) category of serum 25-hydroxyvitamin D levels, highest category of serum 25-hydroxyvitamin D levels associated with
    - decreased overall mortality (hazard ratio [HR] 0.62, 95% CI 0.49-0.78) in analysis of 5 studies with 4,413 patients
    - decreased breast cancer-related mortality (HR 0.57, 95% CI 0.38-0.84) in analysis of 3 studies with 2,636 patients
  + PubMed24582912European journal of cancer20140501Eur J Cancer50815101510 Reference - [24582912Eur J Cancer 2014 May;50(8):1510](http://pubmed.ncbi.nlm.nih.gov/24582912?dopt=Abstract)

Recurrence Risk

Tumor Size and Lymph Node Status

* **higher number of positive lymph nodes and lower number of uninvolved lymph nodes associated with high rates of 10-year locoregional recurrence after mastectomy**

Cohort Study[22776708Ann Oncol 2012 Nov;23(11):2852](http://pubmed.ncbi.nlm.nih.gov/22776708?dopt=Abstract)

studySummary

* + based on retrospective cohort study Cohort Study
  + 8,109 patients from 13 International Breast Cancer Study Group randomized trials who had total mastectomy plus chemotherapy and/or endocrine therapy but not radiation therapy were evaluated for local, axillary, and supraclavicular cancer recurrences and associated risk factors
  + median follow-up 15.2 years
  + 10-year cumulative incidence of chest wall recurrence was highest in patients
    - with ≥ 4 positive lymph nodes (16.5%)
    - with 0-7 uninvolved lymph nodes (15.1%)
    - aged < 40 years (16.1%)
  + 10-year incidence of supraclavicular recurrence was highest in patients with ≥ 4 positive lymph nodes (10.2%)
  + 10-year incidence of axillary recurrence was below 10% for all risk factors examined
  + PubMed22776708Annals of oncology : official journal of the European Society for Medical Oncology20121101Ann Oncol231128522852 Reference - [22776708Ann Oncol 2012 Nov;23(11):2852](http://pubmed.ncbi.nlm.nih.gov/22776708?dopt=Abstract)
* **tumor size > 2 cm may have decreased disease-free survival and time to recurrence in women with node-negative breast cancer**

Cohort Study[mdc7738620pJ Clin Oncol 1995 May;13(5):1144](http://pubmed.ncbi.nlm.nih.gov/7738620?dopt=Abstract)

studySummary

* + based on retrospective cohort study Cohort Study
  + 826 women with node-negative breast cancer treated with mastectomy and axillary dissection from 1927 to 1984 and followed for mean 13.5 years
  + comparing tumors < 2 cm vs. tumors > 2 cm
    - 20-year disease-free survival 79% vs. 64% (p < 0.001)
    - median time to recurrence 48 months vs. 37 months (p = 0.01)
  + PubMed7738620Journal of clinical oncology : official journal of the American Society of Clinical Oncology19950501J Clin Oncol13511441144 Reference - [mdc7738620pJ Clin Oncol 1995 May;13(5):1144](http://pubmed.ncbi.nlm.nih.gov/7738620?dopt=Abstract) , commentary can be found in [mdc8558214pJ Clin Oncol 1996 Jan;14(1):321](http://pubmed.ncbi.nlm.nih.gov/8558214?dopt=Abstract)
* **larger tumor size correlated with lower breast cancer-specific survival, except in women with basal-like breast cancer (BLBC)**

Cohort Study[mnh18600446pcxh43707079pmdc18600446pBreast Cancer Res Treat 2009 Sep;117(1):199](http://pubmed.ncbi.nlm.nih.gov/18600446?dopt=Abstract)

studySummary

* + based on retrospective analysis of data available in Nottingham Breast Cancer Series Cohort Study
  + 1,520 women with breast cancer (196 of whom had basal-like breast cancer) were evaluated for tumor size, nodal status, and survival and followed for median 136 months
  + increasing tumor size associated with worsening breast cancer-specific survival in non-BLBC cases (p < 0.001) but not in BLBC cases (not significant)
  + PubMed18600446Breast cancer research and treatment20090901Breast Cancer Res Treat1171199199 Reference - [mnh18600446pcxh43707079pmdc18600446pBreast Cancer Res Treat 2009 Sep;117(1):199](http://pubmed.ncbi.nlm.nih.gov/18600446?dopt=Abstract)
* **≥ 4 positive lymph nodes and primary tumor > 2 cm may be associated with decreased 20-year disease-free survival**

Cohort Study[mdc8955655pJ Clin Oncol 1996 Dec;14(12):3105](http://pubmed.ncbi.nlm.nih.gov/8955655?dopt=Abstract)

studySummary

* + based on retrospective cohort study Cohort Study
  + 501 women diagnosed with node-positive breast cancer from 1927 to 1987 were treated with radical, extended radical, or modified radical mastectomy and followed for mean 10 years
  + comparing tumors < 2 cm vs. tumors > 2 cm, 20-year disease-free survival 73% vs. 47% (p < 0.001)
  + comparing 1-3 positive lymph nodes vs. ≥ 4 positive lymph nodes, 20-year disease-free survival 63% vs. 36% (p < 0.001)
  + comparing tumors < 1.1 cm vs. 1.1-2 cm vs. > 2 cm in patients with
    - 0 positive nodes, 20-year disease-free survival 79% vs. 79% vs. 64% (p < 0.001)
    - 1 positive node, 20-year disease-free survival 95% vs. 78% vs. 59% (p = 0.003)
    - 2-3 positive nodes, 20-year disease-free survival 73% vs. 73% vs. 53% (p = 0.01)
  + PubMed8955655Journal of clinical oncology : official journal of the American Society of Clinical Oncology19961201J Clin Oncol141231053105 Reference - [mdc8955655pJ Clin Oncol 1996 Dec;14(12):3105](http://pubmed.ncbi.nlm.nih.gov/8955655?dopt=Abstract)
* **metastatic lymph node ratio (MLNR) associated with breast cancer recurrence**

Cohort Study[mnh19488815pcxh43265289pmdc19488815pWorld J Surg 2009 Aug;33(8):1659](http://pubmed.ncbi.nlm.nih.gov/19488815?dopt=Abstract)

studySummary

* + based on retrospective cohort study Cohort Study
  + 441 women (median age 59 years) with T1-2, N1-3 breast cancer included in Castellon (Spain) Cancer Registry
  + recurrence occurred in 26%
  + MLNR is number of metastatic lymph nodes over total number of resected lymph nodes
  + MLNR associated with increased risk of recurrence (hazard ratio 5.2, 95% CI 1.5-17.8), although not after 60 months of follow-up (hazard ratio 1.38, 95% CI 0.02-85.9)
  + comparing MLNR < 20% vs. 20%-60% vs. > 60%, disease-free survival (extrapolated from graph) in 20% vs. 25% vs. 50% (no p value reported)
  + PubMed19488815World journal of surgery20090801World J Surg33816591659 Reference - [mnh19488815pcxh43265289pmdc19488815pWorld J Surg 2009 Aug;33(8):1659](http://pubmed.ncbi.nlm.nih.gov/19488815?dopt=Abstract)
* **primary breast cancer with ≥ 10 involved lymph nodes associated with increased risk of metachronous contralateral breast cancer**

Cohort Study[cxh82203233pmdc22927521pJ Clin Oncol 2012 Oct 1;30(28):3478](http://pubmed.ncbi.nlm.nih.gov/22927521?dopt=Abstract)

studySummary

* + based on prospective cohort study Cohort Study
  + from a cohort of 42,670 women with breast cancer in Sweden from 1992 to 2008, 35,897 women with data available for initial tumor size and nodal status were assessed for risk factors for metachronous contralateral breast cancer
  + 2.5% developed metachronous contralateral breast cancer in median follow-up 9.9 years
  + increased risk of contralateral breast cancer associated with
    - primary breast cancer with ≥ 10 involved lymph nodes compared to node-negative breast cancer (adjusted hazard ratio 1.8, 95% CI 1.2-2.7)
    - tumor of any size with extension to chest wall and/or skin compared to tumor < 2 cm (adjusted hazard ratio 2.2, 95% CI 1.3-3.6)
  + PubMed22927521Journal of clinical oncology : official journal of the American Society of Clinical Oncology20121001J Clin Oncol302834783478 Reference - [cxh82203233pmdc22927521pJ Clin Oncol 2012 Oct 1;30(28):3478](http://pubmed.ncbi.nlm.nih.gov/22927521?dopt=Abstract)
* **larger tumor size and positive nodal status associated with increased risk of locoregional recurrence after neoadjuvant chemotherapy**

Cohort Study[cxh83235280pmdc23032615pJ Clin Oncol 2012 Nov 10;30(32):3960](http://pubmed.ncbi.nlm.nih.gov/23032615?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3488269/)

studySummary

* + based on prospective cohort study Cohort Study
  + 3,088 women with breast cancer from 2 neoadjuvant trials (doxorubicin/cyclophosphamide alone or doxorubicin/cyclophosphamide followed by neoadjuvant/adjuvant docetaxel) were followed for 10 years
  + 10-year incidence of locoregional recurrence was 11.1% overall
  + factors associated with increased risk of locoregional recurrence in overall analysis were
    - tumor size > 5 cm vs. ≤ 5 cm (hazard ratio [HR] 1.51, 95% CI 1.19-1.91)
    - positive vs. negative clinical nodal status (HR 1.61, 95% CI 1.28-2.02)
    - absence of vs. presence of pathologic complete response in patients with negative pathologic nodal status (HR 1.55, 95% CI 1.01-2.39)
    - positive vs. negative pathologic nodal status in patients with pathologic complete response (HR 2.71, 95% CI 1.79-4.09)
  + PubMed23032615Journal of clinical oncology : official journal of the American Society of Clinical Oncology20121110J Clin Oncol303239603960 Reference - [cxh83235280pmdc23032615pJ Clin Oncol 2012 Nov 10;30(32):3960](http://pubmed.ncbi.nlm.nih.gov/23032615?dopt=Abstract) [full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3488269/), editorials can be found at [cxh83235272pmdc23032624pJ Clin Oncol 2012 Nov 10;30(32):3913](http://pubmed.ncbi.nlm.nih.gov/23032624?dopt=Abstract)

Risk for Axillary Recurrence

* **5-year incidence of isolated axillary recurrence 1%**

Cohort Study[mdc16983030pArch Surg 2006 Sep;141(9):867](http://pubmed.ncbi.nlm.nih.gov/16983030?dopt=Abstract)

studySummary

* + based on 19,789 women with stage 0- III breast cancer from 1989 to 2003 Cohort Study
  + 220 had isolated axillary recurrence, with median survival 4.9 years after recurrence (range 2 months to 15 years)
  + PubMed16983030Archives of surgery (Chicago, Ill. : 1920)20060901Arch Surg1419867867 Reference - [mdc16983030pArch Surg 2006 Sep;141(9):867](http://pubmed.ncbi.nlm.nih.gov/16983030?dopt=Abstract)
* **isolated axillary node recurrence after negative sentinel lymph node biopsy (SLNB) is rare (< 1%)**

Systematic Review[21254004Br J Surg 2011 Mar;98(3):326](http://pubmed.ncbi.nlm.nih.gov/21254004?dopt=Abstract)

studySummary

* + based on systematic review of cohort studies Systematic Review
  + systematic review of 45 cohort studies evaluating reporting isolated axillary recurrence after negative SLNB in 23,357 patients with breast cancer followed for median 39 months
  + 127 patients (0.5%) had isolated axillary recurrence
  + PubMed21254004The British journal of surgery20110301Br J Surg983326326 Reference - [21254004Br J Surg 2011 Mar;98(3):326](http://pubmed.ncbi.nlm.nih.gov/21254004?dopt=Abstract)

Risk for Late Recurrence

* **risk for late recurrence (after being disease-free for ≥ 5 years) is 7%-13%**

Cohort Study[18695137J Natl Cancer Inst 2008 Aug 20;100(16):1179](http://pubmed.ncbi.nlm.nih.gov/18695137?dopt=Abstract)[Full Text](http://jnci.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=18695137)

studySummary

* + based on retrospective cohort study Cohort Study
  + 2,838 patients with stage I-III breast cancer who were disease-free for ≥ 5 years after adjuvant or neoadjuvant systemic therapy evaluated
  + among 216 patients (8%) with late recurrence, 5-year residual risk for recurrence was
    - 7% for stage I (95% CI 3%-15%)
    - 11% for stage II (95% CI 9%-13%)
    - 13% for stage III (95% CI 10%-17%)
  + late recurrence was associated with stage, grade, hormone receptor status, and endocrine therapy
  + PubMed18695137Journal of the National Cancer Institute20080820J Natl Cancer Inst1001611791179 Reference - [18695137J Natl Cancer Inst 2008 Aug 20;100(16):1179](http://pubmed.ncbi.nlm.nih.gov/18695137?dopt=Abstract)[full-text](http://jnci.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=18695137)

Other Risk Factors for Recurrence

* unique\_1933453421\_\_LI\_UY3\_JRP\_2ZBEU10212310/21/2023 08:55:15 PMevidenceUpdatestandardOncologic\_DiseaseAsian race and Black race each associated with increased risk of locoregional recurrence compared to White race among adults ≤ 75 years old with hormone receptor-positive, ERBB2-negative node-negative breast cancer (JAMA Surg 2023 Jun 1)

**Asian race and Black race each associated with increased risk of locoregional recurrence compared to White race among adults ≤ 75 years old with hormone receptor-positive, *ERBB2*-negative node-negative breast cancer**

Cohort Study[37043210JAMA Surg 2023 Jun 1;158(6):583](http://pubmed.ncbi.nlm.nih.gov/37043210?dopt=Abstract)

studySummary

* + Cohort Studybased on cohort analysis of randomized trial
  + 9,369 adults ≤ 75 years old with hormone receptor-positive, *ERBB2*-negative (formerly *HER2* negative), node-negative breast cancer in [TAILORx trial](https://dpa-pde-oxford.shinyapps.io/management/chemotherapy-for-early-and-locally-advanced-breast-cancer#TOPIC_F1X_FJL_GVB__ANC_267165506) who were randomized to endocrine therapy alone vs. chemotherapy plus endocrine therapy based on recurrence scores and had data available on race and ethnicity were assessed for locoregional recurrence
    - 4.6% were Asian, 7.2% Black, 9.4% Hispanic, and 78.8% White
    - median duration of endocrine therapy ranged from 61.1 months to 65.9 months across racial and ethnic groups
  + at baseline
    - Asian, Black, and Hispanic patients were younger than White patients (median age 52-54 years vs. 56 years)
    - Asian patients had higher proportion of patients with recurrence score < 11 points compared to White patients (20.8% vs. 16.6%)
    - Hispanic and Black patients had higher proportion of patients with recurrence score > 25 points compared to White patients (16.7%-17.3% vs. 13.9%)
  + locoregional recurrence was defined as recurrence in ipsilateral breast, skin, chest wall, or regional node without concurrent distant recurrence
  + median follow-up was 94.8 months
  + estimated 8-year locoregional recurrence rates (p < 0.001 overall)
    - 3.6% in Asian patients
    - 3.9% in Black patients
    - 3.1% in Hispanic patients
    - 1.8% in White patients
  + compared to White race, increased risk of locoregional recurrence associated with
    - Asian race (adjusted hazard ratio [HR] 1.91, 95% CI 1.12-3.29)
    - Black race (adjusted HR 1.78, 95% CI 1.15-2.77)
  + Hispanic ethnicity associated with nonsignificant increase in risk of locoregional recurrence compared to White race (adjusted HR 1.51, 95% CI 0.95-2.4)
  + locoregional recurrence associated with increased breast cancer mortality (adjusted HR 5.71, 95% CI 3.5-9.31)
  + Reference - [37043210JAMA Surg 2023 Jun 1;158(6):583](http://pubmed.ncbi.nlm.nih.gov/37043210?dopt=Abstract), editorial can be found in [37043213JAMA Surg 2023 Jun 1;158(6):592](http://pubmed.ncbi.nlm.nih.gov/37043213?dopt=Abstract)
* **women < 35 years old with operable breast cancer have higher recurrence rate than older women**

Cohort Study[mnh15546499paph29336656pa9h29336656pafh29336656pcxh29336656pmdc15546499pBMC Cancer 2004 Nov 17;4:82](http://pubmed.ncbi.nlm.nih.gov/15546499?dopt=Abstract)[Full Text](http://www.biomedcentral.com/1471-2407/4/82)

studySummary

* + based on retrospective cohort study Cohort Study
  + 2,040 women who had surgery for primary invasive breast cancer from 1990 to 1999 followed for median 74 months
  + 12.5% were < 35 years old
  + compared to age > 35 years, age < 35 years associated with increased risk of recurrence (adjusted hazard ratio 1.7, 95% CI 1.1-2.6)
  + comparing age < 35 years vs. > 35 years, 5-year recurrence rate 30.4% vs. 18.7% (p < 0.001)
  + PubMed15546499BMC cancer20041117BMC Cancer48282 Reference - [mnh15546499paph29336656pa9h29336656pafh29336656pcxh29336656pmdc15546499pBMC Cancer 2004 Nov 17;4:82](http://pubmed.ncbi.nlm.nih.gov/15546499?dopt=Abstract) [full-text](http://www.biomedcentral.com/1471-2407/4/82)
* women < 35 years old may have increased risk for occurrence of metachronous contralateral breast cancer
  + 45,229 women with operable stage I-IIIA breast cancer evaluated
  + median follow-up 5.8 years
  + 1,477 developed new cancer in contralateral breast (metachronous contralateral breast cancer)
  + standardized incidence ratios for metachronous contralateral breast cancers
    - 11.4 for women < 35 years old (95% CI 8.6-14.8)
    - 4.9 for women aged 35-39 years (95% CI 3.9-6.1)
    - 2.4 for women aged 40-49 years (95% CI 2.1-2.7)
    - 1.8 for women aged 50-59 years (95% CI 1.5-2)
    - 1.5 for women aged 60-69 years (95% CI 1.3-1.8)
    - 1.7 for women aged 70-79 years (95% CI 1.5-2)
    - 1.2 for women ≥ 80 years old (95% CI 0.9-1.6)
  + Reference - [mnh17687645pcxh33052959pmdc17687645pBreast Cancer Res Treat 2008 Jul;110(1):189](http://pubmed.ncbi.nlm.nih.gov/17687645?dopt=Abstract) [full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/17687645/)
* **anemia developing during chemotherapy may be associated with risk for local recurrence in premenopausal women with primary breast cancer**

Cohort Study[18381948Clin Cancer Res 2008 Apr 1;14(7):2082](http://pubmed.ncbi.nlm.nih.gov/18381948?dopt=Abstract)[Full Text](http://clincancerres.aacrjournals.org/content/14/7/2082.long)

studySummary

* + based on retrospective cohort study Cohort Study
  + 424 premenopausal women with early-stage primary breast cancer and hormone receptor-expressing tumors had adjuvant cyclophosphamide/methotrexate/5-fluorouracil (CMF) and were followed for median 5 years
  + patients with < 3 cycles of CMF or without serum hemoglobin levels at between cycles 3 and 6 of CMF were excluded
  + 18.2% developed anemia (hemoglobin < 12 g/dL [120 g/L]) while on CMF therapy
  + local relapse occurred in 19.6% anemic vs. 8.9% nonanemic patients (p = 0.0006)
  + PubMed18381948Clinical cancer research : an official journal of the American Association for Cancer Research20080401Clin Cancer Res14720822082 Reference - [18381948Clin Cancer Res 2008 Apr 1;14(7):2082](http://pubmed.ncbi.nlm.nih.gov/18381948?dopt=Abstract)[full-text](http://clincancerres.aacrjournals.org/content/14/7/2082.long)
  + Whether patients with and without anemia had similar chemotherapy durations was not reported. Anemia as a prognostic factor could be confounded by interruptions or earlier termination of chemotherapy.
* **beta-blockers may be associated with increased risk of breast cancer recurrence**

Cohort Study[cxh88102092pmdc23650417pJ Clin Oncol 2013 Jun 20;31(18):2265](http://pubmed.ncbi.nlm.nih.gov/23650417?dopt=Abstract)

studySummary

* + based on cohort study Cohort Study
  + 18,733 women with nonmetastatic breast cancer were analyzed
  + median follow-up 6.8 years, 19.5% were ever users of any beta-blocker
  + compared with never use, 10-year risk of breast cancer recurrence
    - increased with any beta-blocker in adjusted analysis (adjusted hazard ratio [HR] 1.3, 95% CI 1.1-1.5), but not increased in unadjusted analysis
    - not significantly increased with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers
  + PubMed23650417Journal of clinical oncology : official journal of the American Society of Clinical Oncology20130620J Clin Oncol311822652265 Reference - [cxh88102092pmdc23650417pJ Clin Oncol 2013 Jun 20;31(18):2265](http://pubmed.ncbi.nlm.nih.gov/23650417?dopt=Abstract)
* **higher serum estrogen levels may be associated with increased risk for recurrence or new primary breast cancer**

Case-Control Study[18323413Cancer Epidemiol Biomarkers Prev 2008 Mar;17(3):614](http://pubmed.ncbi.nlm.nih.gov/18323413?dopt=Abstract)[Full Text](http://cebp.aacrjournals.org/content/17/3/614.long)

studySummary

* + based on nested case-control study Case-Control Study
  + Women's Healthy Eating and Living Study (WHEL) was randomized diet trial with breast cancer patients followed for mean 7.3 years
  + 153 peri- or postmenopausal women with recurrent or new primary early-stage breast cancer were matched to 153 recurrence-free controls from WHEL
  + risk of recurrence or new cancer increased with increasing baseline concentrations of total estradiol, bioavailable estradiol, and free estradiol
  + PubMed18323413Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology20080301Cancer Epidemiol Biomarkers Prev173614614 Reference - [18323413Cancer Epidemiol Biomarkers Prev 2008 Mar;17(3):614](http://pubmed.ncbi.nlm.nih.gov/18323413?dopt=Abstract)[full-text](http://cebp.aacrjournals.org/content/17/3/614.long)
* **stressful life experiences do not increase recurrence risk**

Cohort Study[12065263BMJ 2002 Jun 15;324(7351):1420](http://pubmed.ncbi.nlm.nih.gov/12065263?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC115851/)

studySummary

* + based on prospective cohort study Cohort Study
  + 170 women < 60 years old and newly diagnosed with operable breast cancer from 1991 to 1994 were interviewed about stressful life experiences and depression every 18 months, beginning 1 year before diagnosis and continuing up to 5 years after diagnosis or to recurrence
  + 76% overall 5-year relapse-free survival
  + recurrence confirmed in 31.6%
  + compared to 0 severely stressful life experiences before or after diagnosis, ≥ 1 severely stressful life experiences after diagnosis associated with decreased risk of recurrence (hazard ratio 0.52, 95% CI 0.29-0.95), but no association before diagnosis
  + PubMed12065263BMJ (Clinical research ed.)20020615BMJ324735114201420 Reference - [12065263BMJ 2002 Jun 15;324(7351):1420](http://pubmed.ncbi.nlm.nih.gov/12065263?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC115851/), commentary can be found in [12218002BMJ 2002 Sep 7;325(7363):548](http://pubmed.ncbi.nlm.nih.gov/12218002?dopt=Abstract)

BRCA Mutations

* ***BRCA1* and *BRCA2* (breast cancer susceptibility genes) mutation carriers have similar prognosis (survival and distant recurrences) as patients with sporadic breast cancer**

Cohort Study[J Clin Oncol 2012 Jan 1;30(1):19](http://pubmed.ncbi.nlm.nih.gov/22147742-breast-cancer-prognosis-in-brca1-and-brca2-mutation-carriers-an-international-prospective-breast-cancer-family-registry-population-based-cohort-study/?dopt=Abstract)

studySummary

* + Cohort Study based on cohort study
  + prospective cohort study of 3,220 women (mean age 45.3 years) with incident breast cancer in Canada, United States, and Australia from 1995 to 2000
    - mean follow-up 7.9 years
    - 93 women had BRCA1 mutations, 71 had BRCA2 mutations, 1 had both mutations
    - 1,550 had sporadic breast cancer
    - 1,505 had familial breast cancer (without known BRCA1 or BRCA2 mutations)
    - no significant differences in mortality or distant recurrence in multivariate analyses comparing carriers of BRCA1 or BRCA2 mutations and patients with sporadic breast cancer
    - BRCA2 carriers had higher mortality and risk for distant recurrence in univariate analysis but no significant difference after adjusting for age, tumor stage and grade, nodal status, hormonal receptors, and year of diagnosis
    - Reference - [cxh70106115pmdc22147742pJ Clin Oncol 2012 Jan 1;30(1):19](http://pubmed.ncbi.nlm.nih.gov/22147742?dopt=Abstract) , editorial can be found in [cxh70106110pmdc22147741pJ Clin Oncol 2012 Jan 1;30(1):2](http://pubmed.ncbi.nlm.nih.gov/22147741?dopt=Abstract)
  + PubMed22147742Journal of clinical oncology : official journal of the American Society of Clinical OncologyJ Clin Oncol2012010130119-2619Reference - [J Clin Oncol 2012 Jan 1;30(1):19](http://pubmed.ncbi.nlm.nih.gov/22147742-breast-cancer-prognosis-in-brca1-and-brca2-mutation-carriers-an-international-prospective-breast-cancer-family-registry-population-based-cohort-study/?dopt=Abstract), editorial can be found in
  + breast cancer-specific mortality not significantly different in carriers of BRCA1 and BRCA2 mutations in medical record review of 1,545 women with breast cancer ([17625123N Engl J Med 2007 Jul 12;357(2):115](http://pubmed.ncbi.nlm.nih.gov/17625123?dopt=Abstract)[full-text](http://www.nejm.org/doi/full/10.1056/NEJMoa070608#t=article)), editorial can be found in [17625130N Engl J Med 2007 Jul 12;357(2):175](http://pubmed.ncbi.nlm.nih.gov/17625130?dopt=Abstract), commentary can be found in [17928608N Engl J Med 2007 Oct 11;357(15):1555](http://pubmed.ncbi.nlm.nih.gov/17928608?dopt=Abstract)
* ***BRCA* mutation carriers have similar rates of recurrence after breast-conserving surgery and radiation therapy compared to nonmutation carriers**

Cohort Study[16140006Eur J Cancer 2005 Oct;41(15):2304](http://pubmed.ncbi.nlm.nih.gov/16140006?dopt=Abstract)

studySummary

* + based on retrospective cohort study Cohort Study
  + 131 patients (median age 43 years) with family history of breast and/or ovarian cancer treated with breast-conserving surgery and radiation therapy screened for BRCA1 and BRCA2 gene mutations and 261 women with breast cancer and without family history of breast cancer were evaluated
  + median follow-up 8.75 years
  + BRCA1/2 mutations found in 20.6% with family history
  + decreasing age associated with breast cancer recurrence (p < 0.05)
  + no significant differences in breast cancer recurrence as first event

| Comparing Recurrence by Tumor Type | | | |
| --- | --- | --- | --- |
|  | **Women With BRCA Mutations** | **Women With Family History but no Mutations** | **Women Without Family History** |
| Median time to breast cancer recurrence | 80 months | 39 months | 46 months |
| Breast cancer recurrence | 24% | 22% | 19% |
| Contralateral breast cancer | 37% | 18.3%\* | 7.3%\* |
| Abbreviation: BRCA, breast cancer susceptibility gene.  \* p < 0.001 vs. BRCA mutations. | | | |

* + PubMed16140006European journal of cancer20051001Eur J Cancer411523042304 Reference - [16140006Eur J Cancer 2005 Oct;41(15):2304](http://pubmed.ncbi.nlm.nih.gov/16140006?dopt=Abstract)

Pregnancy-Associated Breast Cancer

* there is mixed evidence regarding outcomes in women with pregnancy-associated breast cancer, which may be attributed to
  + the years in which the study was conducted (in older studies there may have been further delays in treatment or substandard treatment offered)
  + timing of diagnosis (during pregnancy vs. postpartum vs. lactation)
  + PubMed28232597The oncologistOncologist20170301223324-334324Reference - [Oncologist 2017 Mar;22(3):324](http://pubmed.ncbi.nlm.nih.gov/28232597)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5344634/)
* **female persons with pregnancy-associated breast cancer have similar number of hospitalizations and similar length of stay as women with history of breast cancer**

Cohort Study[Gynecol Obstet Invest 2019;84(1):79](http://pubmed.ncbi.nlm.nih.gov/30219806)[Full Text](https://www.karger.com/Article/FullText/493128)

studySummary

* + Cohort Study based on retrospective cohort study
  + 69 pregnant women with either current (pregnancy-associated) breast cancer or history of breast cancer between 2004 and 2015 were included
  + 22 (32%, mean age 35 years) had pregnancy-associated breast cancer and 47 women (68%, mean age 37 years) had history of breast cancer
  + 13 women (59%) with pregnancy-associated breast cancer received antepartum chemotherapy
  + comparing women with pregnancy-associated breast cancer vs. those with history of breast cancer
    - labor induction in 50% vs. 32.6% (p = 0.045)
    - preterm birth in 63.6% vs. 8.7% (p < 0.0001)
  + no significant difference in number of antepartum or postpartum hospitalizations or length of hospital stay
  + PubMed30219806Gynecologic and obstetric investigationGynecol Obstet Invest2019010184179-8579Reference - [Gynecol Obstet Invest 2019;84(1):79](http://pubmed.ncbi.nlm.nih.gov/30219806)[full-text](https://www.karger.com/Article/FullText/493128)
* **female persons with pregnancy-associated breast cancer who electively terminate their pregnancy do not appear to have increased survival compared to those who continue pregnancy through to a live birth (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cohort Study[Cancer J 2010 Jan;16(1):76](http://pubmed.ncbi.nlm.nih.gov/20164696)

studySummary

* + Cohort Study based on cohort study
  + 130 women (mean age at diagnosis 34 years) with pregnancy-associated breast cancer from the international Cancer and Pregnancy Registry were included
    - included women diagnosed with breast cancer while pregnant or up to 6 weeks postpartum
    - 99 women (76%) were prospectively enrolled and 31 women (24%) were retrospectively enrolled
  + 120 women (92%) were diagnosed with a primary breast tumor, 8 (6%) with recurrence of breast cancer, and 2 (1.5%) with a new primary cancer
  + 10 women (8%) electively terminated their pregnancy and 6 (5%) had spontaneous abortions prior to 13 weeks gestational age
  + 113 women (87%) were followed for mean 3.14 years
    - 30 women (26.5%) had recurrence occurring at a mean 16 months after delivery; 20 (67% of those with recurrence) had stage IV disease at time of recurrence
    - 1 woman (0.9%) had a new primary
    - overall survival for 103 women with a primary breast tumor who continued pregnancy to birth was
      * 100% in women with stage I disease
      * 86% in women with stage II disease
      * 86% in women with stage III disease
      * 0% in women with stage IV disease
    - comparing women who electively terminated the pregnancy vs. those who continued pregnancy through to a live birth, survival was 83% vs. 85% (not significant)
  + PubMed20164696Cancer journal (Sudbury, Mass.)Cancer J2010010116176-8276Reference - [Cancer J 2010 Jan;16(1):76](http://pubmed.ncbi.nlm.nih.gov/20164696)
* **pregnancy-associated breast cancer (PABC) may be associated with poorer survival**

Case-Control Study[18591310Obstet Gynecol 2008 Jul;112(1):71](http://pubmed.ncbi.nlm.nih.gov/18591310?dopt=Abstract)

studySummary

* + based on case-control study Case-Control Study
  + 797 female persons with PABC compared to 4,177 age-matched controls with breast cancer
  + PABC defined as occurring within 9 months before to 1 year after delivery
  + comparing PABC cases vs. controls
    - mortality 39.2% vs. 33.4% (p = 0.002)
    - pregnancy-associated cases presented with more advanced disease, larger tumors, and increased percentage of hormone receptor-negative tumors
  + other factors associated with significantly increased mortality included advanced stage, race (African American patients > non-Hispanic White patients), hormone receptor negative tumors, and pregnancy
  + PubMed18591310Obstetrics and gynecology20080701Obstet Gynecol11217171 Reference - [18591310Obstet Gynecol 2008 Jul;112(1):71](http://pubmed.ncbi.nlm.nih.gov/18591310?dopt=Abstract)
* **female persons < 35 years old with PABC may have similar rates of survival, recurrence, and distant metastases compared to other young female persons with breast cancer**

Cohort Study[19204903Cancer 2009 Mar 15;115(6):1174](http://pubmed.ncbi.nlm.nih.gov/19204903?dopt=Abstract)[Full Text](http://onlinelibrary.wiley.com/doi/10.1002/cncr.24165/full)

studySummary

* + based on retrospective cohort study Cohort Study
  + 652 female persons ≤ 35 years old with breast cancer evaluated
  + 104 breast cancers were pregnancy-associated
  + median follow-up for living patients 114 months
  + comparing patients with PABC vs. non-PABC
    - overall survival 64.6% vs. 64.8% (not significant)
    - 10-year locoregional recurrence rate 23.4% vs. 19.2% (not significant)
    - distant metastases in 45.1% vs. 38.9% (not significant)
  + PABC had significantly more advanced T classification, N classification, and stage group (p < 0.04)
  + PubMed19204903Cancer20090315Cancer115611741174 Reference - [19204903Cancer 2009 Mar 15;115(6):1174](http://pubmed.ncbi.nlm.nih.gov/19204903?dopt=Abstract)[full-text](http://onlinelibrary.wiley.com/doi/10.1002/cncr.24165/full)
* **diagnosis during lactation associated with increased risk of cause-specific death**

Cohort Study[mdc19029418pJ Clin Oncol 2009 Jan 1;27(1):45](http://pubmed.ncbi.nlm.nih.gov/19029418?dopt=Abstract)

studySummary

* + based on cohort study Cohort Study
  + 42,511 female persons aged 16-49 years, diagnosed with cancer from 1967 to 2002
  + cohort classified as not pregnant, pregnant, or lactating at time of cancer diagnosis
  + increased risk of cause-specific death if lactating at time of diagnosis of ovarian cancer (hazard ratio 1.95, p < 0.05)
  + PubMed19029418Journal of clinical oncology : official journal of the American Society of Clinical Oncology20090101J Clin Oncol2714545 Reference - [mdc19029418pJ Clin Oncol 2009 Jan 1;27(1):45](http://pubmed.ncbi.nlm.nih.gov/19029418?dopt=Abstract)
* **recent pregnancy (within 2 years of diagnosis) may be a negative prognostic factor**

Cohort Study[Obstet Gynecol 2008 May;111(5):1167](http://pubmed.ncbi.nlm.nih.gov/18448751-relationship-of-time-since-childbirth-and-other-pregnancy-factors-to-premenopausal-breast-cancer-prognosis/?dopt=Abstract)Cohort Study[BMJ 1997 Oct 4;315(7112):851](http://pubmed.ncbi.nlm.nih.gov/9353505-time-since-childbirth-and-prognosis-in-primary-breast-cancer-population-based-study/?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2127579/)

studySummary

* + Cohort StudyCohort Study based on 2 cohort studies
  + cohort study of female persons in Nova Scotia giving birth from 1980 to 2001
    - among 123,323 female persons giving birth, 716 were diagnosed with invasive breast cancer
    - female persons with < 2 years between childbirth and diagnosis of breast cancer had significantly increased risk for having later-stage disease and poorer survival than women with interval ≥ 5 years
    - PubMed18448751Obstetrics and gynecologyObstet Gynecol2008050111151167-731167Reference - [Obstet Gynecol 2008 May;111(5):1167](http://pubmed.ncbi.nlm.nih.gov/18448751-relationship-of-time-since-childbirth-and-other-pregnancy-factors-to-premenopausal-breast-cancer-prognosis/?dopt=Abstract)
  + retrospective study of 5,652 women < 46 years old at time of diagnosis of primary breast cancer
    - female persons diagnosed within 2 years after last childbirth had 58.7% five-year survival and 46.1% ten-year survival
    - female persons whose last childbirth was > 2 years before diagnosis had 78.4% five-year survival and 66% ten-year survival
    - PubMed9353505BMJ (Clinical research ed.)BMJ199710043157112851-5851Reference - [BMJ 1997 Oct 4;315(7112):851](http://pubmed.ncbi.nlm.nih.gov/9353505-time-since-childbirth-and-prognosis-in-primary-breast-cancer-population-based-study/?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2127579/)

Pregnancy After Breast Cancer

* unique\_1274822958\_\_LI\_MV1\_FK5\_5ZBEU12182312/18/2023 04:28:22 PMevidenceUpdatestandardFamily\_Medicine Internal\_Medicine Obstetric\_and\_Gynecologic\_Conditions Oncologic\_Disease Primary\_Carepregnancy after breast cancer does not appear to increase overall or disease-specific mortality in persons with pathogenic BRCA1 or BRCA2 variant (JAMA 2023 Dec 7 early online)

**pregnancy after breast cancer does not appear to increase overall or disease-specific mortality in persons with pathogenic *BRCA1* or *BRCA2* variant**

Cohort Study[38059899JAMA 2023 Dec 7 early online](http://pubmed.ncbi.nlm.nih.gov/38059899?dopt=Abstract)

studySummary

* + Cohort Study based on retrospective cohort study
  + 4,732 female persons with pathogenic *BRCA1* or *BRCA2* variant diagnosed with invasive breast cancer at age ≤ 40 years (median age at diagnosis 35 years) were followed for median 7.8 years
  + exclusion criteria included history of other cancer, de novo stage IV breast cancer, and lack of data for post-treatment pregnancy
  + during follow-up, 659 patients (median age at contraception 34 years) had ≥ 1 pregnancy after breast cancer
    - cumulative incidence of pregnancy at 10 years 22%
    - median time from breast cancer diagnosis to conception 3.5 years
    - 6.9% had induced abortion and 9.7% had miscarriage
  + among 517 patients with completed pregnancy
    - 91% delivered at ≥ 37 weeks gestation
    - 10.4% had twins
    - pregnancy complication in 6.4%
    - delivery complication in 5.2%
    - breastfeeding in 33% of 403 patients with data
    - congenital anomaly in 0.9% of 470 infants with data
  + pregnancy associated with reduced
    - overall mortality (adjusted hazard ratio [HR] for death 0.58, 95% CI 0.4-0.85)
    - breast cancer-specific mortality (adjusted HR for death 0.6, 95% CI 0.4-0.88)
  + no significant difference in disease-free survival comparing patients who had pregnancy to patients with no pregnancy (adjusted HR 0.99, 95% CI 0.81-1.2)
  + Reference - [38059899JAMA 2023 Dec 7 early online](http://pubmed.ncbi.nlm.nih.gov/38059899?dopt=Abstract)
* **pregnancy after breast cancer does not appear to increase mortality**

Systematic Review[20943370Eur J Cancer 2011 Jan;47(1):74](http://pubmed.ncbi.nlm.nih.gov/20943370?dopt=Abstract)

studySummary

* + based on systematic review Systematic Review
  + systematic review of 7 case-control studies and 7 cohort studies evaluating effect of pregnancy on overall survival of women with history of breast cancer
  + meta-analysis included 1,244 women who got pregnant and 18,145 women with no pregnancy after history of breast cancer
  + pregnancy following breast cancer diagnosis associated with reduced risk of death (relative risk [RR] 0.59, 90% CI 0.5-0.7)
  + no significant association in subgroup analysis in women known to be free of relapse (RR 0.85, 95% CI 0.53-1.35)
  + PubMed20943370European journal of cancer20110101Eur J Cancer4717474 Reference - [20943370Eur J Cancer 2011 Jan;47(1):74](http://pubmed.ncbi.nlm.nih.gov/20943370?dopt=Abstract)

Quality of Life

* **suboptimal health-related quality of life after diagnosis reported in young Black female breast cancer survivors**

Systematic Review[mnh27601138pcxh118527374pmdc27601138pBreast Cancer Res Treat 2016 Nov;160(1):1](http://pubmed.ncbi.nlm.nih.gov/27601138?dopt=Abstract)

studySummary

* + based on systematic review with limited evidence Systematic Review
  + systematic review of 6 cross-sectional studies evaluating health-related quality of life in 3,805 female breast cancer survivors
    - 2 studies included only young women (< 50 years old at diagnosis), 3 studies included only Black women, and 1 study included only young Black women
    - time since breast cancer diagnosis varied across studies (≤ 12 months in 1 study, ≥ 12 months in 2 studies, and no specific timing in 3 studies)
  + meta-analyses not performed due to heterogeneity in health-related quality of life assessment tools among studies
  + after diagnosis, young Black breast cancer survivors reported
    - worse psychological well-being (including fear, anxiety, or depression) compared to older Black survivors or young Black women without breast cancer in 5 studies
    - substantial decline in physical well-being and functioning compared to older Black breast cancer survivors in 2 studies
    - higher levels of financial distress compared to young White breast cancer survivors in 1 study
    - higher levels of emotional support compared to older Black survivors in 1 study
  + PubMed27601138Breast cancer research and treatment20161101Breast Cancer Res Treat160111 Reference - [mnh27601138pcxh118527374pmdc27601138pBreast Cancer Res Treat 2016 Nov;160(1):1](http://pubmed.ncbi.nlm.nih.gov/27601138?dopt=Abstract)

Prevention and Screening

Prevention and Screening

Prevention

Lifestyle changes

Recommendations

* Oncologic\_DiseaseAmerican Cancer Society (ACS) guideline for diet and physical activity for cancer prevention (CA Cancer J Clin 2020 Jul)01/11/2021 11:15:14 AMAmerican Cancer Society (ACS) guideline for diet and physical activity for cancer prevention
  + achieve and maintain healthy body weight throughout life; this includes maintaining body weight within a healthy range and avoiding weight gain as an adult
  + be physically active
    - for adults, this includes meeting weekly goal of 150-300 minutes of moderate-intensity or 75-150 minutes of vigorous-intensity exercise (or equivalent combination); achieving ≥ 300 minutes is ideal
    - for children and adolescents, goal is attaining ≥ 1 hr of moderate- or vigorous-intensity activity each day
    - limit sedentary behaviors, such as sitting, lying down, and watching television or other screens
  + follow healthy eating pattern regardless of age
    - healthy eating pattern includes consumption of
      * nutrient-dense foods, in amounts that help achieve and maintain healthy body weight
      * variety of vegetables, including dark green, red, and orange vegetables, legumes (beans and peas which are rich in fiber), and others
      * fruits, especially whole fruits in a variety of colors
      * whole grains
    - healthy eating pattern does not include red and processed meats, sugar-sweetened beverages, highly processed foods, and refined grains
  + avoid alcohol if possible; if patient chooses to drink alcohol, encourage limiting consumption to ≤ 1 drink/day for women and ≤ 2 drinks/day for men
  + recommendations for public, private, and community organizations include working together to implement policy and environmental changes to
    - support increased access to affordable, nutritious foods
    - provide safe and accessible opportunities for physical activity
    - limit alcohol for all individuals
  + PubMed32515498CA: a cancer journal for cliniciansCA Cancer J Clin20200701704245-271245Reference - [CA Cancer J Clin 2020 Jul;70(4):245](http://pubmed.ncbi.nlm.nih.gov/32515498)[full-text](https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21591)

Physical activity

* **increase in physical activity associated with greater risk reduction for breast cancer**

Systematic Review[27510511BMJ 2016 Aug 9;354:i3857](http://pubmed.ncbi.nlm.nih.gov/27510511?dopt=Abstract)[Full Text](http://www.bmj.com/content/354/bmj.i3857.long)

studySummary

* + based on systematic review of cohort studies Systematic Review
  + systematic review of 174 prospective cohort studies evaluating effect of physical activity on comorbidities in adults
  + 35 studies evaluated effect on breast cancer, with total follow-up > 50 million person-years
  + overall, higher levels of total physical activity (> 3,000 metabolic equivalent [MET] minutes/week) associated with significant decrease in risk of breast cancer
  + greatest risk reduction observed from 600 MET minutes/week (minimum recommended level by World Health Organization) up to 3,000-4,000 MET minutes/week, with minimal risk reduction above that
    - increasing physical activity from 600 to 3,600 MET minutes/week associated with 4% additional reduction in risk of breast cancer
    - further increase in physical activity up to 9,000 MET minutes/week associated with only 2% additional risk reduction
  + PubMed27510511BMJ (Clinical research ed.)20160809BMJ354i3857i3857 Reference - [27510511BMJ 2016 Aug 9;354:i3857](http://pubmed.ncbi.nlm.nih.gov/27510511?dopt=Abstract)[full-text](http://www.bmj.com/content/354/bmj.i3857.long)
* individual cohort studies included in systematic review above
  + **physical activity may reduce risk of breast cancer in postmenopausal women**

Cohort Study[Arch Intern Med 2010 Oct 25;170(19):1758](http://pubmed.ncbi.nlm.nih.gov/20975025/)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3142573/)

studySummary

* + - Cohort Study based on multiple cohort studies
    - based on cohort of 95,396 postmenopausal women from Nurses' Health Study
      * 4,728 incident cases of invasive breast cancer in 20-year follow-up
      * physical activity equivalent to brisk walking 1 hour/day associated with reduced risk of breast cancer compared to physical activity < 1 hour/week (hazard ratio [HR] 0.85, 95% CI 0.78-0.93)
      * among women with exercise equivalent to average-pace walking for 30 minutes/day at time of menopause, women who increase physical activity had reduced breast cancer risk compared to women who did not increase activity (HR 0.9, 95% CI 0.82-0.91)
    - PubMed20975025Archives of internal medicineArch Intern Med20101025170191758-641758Reference - [Arch Intern Med 2010 Oct 25;170(19):1758](http://pubmed.ncbi.nlm.nih.gov/20975025/), [full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3142573/), commentary can be found in [Arch Intern Med 2010 Nov 8;170(20):1792](http://pubmed.ncbi.nlm.nih.gov/21059970/)
    - other cohort studies finding association of physical activity and reduced risk for breast cancer
      * 74,171 women aged 50-79 years followed for mean 4.7 years, of whom 1,780 developed breast cancer ([mdc12966124pJAMA 2003 Sep 10;290(10):1331](http://pubmed.ncbi.nlm.nih.gov/12966124?dopt=Abstract) ), editorial can be found in [mdc12966131pJAMA 2003 Sep 10;290(10):1377](http://pubmed.ncbi.nlm.nih.gov/12966131?dopt=Abstract) , commentary can be found in [mdc14693869pJAMA 2003 Dec 24;290(24):3193](http://pubmed.ncbi.nlm.nih.gov/14693869?dopt=Abstract) , [CMAJ 2004 Mar 2;170(5):787](http://www.cmaj.ca/content/170/5/787.full), [15782064Clin J Sport Med 2005 Mar;15(2):115](http://pubmed.ncbi.nlm.nih.gov/15782064?dopt=Abstract)
      * 41,836 postmenopausal women followed for up to 18 years (mean 13.3 years), of whom 2,548 developed breast cancer ([mdc17159013pArch Intern Med 2006 Dec 11;166(22):2478](http://pubmed.ncbi.nlm.nih.gov/17159013?dopt=Abstract) [mdc17159013pfull-text](http://pubmed.ncbi.nlm.nih.gov/17159013?dopt=Abstract) ), commentary can be found in [mdc17698694pArch Intern Med 2007 Aug 13-27;167(15):1690](http://pubmed.ncbi.nlm.nih.gov/17698694?dopt=Abstract)
  + **strenuous long-term exercise associated with reduced risk for breast cancer**

Cohort Study[mdc17325304pArch Intern Med 2007 Feb 26;167(4):408](http://pubmed.ncbi.nlm.nih.gov/17325304?dopt=Abstract)

studySummary

* + - based on prospective cohort study Cohort Study
    - 110,599 women aged 20-79 years followed for 7 years
    - 2,649 developed invasive breast cancer and 593 developed in situ breast cancer
    - compared to strenuous exercise < 0.5 hours/week, strenuous exercise > 5 hours/week associated with decreased risk of invasive breast cancer (relative risk 0.8, 95% CI 0.7-0.9)
    - PubMed17325304Archives of internal medicine20070226Arch Intern Med1674408408 Reference - [mdc17325304pArch Intern Med 2007 Feb 26;167(4):408](http://pubmed.ncbi.nlm.nih.gov/17325304?dopt=Abstract)
  + **total leisure-time physical activity associated with reduced risk for premenopausal breast cancer**

Cohort Study[18477801J Natl Cancer Inst 2008 May 21;100(10):728](http://pubmed.ncbi.nlm.nih.gov/18477801?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3743226/)

studySummary

* + - based on prospective cohort study Cohort Study
    - 64,777 premenopausal women in Nurses' Health Study II reported leisure-time physical activity from age 12 years to time of questionnaire and were followed for 6 years
    - 550 women developed premenopausal breast cancer
    - women with mean total activity ≥ 39 MET hours/week (equivalent to 3.25 hours/week of running or 13 hours/week of walking) during lifetime had reduced risk of premenopausal breast cancer (relative risk [RR] 0.77, 95% CI 0.64-0.93) compared to women reporting less activity
    - age-adjusted incidence rate of breast cancer per 100,000 person-years
      * 136 for mean ≥ 54 MET/hours/week over lifetime
      * 194 for mean < 21 MET/hours/week over lifetime
    - PubMed18477801Journal of the National Cancer Institute20080521J Natl Cancer Inst10010728728 Reference - [18477801J Natl Cancer Inst 2008 May 21;100(10):728](http://pubmed.ncbi.nlm.nih.gov/18477801?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3743226/)

Diet

* low-fat diet
  + **reducing dietary fat intake to < 20% of calories may be associated with small reductions in breast cancer incidence and long-term breast cancer mortality in postmenopausal women without prior breast cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Randomized Trial[mdc16467232pJAMA 2006 Feb 8;295(6):629](http://pubmed.ncbi.nlm.nih.gov/16467232?dopt=Abstract)Randomized Trial[J Clin Oncol 2020 May 1;38(13):1419](http://pubmed.ncbi.nlm.nih.gov/32031879)

Oncologic\_Disease Primary\_Carereducing dietary fat intake to < 20% of calories may be associated with small reductions in breast cancer incidence and long-term breast cancer mortality in postmenopausal women without prior breast cancer (J Clin Oncol 2020 May 1)12/08/2020 12:08:19 PMstudySummary2

* + - based on randomized trial with borderline significance for breast cancer incidence and post hoc follow-up study Randomized TrialRandomized Trialfor breast cancer mortality
    - 48,835 postmenopausal women aged 50-79 years without prior breast cancer were randomized to dietary modification vs. control
      * dietary intervention designed with goals of reducing intake of total fat to 20% of calories and increasing consumption of fruits and vegetables to at least 5 servings daily and grains to at least 6 servings daily
      * mean follow-up of 8.1 years
      * mean estimated total fat consumption (as percentage of calories) comparing dietary modification vs. control
        + at 1 year 24.3% vs. 35.1%
        + at 6 years 28.8% vs. 37%
      * comparing dietary modification vs. control
        + annualized incidence of invasive breast cancer 0.42% vs. 0.45% (p = 0.09)
        + cumulative incidence 3.35% vs. 3.66% (p = 0.07)
        + annualized breast cancer mortality 0.02% vs. 0.02% (not significant)
      * subgroup analyses found significant risk reduction with intervention for adherent women and for women with high-fat diet (> 36.8%) at baseline
      * PubMed16467232JAMA20060208JAMA2956629629 Reference - [mdc16467232pJAMA 2006 Feb 8;295(6):629](http://pubmed.ncbi.nlm.nih.gov/16467232?dopt=Abstract) , editorial can be found in [mdc16467239pJAMA 2006 Feb 8;295(6):691](http://pubmed.ncbi.nlm.nih.gov/16467239?dopt=Abstract) , commentary can be found in [mdc16849657pJAMA 2006 Jul 19;296(3):278](http://pubmed.ncbi.nlm.nih.gov/16849657?dopt=Abstract) , [mnh16813355tmdc16813355tACP J Club 2006 Jul-Aug;145(1):6](http://pubmed.ncbi.nlm.nih.gov/16813355?dopt=Abstract) , [17076013Evid Based Nurs 2006 Oct;9(4):112](http://pubmed.ncbi.nlm.nih.gov/17076013?dopt=Abstract)
      * reduced-fat diet associated with increased 10-year survival in women with incident breast cancer during trial in post hoc analysis including 1,764 women ([JAMA Oncol 2018 Oct 1;4(10):e181212](http://pubmed.ncbi.nlm.nih.gov/29800122?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6233778/))
    - all women included in post-hoc follow-up study at median 19.6 years
      * comparing dietary modification vs. control
        + annualized breast cancer mortality 0.037% vs. 0.047% (p = 0.02, NNT 10,000 per year)
        + annualized all-cause mortality after breast cancer 0.12% vs. 0.14% (p = 0.01, NNT 5,000 per year)
      * no significant differences in
        + breast cancer incidence (hazard ratio 0.95, 95% CI 0.89-1.02), but CI cannot exclude differences that may be clinically important
        + overall mortality (hazard ratio 0.98, 95% CI 0.95-1.01), but CI cannot exclude differences that may be clinically important
      * PubMed32031879Journal of clinical oncology : official journal of the American Society of Clinical OncologyJ Clin Oncol2020050138131419-14281419Reference - [J Clin Oncol 2020 May 1;38(13):1419](http://pubmed.ncbi.nlm.nih.gov/32031879)
  + **lower fat intake may not be associated with decreased risk of cancer in women with high risk for breast cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Randomized Trial[21199800Cancer Res 2011 Jan 1;71(1):123](http://pubmed.ncbi.nlm.nih.gov/21199800?dopt=Abstract)[Full Text](http://cancerres.aacrjournals.org/content/71/1/123.long)

studySummary

* + - based on randomized trial with low adherence rate Randomized Trial
    - 4,690 women with extensive mammographic density randomized to intensive dietary counseling (goal fat 15% of calories, carbohydrates 65% of calories) vs. control for mean 10 years
    - 32% with intervention had fat intake > 25% of calories at 8-10 years
    - no significant difference in invasive breast cancer or total breast cancer incidence
    - PubMed21199800Cancer research20110101Cancer Res711123123 Reference - [21199800Cancer Res 2011 Jan 1;71(1):123](http://pubmed.ncbi.nlm.nih.gov/21199800?dopt=Abstract)[full-text](http://cancerres.aacrjournals.org/content/71/1/123.long)
* phytoestrogens
  + **soy intake might be associated with decreased risk of breast cancer and increased breast cancer survival**

Systematic Review[aph92671416pa9h92671416pafh92671416pcxh92671416pmdc24312387pPLoS One 2013;8(11):e81968](http://pubmed.ncbi.nlm.nih.gov/24312387?dopt=Abstract)[Full Text](http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0081968)

studySummary

* + - based on systematic review of mostly observational studies Systematic Review
    - systematic review of 131 studies (40 randomized trials, 11 uncontrolled trials, 80 observational studies) evaluating the efficacy of soy and red clover in breast cancer treatment and prevention
    - 127 studies focused on soy, 4 focused on red clover
    - no meta-analyses performed due to heterogeneity
    - higher consumption of soy foods and/or soy isoflavones associated with
      * decreased risk of primary breast cancer in 30 studies
      * increased breast cancer survival in 5 studies
      * decreased breast cancer recurrence in 2 prospective cohort studies
      * reduced circulating estrogen in 3 randomized trials
    - no significant difference in
      * breast cancer risk in 29 studies
      * breast cancer survival in 3 prospective cohort studies
      * breast cancer recurrence in 3 prospective cohort studies
      * hot flashes or menopausal symptoms in breast cancer patients in 5 randomized trials
      * circulating estrogen levels in 15 randomized trials
    - 1 nested cast-control study found a small increased risk of breast cancer with higher serum levels of the isoflavone daidzein, but no other studies found a negative impact of soy
    - no significant differences in hot flashes or risk of breast cancer with red clover in 2 randomized trials
    - PubMed24312387PloS one201301PLoS One811e81968e81968 Reference - [aph92671416pa9h92671416pafh92671416pcxh92671416pmdc24312387pPLoS One 2013;8(11):e81968](http://pubmed.ncbi.nlm.nih.gov/24312387?dopt=Abstract) [full-text](http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0081968)
  + **meta-analysis concluded that soy intake may be associated with small reduction in breast cancer risk**

Meta-analysis[J Natl Cancer Inst 2006 Apr 5;98(7):459](http://pubmed.ncbi.nlm.nih.gov/16595782/)

studySummary

* + - Meta-analysis based on meta-analysis combined 12 case-control studies, 2 nested case-control studies, and 4 cohort studies
    - only 1 of 4 cohort studies (studies with lesser likelihood of bias) and neither of 2 nested case-control studies suggested inverse association between soy intake and breast cancer risk
    - Reference - [16595782J Natl Cancer Inst 2006 Apr 5;98(7):459](http://pubmed.ncbi.nlm.nih.gov/16595782?dopt=Abstract)[full-text](http://jnci.oxfordjournals.org/content/98/7/430.long)
    - PubMed16595782Journal of the National Cancer InstituteJ Natl Cancer Inst20060405987459-71459Reference - [J Natl Cancer Inst 2006 Apr 5;98(7):459](http://pubmed.ncbi.nlm.nih.gov/16595782/), editorial can be found in [16595771J Natl Cancer Inst 2006 Apr 5;98(7):430](http://pubmed.ncbi.nlm.nih.gov/16595771?dopt=Abstract)
  + **higher soy intake may be associated with reduced risk for breast cancer in postmenopausal women**

Cohort Study[mnh18594543paph32868421pa9h32868421pbyh32868421pafh32868421pcxh32868421pmdc18594543pBr J Cancer 2008 Jul 8;99(1):196](http://pubmed.ncbi.nlm.nih.gov/18594543?dopt=Abstract)[Full Text](http://www.nature.com/bjc/journal/v99/n1/full/6604448a.html)

studySummary

* + - based on prospective cohort study Cohort Study
    - 35,303 Chinese women in Singapore followed for ≥ 7 years
    - 629 women developed breast cancer
    - risk for breast cancer was reduced for women with soy intake > 10.6 mg isoflavone per 1,000 kcal compared to women with intake < 10.6 mg (relative risk [RR] 0.82, 95% CI 0.7-0.97)
    - postmenopausal women had highest risk reduction (RR 0.74, 95% CI 0.61-0.9), reduction not observed for premenopausal women
    - PubMed18594543British journal of cancer20080708Br J Cancer991196196 Reference - [mnh18594543paph32868421pa9h32868421pbyh32868421pafh32868421pcxh32868421pmdc18594543pBr J Cancer 2008 Jul 8;99(1):196](http://pubmed.ncbi.nlm.nih.gov/18594543?dopt=Abstract) [full-text](http://www.nature.com/bjc/journal/v99/n1/full/6604448a.html)
  + **reduced risk associated with soy intake may differ by receptor status**

Case-Control Study[18623079Int J Cancer 2008 Oct 1;123(7):1674](http://pubmed.ncbi.nlm.nih.gov/18623079?dopt=Abstract)

studySummary

* + - based on case-control study Case-Control Study
    - 678 women with breast cancer matched to 3,390 controls without breast cancer
    - reduced risk for breast cancer was associated with soy intake in top tertile for
      * estrogen receptor-positive cancers (odds ratio [OR] 0.74, 95% CI 0.58-0.94)
      * human epidermal growth factor receptor 2 (HER2)-negative cancers (OR 0.78, 95% CI 0.61-0.99)
      * estrogen receptor-positive/progesterone receptor-positive/HER2 cancers (OR 0.73, 95% CI 0.54-0.97) when all receptors jointly examined
    - PubMed18623079International journal of cancer20081001Int J Cancer123716741674 Reference - [18623079Int J Cancer 2008 Oct 1;123(7):1674](http://pubmed.ncbi.nlm.nih.gov/18623079?dopt=Abstract)
  + high dietary intake of isoflavones and mammalian lignans NOT associated with breast cancer risk in Dutch cohort of 15,555 women aged 49-70 years ([mdc14749235pAm J Clin Nutr 2004 Feb;79(2):282](http://pubmed.ncbi.nlm.nih.gov/14749235?dopt=Abstract) [full-text](http://ajcn.nutrition.org/content/79/2/282.long)), editorial can be found in [mdc14749221pAm J Clin Nutr 2004 Feb;79(2):183](http://pubmed.ncbi.nlm.nih.gov/14749221?dopt=Abstract) [full-text](http://ajcn.nutrition.org/content/79/2/183.long), commentary can be found in [mdc15277184pAm J Clin Nutr 2004 Aug;80(2):528](http://pubmed.ncbi.nlm.nih.gov/15277184?dopt=Abstract) [full-text](http://ajcn.nutrition.org/content/80/2/528.long)
  + tofu or isoflavone intake associated with lower risk of breast cancer in premenopausal but not postmenopausal Japanese women in case-control study with 167 cases and 854 controls ([mnh15942624paph17550698pa9h17550698pbyh17550698pafh17550698pcxh17550698pmdc15942624pBr J Cancer 2005 Jul 11;93(1):15](http://pubmed.ncbi.nlm.nih.gov/15942624?dopt=Abstract) [full-text](http://www.nature.com/bjc/journal/v93/n1/full/6602659a.html))
  + high dietary intake of phytoestrogens associated with reduced risk of breast cancer in case-control study with 144 pairs ([aph9710103879ta9h9710103879tbyh9710103879tafh9710103879tbeh9710103879thch9710103879tnyh9710103879tnxh9710103879tbth9710103879tpbh9710103879tcxh9710103879tLancet 1997 Oct 4;350(9083):990](http://pubmed.ncbi.nlm.nih.gov/9329514?dopt=Abstract) in Altern Ther Health Med 1998 Jan;4(1):97), editorial can be found in [aph9710103872ta9h9710103872tbyh9710103872tafh9710103872tbeh9710103872thch9710103872tnyh9710103872tnxh9710103872tbth9710103872tpbh9710103872tcxh9710103872tLancet 1997 Oct 4;350(9083):971](http://pubmed.ncbi.nlm.nih.gov/9329507?dopt=Abstract), commentary can be found in [9439513Lancet 1998 Jan 10;351(9096):137](http://pubmed.ncbi.nlm.nih.gov/9439513?dopt=Abstract); phytoestrogens found mainly in soy products and other legumes ([8875551Nutr Cancer 1996;26(2):123](http://pubmed.ncbi.nlm.nih.gov/8875551?dopt=Abstract))
* vitamins and minerals
  + **calcium and vitamin D intake have inconsistent evidence for effect on breast cancer risk**

Systematic Review[Breast Cancer Res Treat 2010 Jun;121(2):469](http://pubmed.ncbi.nlm.nih.gov/19851861/)

studySummary

* + - Systematic Review based on systematic review of observational studies and randomized trial with methodological limitations
    - systematic review of observational studies evaluating vitamin D intake, calcium intake, circulating 25(OH)D levels and/or 1-alpha,25(OH)2D levels
      * factors associated with reduced risk of breast cancer
        + highest vitamin D intake (compared to lowest intake) (relative risk [RR] 0.91, 95% CI 0.85-1) using random-effects model (results significant using fixed-effects model) in analysis of 11 studies
        + highest calcium intake (compared with lowest intake) (RR 0.81, 95% CI 0.72-0.9) in analysis of 15 studies; association became borderline significant after adjusting for publication bias
        + highest levels of circulating 25(OD)D (compared with lowest levels) (odds ratio 0.55, 95% CI 0.38-0.8) in analysis of 7 studies
      * no significant relationship between circulating 1-alpha,23(OH)2D and risk of breast cancer in analysis of 4 studies
    - PubMed19851861Breast cancer research and treatmentBreast Cancer Res Treat201006011212469-77469Reference - [Breast Cancer Res Treat 2010 Jun;121(2):469](http://pubmed.ncbi.nlm.nih.gov/19851861/)
  + 36,282 postmenopausal women randomized to calcium carbonate (elemental calcium 500 mg) plus vitamin D3 200 units vs. placebo orally twice daily for mean 7 years
    - no significant difference in incidence of invasive breast cancer (3.1% vs. 3.2%, hazard ratio [HR] 0.96, 95% CI 0.85-1.09)
    - Reference - [19001601J Natl Cancer Inst 2008 Nov 19;100(22):1581](http://pubmed.ncbi.nlm.nih.gov/19001601?dopt=Abstract)[full-text](http://jnci.oxfordjournals.org/content/100/22/1581.long), editorial can be found in [19001596J Natl Cancer Inst 2008 Nov 19;100(22):1562](http://pubmed.ncbi.nlm.nih.gov/19001596?dopt=Abstract)[full-text](http://jnci.oxfordjournals.org/content/100/22/1562.long), commentary can be found in [19401545J Natl Cancer Inst 2009 May 6;101(9):690](http://pubmed.ncbi.nlm.nih.gov/19401545?dopt=Abstract)[full-text](http://jnci.oxfordjournals.org/content/101/9/690.1.long)
    - Multiple factors limit the ability of this study to find significant differences, potentially invalidating the finding of no effect: the baseline calcium intakes close to 1,200 mg/day are higher than most population studies; only 59% of patients in the intervention group were taking intended doses of supplements at the end of study; personal use of any calcium supplementation reported by 54% patients at study baseline and 69% patients at 9 years with mean dose 325-425 mg/day ([16481636N Engl J Med 2006 Feb 16;354(7):684](http://pubmed.ncbi.nlm.nih.gov/16481636?dopt=Abstract)[full-text](http://www.nejm.org/doi/full/10.1056/NEJMoa055222#t=article)).
  + **moderate daily dietary folate intake associated with decreased risk of breast cancer compared to lower intake in women**

Systematic Review[mnh24667649paph95790222pa9h95790222pbyh95790222pafh95790222pcxh95790222pmdc24667649pBr J Cancer 2014 Apr 29;110(9):2327](http://pubmed.ncbi.nlm.nih.gov/24667649?dopt=Abstract)

studySummary

* + - based on systematic review of observational studies Systematic Review
    - systematic review of 42 observational studies (16 prospective cohort studies and 26 case-control studies) evaluating dietary folate intake and risk of breast cancer in 782,714 women
    - categories of folate intake varied across studies, women stratified by daily folate intake
    - in analysis of prospective cohort studies, compared to daily dietary folate intake < 153 mcg
      * intake 153-400 mcg associated with significantly decreased risk of breast cancer
      * intake > 400 mcg did not significantly reduce risk of breast cancer
    - in analysis of case-control studies, 100 mcg increase in daily dietary folate intake associated with decreased risk of breast cancer compared to daily dietary folate intake < 130.5 mcg
    - in subgroup of women with higher alcohol consumption, higher daily dietary folate intake associated with decreased risk of breast cancer (odds ratio 0.6, 95% CI 0.45-0.82) in analysis of 6 studies, results limited by significant heterogeneity
    - no significant association between circulating folate levels and risk of breast cancer in analysis of 8 studies
    - PubMed24667649British journal of cancer20140429Br J Cancer110923272327 Reference - [mnh24667649paph95790222pa9h95790222pbyh95790222pafh95790222pcxh95790222pmdc24667649pBr J Cancer 2014 Apr 29;110(9):2327](http://pubmed.ncbi.nlm.nih.gov/24667649?dopt=Abstract)
  + **combined folic acid, vitamin B6, and vitamin B12 not associated with risk of total invasive cancer, breast cancer, or cancer mortality in women at high risk for cardiovascular disease**

Randomized Trial[mdc18984888pJAMA 2008 Nov 5;300(17):2012](http://pubmed.ncbi.nlm.nih.gov/18984888?dopt=Abstract)[Full Text](http://jama.jamanetwork.com/article.aspx?articleid=182828)

studySummary

* + - based on randomized trial with allocation concealment not stated Randomized Trial
    - 5,442 female health professionals ≥ 42 years old with ≥ 3 coronary risk factors were randomized to combination folic acid 2.5 mg, vitamin B6 50 mg, and vitamin B12 1 mg vs. placebo daily for 7.3 years
    - no significant differences in rates of total invasive cancer, breast cancer, or death from cancer
    - PubMed18984888JAMA20081105JAMA3001720122012 Reference - Women's Antioxidant and Folic Acid Cardiovascular Study ([mdc18984888pJAMA 2008 Nov 5;300(17):2012](http://pubmed.ncbi.nlm.nih.gov/18984888?dopt=Abstract) [full-text](http://jama.jamanetwork.com/article.aspx?articleid=182828)), commentary can be found in [mnh19306491tmdc19306491tAnn Intern Med 2009 Mar 17;150(6):JC3](http://pubmed.ncbi.nlm.nih.gov/19306491?dopt=Abstract)
  + high folate and vitamin B6 intake associated with lower risk of breast cancer in nested case-control study (712 pairs) from Nurses' Health Study ([12618502J Natl Cancer Inst 2003 Mar 5;95(5):373](http://pubmed.ncbi.nlm.nih.gov/12618502?dopt=Abstract)[full-text](http://jnci.oxfordjournals.org/content/95/5/373.long) in Prescriber's Letter 2003 May;10(5):28), commentary can be found in [12865462J Natl Cancer Inst 2003 Jul 16;95(14):1091](http://pubmed.ncbi.nlm.nih.gov/12865462?dopt=Abstract)[full-text](http://jnci.oxfordjournals.org/content/95/14/1091.1.long)
  + vitamin A has inconsistent evidence
    - vitamin A intake or supplementation associated with reduced risk of breast cancer in prospective cohort study ([8292129N Engl J Med 1993 Jul 22;329(4):234](http://pubmed.ncbi.nlm.nih.gov/8292129?dopt=Abstract)[full-text](http://www.nejm.org/doi/full/10.1056/NEJM199307223290403#t=article)), commentary can be found in [8413486N Engl J Med 1993 Nov 18;329(21):1579](http://pubmed.ncbi.nlm.nih.gov/8413486?dopt=Abstract)
    - fenretinide (a form of vitamin A) did not prevent recurrent breast cancer in 5-year trial although possible benefit reported in premenopausal subgroup ([10547391J Natl Cancer Inst 1999 Nov 3;91(21):1847](http://pubmed.ncbi.nlm.nih.gov/10547391?dopt=Abstract)[full-text](http://jnci.oxfordjournals.org/content/91/21/1847.full), [mdc16014596pJAMA 2005 Jul 13;294(2):218](http://pubmed.ncbi.nlm.nih.gov/16014596?dopt=Abstract) [full-text](http://jama.jamanetwork.com/article.aspx?articleid=201218)), commentary can be found in [mdc16333000pJAMA 2005 Dec 7;294(21):2695](http://pubmed.ncbi.nlm.nih.gov/16333000?dopt=Abstract)
* green tea
  + **green tea associated with decreased risk of breast cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[Medicine (Baltimore) 2019 Jul;98(27):e16147](https://pubmed.ncbi.nlm.nih.gov/31277115)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6635178/)

studySummary

* + - Systematic Review based on systematic review of case-control studies
    - systematic review of 14 case-control studies evaluating association between green tea and risk of breast cancer in 14,058 female adults with current diagnosis or history of breast cancer and 15,043 female adults without history of breast cancer
      * 5,384 adults with current diagnosis or history of breast cancer diagnosis regularly consumed green tea
      * 6,142 adults without history of breast cancer regularly consumed green tea
    - measure of green tea consumption varied among studies (grams/month, grams/year, cups/day, or cups/week)
    - green tea consumption associated with decreased risk of breast cancer (odds ratio 0.83, 95% CI 0.72-0.96) in analysis of all studies, results limited by significant heterogeneity
    - PubMed32118296The Cochrane database of systematic reviewsCochrane Database Syst Rev202003023CD005004CD005004Reference - [Medicine (Baltimore) 2019 Jul;98(27):e16147](https://pubmed.ncbi.nlm.nih.gov/31277115)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6635178/)
* other dietary considerations
  + **omega-3 fatty acid supplementation may not reduce risk of breast cancer in adults without history of cancer or cardiovascular disease**

Randomized Trial[30415629N Engl J Med 2018 Nov 10 early online](http://pubmed.ncbi.nlm.nih.gov/30415629?dopt=Abstract)[Full Text](https://www.nejm.org/doi/10.1056/NEJMoa1809944?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov)

studySummaryomega-3 fatty acid supplementation may not reduce risk of breast cancer in adults without history of cancer or cardiovascular disease (N Engl J Med 2018 Nov 10 early online)11/26/2018 02:32:00 PMFamily\_MedicineGeriatricsPrimary\_CareFamily\_Medicine Geriatrics Primary\_Careomega-3 fatty acid supplementation may not reduce risk of breast cancer in adults without history of cancer or cardiovascular disease (N Engl J Med 2018 Nov 10 early online)11/26/2018 02:32:00 PM230415629

* + - based on randomized trial with wide confidence intervals Randomized Trial
    - 25,871 adults (men ≥ 50 years old and women ≥ 55 years old) without history of cancer or cardiovascular disease were randomized in 2-by-2 factorial design to
      * omega-3 fatty acids (marine n-3 fatty acids) 1 g orally once daily vs. placebo
      * vitamin D3 (cholecalciferol) 2,000 units orally once daily vs. placebo
    - median follow-up 5.3 years
    - 82% took ≥ 66% of omega-3 or placebo capsules, 100% included in analysis
    - comparing omega-3 fatty acid supplementation vs. placebo
      * breast cancer in 0.9% vs. 1% (hazard ratio 0.9, 95% CI 0.7-1.16), not significant, but CI includes possibility of benefit or harm
      * invasive cancer of any type in 6.3% vs. 6.2% (not significant)
      * cancer-related mortality 1.3% vs. 1.4% (hazard ratio 0.97, 95% CI 0.79-1.2), not significant, but CI includes possibility of benefit or harm
      * all-cause mortality 3.8% vs. 3.7% (not significant)
    - no significant differences in
      * risk of major cardiovascular events (composite of myocardial infarction, stroke, and cardiovascular mortality)
      * monitored safety conditions including gastrointestinal bleeding, blood in urine, easy bruising, frequent nosebleeds, or kidney failure or dialysis
      * adverse events including stomach upset or pain, nausea, constipation, and diarrhea
    - no significant association between vitamin D supplementation and risk of invasive cancer of any type (for details, see VITAL trial [vitamin D arm] in [Vitamin D Intake and Supplementation](https://dpa-pde-oxford.shinyapps.io/drug-review/vitamin-d-intake-and-supplementation))
    - no significant interaction between omega-3 and vitamin D supplementation
    - PubMed30415629The New England journal of medicine20181110N Engl J Medearly onlineearly online Reference - VITAL trial (omega-3 arm) ([30415629N Engl J Med 2018 Nov 10 early online](http://pubmed.ncbi.nlm.nih.gov/30415629?dopt=Abstract)[full-text](https://www.nejm.org/doi/10.1056/NEJMoa1809944?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov)), editorial can be found in [30415594N Engl J Med 2018 Nov 10 early online](http://pubmed.ncbi.nlm.nih.gov/30415594?dopt=Abstract)
  + **omega-3 fatty acid intake not clearly associated with cancer incidence (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[JAMA 2006 Jan 25;295(4):403](http://pubmed.ncbi.nlm.nih.gov/16434631/)[Full Text](http://jama.jamanetwork.com/article.aspx?articleid=202260)

studySummary

* + - Systematic Review based on systematic review of observational studies
    - systematic review of 38 articles describing 20 prospective cohorts for 11 different types of cancer
      * 65 estimates of association between omega-3 fatty acid consumption and cancer were reported, data not pooled due to heterogeneity
      * for breast cancer, 1 estimate was for increased risk, 3 estimates were for decreased risk, and 7 estimates did not find significant association
    - PubMed16434631JAMAJAMA200601252954403-15403Reference - [JAMA 2006 Jan 25;295(4):403](http://pubmed.ncbi.nlm.nih.gov/16434631/)[full-text](http://jama.jamanetwork.com/article.aspx?articleid=202260), correction can be found in JAMA 2006 Apr 26;295(16):1900, commentary can be found in [JAMA 2006 Jul 19;296(3):282](http://pubmed.ncbi.nlm.nih.gov/16849660/)
  + high levels of dietary n-3 fatty acids from fish or shellfish associated with reduced risk of breast cancer in cohort study of 35,298 Singapore Chinese women aged 45-74 years followed 2-7 years ([mnh14583770paph11234753pa9h11234753pbyh11234753pafh11234753pcxh11234753pmdc14583770pBr J Cancer 2003 Nov 3;89(9):1686](http://pubmed.ncbi.nlm.nih.gov/14583770?dopt=Abstract) [full-text](http://www.nature.com/bjc/journal/v89/n9/full/6601340a.html))
  + high fiber and low-fat diet associated with reduced risk of breast cancer in analysis of 11,726 postmenopausal women from Malmö Diet and Cancer cohort who were interviewed about diet history ([mnh14710218paph11862110pa9h11862110pbyh11862110pafh11862110pcxh11862110pmdc14710218pBr J Cancer 2004 Jan 26;90(1):122](http://pubmed.ncbi.nlm.nih.gov/14710218?dopt=Abstract) [full-text](http://www.nature.com/bjc/journal/v90/n1/full/6601516a.html))
  + increased consumption of onions and garlic may be associated with reduced incidence of numerous types of cancer ([mdc17093154pAm J Clin Nutr 2006 Nov;84(5):1027](http://pubmed.ncbi.nlm.nih.gov/17093154?dopt=Abstract) [full-text](http://ajcn.nutrition.org/content/84/5/1027.long))
  + neither tomato nor lycopene intake found to reduce risk of breast cancer on FDA review for premarket approval of qualified health claim ([17623802J Natl Cancer Inst 2007 Jul 18;99(14):1074](http://pubmed.ncbi.nlm.nih.gov/17623802?dopt=Abstract)[full-text](http://jnci.oxfordjournals.org/content/99/14/1074.long)), editorial can be found in [17623795J Natl Cancer Inst 2007 Jul 18;99(14):1060](http://pubmed.ncbi.nlm.nih.gov/17623795?dopt=Abstract)[full-text](http://jnci.oxfordjournals.org/content/99/14/1060.long)

Limiting alcohol intake

* **increased alcohol intake may be risk factor for breast cancer**

Meta-analysis[8039145Cancer 1994 Aug 1;74(3 Suppl):1101](http://pubmed.ncbi.nlm.nih.gov/8039145?dopt=Abstract)

studySummary

* + based on meta-analysis of > 50 epidemiological studies Meta-analysis
  + 25% increased risk of breast cancer with 2 drinks/day and dose-response relationship
  + PubMed8039145Cancer19940801Cancer743 Suppl11011101 Reference - [8039145Cancer 1994 Aug 1;74(3 Suppl):1101](http://pubmed.ncbi.nlm.nih.gov/8039145?dopt=Abstract)
* moderate alcohol consumption (≥ 30 g/day) associated with increased risk for breast cancer among 38,454 women in Women's Health Study followed for mean 10 years ([17204515Am J Epidemiol 2007 Mar 15;165(6):667](http://pubmed.ncbi.nlm.nih.gov/17204515?dopt=Abstract)[full-text](http://aje.oxfordjournals.org/content/165/6/667.long))

Chemoprevention

* [United States Preventive Services Task Force (USPSTF) recommendations](https://dpa-pde-oxford.shinyapps.io/prevention/chemoprevention-of-breast-cancer#RECOMMENDATIONS) on chemoprevention of breast cancer
  + tamoxifen or raloxifene not recommended for women at low or average risk of breast cancer ([USPSTF Grade D](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__SNIPPET-POINTER_1657691660))
  + discussion of benefits and risks recommended for women at HIGH risk of breast cancer and at low risk for adverse effects of chemoprevention ([USPSTF Grade B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__SNIPPET-POINTER_1657691660))
  + [Breast Cancer Risk Assessment Tool](http://www.cancer.gov/bcrisktool/) can be used to determine breast cancer risk
* [tamoxifen and raloxifene](https://dpa-pde-oxford.shinyapps.io/prevention/chemoprevention-of-breast-cancer#REDUCERISK) each reduce risk of invasive breast cancer but increase risk of venous thromboembolism ([level 1 [likely reliable] evidence](https://www.dynamed.com/home/editorial/editorial-process))
  + [tamoxifen](https://dpa-pde-oxford.shinyapps.io/prevention/chemoprevention-of-breast-cancer#TAMOXIFEN) 20 mg once daily for 5 years in high-risk women reduces risk of invasive breast cancer (NNT 77) but increases risks for endometrial cancer (NNH 322), pulmonary embolism (NNH 500), bothersome hot flashes (NNH 6), bothersome vaginal discharge (NNH 11), cataracts (NNH 77), and possibly stroke
  + [raloxifene](https://dpa-pde-oxford.shinyapps.io/prevention/chemoprevention-of-breast-cancer#RALOXIFENE) 60 mg once daily for 3-4 years reduces risk of breast cancer (NNT 126) but increases risks for venous thromboembolic disease (NNH 143), hot flashes (NNH 25), and leg cramps (NNH 33)
  + [tamoxifen and raloxifene](https://dpa-pde-oxford.shinyapps.io/prevention/chemoprevention-of-breast-cancer#TAMOXIFEN_AND_RALOXIFENE) have similar efficacy for reducing risk for invasive breast cancer ([level 1 [likely reliable] evidence](https://www.dynamed.com/home/editorial/editorial-process))
* [exemestane](https://dpa-pde-oxford.shinyapps.io/prevention/chemoprevention-of-breast-cancer#AROMATASE_INHIBITORS) 25 mg once daily may reduce risk of invasive breast cancer in postmenopausal women at risk for breast cancer ([level 2 [mid-level] evidence](https://www.dynamed.com/home/editorial/editorial-process))
* see [Chemoprevention of Breast Cancer](https://dpa-pde-oxford.shinyapps.io/prevention/chemoprevention-of-breast-cancer) for details
* review of tamoxifen, raloxifene, and surgery as methods to reduce risk of breast cancer can be found in [10900280N Engl J Med 2000 Jul 20;343(3):191](http://pubmed.ncbi.nlm.nih.gov/10900280?dopt=Abstract)

Nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin

* **any NSAID use and specific NSAIDs ibuprofen, acetaminophen, and cyclooxygenase (COX)-2 inhibitors may be associated with decreased risk of breast cancer**

Systematic Review[mnh25589172pcxh100671740pmdc25589172pBreast Cancer Res Treat 2015 Jan;149(2):525](http://pubmed.ncbi.nlm.nih.gov/25589172?dopt=Abstract)

studySummary

* + based on systematic review of observational studies Systematic Review
  + systematic review of 49 observational studies (23 case-control studies, 24 cohort studies, and 2 studies from same randomized trial) evaluating association between NSAID use and risk of invasive breast cancer
  + effect estimates based on highest NSAID dose or longest duration of use
  + any NSAID use associated with nonsignificant decrease in risk of breast cancer (risk ratio [RR] 0.97, 95% CI 0.94-1) in analysis of 12 cohort studies, results limited by significant heterogeneity
  + specific NSAIDs associated with decreased risk of breast cancer
    - acetaminophen (odds ratio [OR] 0.85, 95% CI 0.76-0.95) in analysis of 8 case-control studies, results limited by significant heterogeneity
    - COX-2 inhibitors (OR 0.9, 95% CI 0.87-0.93) in analysis of 5 case-control studies, results limited by significant heterogeneity
  + no significant decrease in risk of breast cancer with
    - ibuprofen in analysis of 6 case-control studies
    - aspirin in analysis of 13 cohort studies
    - non-aspirin NSAID in analysis of 8 cohort studies
  + PubMed25589172Breast cancer research and treatment20150101Breast Cancer Res Treat1492525525 Reference - [mnh25589172pcxh100671740pmdc25589172pBreast Cancer Res Treat 2015 Jan;149(2):525](http://pubmed.ncbi.nlm.nih.gov/25589172?dopt=Abstract)
* **NSAID use may be associated with reduced risk for breast cancer**

Systematic Review[18840819J Natl Cancer Inst 2008 Oct 15;100(20):1439](http://pubmed.ncbi.nlm.nih.gov/18840819?dopt=Abstract)[Full Text](http://jnci.oxfordjournals.org/content/100/20/1439.long)

studySummary

* + based on systematic review and meta-analysis of 38 studies (18 cohort, 19 case-control, 1 clinical trial) evaluating NSAID use and breast cancer risk in 2,788,715 patients Systematic Review
  + NSAID use associated with reduced risk for breast cancer overall (relative risk [RR] 0.88, 95% CI 0.84-0.93)
  + aspirin use associated with reduced risk for breast cancer (RR 0.87, 95% CI 0.82-0.92)
  + ibuprofen use associated with reduced risk (RR 0.79, 95% CI 0.64-0.97)
  + PubMed18840819Journal of the National Cancer Institute20081015J Natl Cancer Inst1002014391439 Reference - [18840819J Natl Cancer Inst 2008 Oct 15;100(20):1439](http://pubmed.ncbi.nlm.nih.gov/18840819?dopt=Abstract)[full-text](http://jnci.oxfordjournals.org/content/100/20/1439.long), editorial can be found in [18840814J Natl Cancer Inst 2008 Oct 15;100(20):1420](http://pubmed.ncbi.nlm.nih.gov/18840814?dopt=Abstract)[full-text](http://jnci.oxfordjournals.org/content/100/20/1420.long)
* not all studies consistently find reduced risk with NSAID use
  + **neither NSAID nor acetaminophen use associated with reduced risk of breast cancer in premenopausal women**

Cohort Study[mdc19171806pArch Intern Med 2009 Jan 26;169(2):115](http://pubmed.ncbi.nlm.nih.gov/19171806?dopt=Abstract)[Full Text](http://archinte.jamanetwork.com/article.aspx?articleid=414730)

studySummary

* + - based on prospective cohort study Cohort Study
    - 112,292 premenopausal women in Nurses' Health Study II aged 25-42 years at baseline were followed for 14 years
    - 1,345 incident cases of premenopausal breast cancer
    - no significant associations between breast cancer risk and
      * aspirin use
      * nonaspirin NSAID use
      * acetaminophen use
    - associations did not vary with duration or frequency of use or dosage
    - PubMed19171806Archives of internal medicine20090126Arch Intern Med1692115115 Reference - [mdc19171806pArch Intern Med 2009 Jan 26;169(2):115](http://pubmed.ncbi.nlm.nih.gov/19171806?dopt=Abstract) [full-text](http://archinte.jamanetwork.com/article.aspx?articleid=414730), editorial can be found in Arch Intern Med 2009 Jan 26;169(2):121 [PDF](http://archinte.jamanetwork.com/data/Journals/INTEMED/5734/ioi80157_115_121.pdf)
  + NSAID use not associated with risk for breast cancer, except daily aspirin use may be associated with reduced risk for estrogen receptor-positive breast cancer in cohort of 127,383 women aged 51-72 years followed for up to 7 years ([18447943Breast Cancer Res 2008 Apr 30;10(2):R38](http://pubmed.ncbi.nlm.nih.gov/18447943?dopt=Abstract)[full-text](http://breast-cancer-research.com/content/10/2/R38))
* frequent use of aspirin > 100 mg/day, nonselective NSAIDs, or COX-2 inhibitors associated with reduced risk of breast cancer in case-control study with 1,090 cases and 44,990 controls ([mnh16343343paph31614042pa9h31614042pafh31614042pcxh31614042pmdc16343343pBMC Cancer 2005 Dec 12;5:159](http://pubmed.ncbi.nlm.nih.gov/16343343?dopt=Abstract) [full-text](http://www.biomedcentral.com/1471-2407/5/159))
* **aspirin 100 mg every other day in women does not prevent cancer**

Randomized Trial[mdc15998890pJAMA 2005 Jul 6;294(1):47](http://pubmed.ncbi.nlm.nih.gov/15998890?dopt=Abstract)[Full Text](http://jama.jamanetwork.com/article.aspx?articleid=201173)

studySummary

* + based on randomized trial with low adherence Randomized Trial
  + 39,876 healthy women > 45 years old who completed 3-month placebo run-in period were randomized to aspirin 100 mg vs. placebo orally every other day (and also randomized to vitamin E 600 units vs. placebo orally every other day) for mean 10 years (range 8-11 years)
  + 76% of women reported taking at least two-thirds of assigned aspirin or placebo tablets at 5 years (67% at 10 years)
  + no significant differences in incidence of any cancer excluding nonmelanoma skin cancer (7.2% vs. 7.2%), any cancer death (1.4% vs. 1.5%), breast cancer (3.05% vs. 3.12%), colon cancer (0.52% vs. 0.56%), rectal cancer (0.15% vs. 0.13%), lung cancer (0.45% vs. 0.58%, p = 0.08), or leukemia (0.19% vs. 0.12%, p = 0.1)
  + PubMed15998890JAMA20050706JAMA29414747 Reference - Women's Health Study ([mdc15998890pJAMA 2005 Jul 6;294(1):47](http://pubmed.ncbi.nlm.nih.gov/15998890?dopt=Abstract) [full-text](http://jama.jamanetwork.com/article.aspx?articleid=201173)), editorial can be found in [mdc15998897pJAMA 2005 Jul 6;294(1):105](http://pubmed.ncbi.nlm.nih.gov/15998897?dopt=Abstract) , commentary can be found in [mdc16287949pJAMA 2005 Nov 16;294(19):2432](http://pubmed.ncbi.nlm.nih.gov/16287949?dopt=Abstract) , [17213052Evid Based Med 2006 Feb;11(1):10](http://pubmed.ncbi.nlm.nih.gov/17213052?dopt=Abstract), [mnh16388558tmdc16388558tACP J Club 2006 Jan-Feb;144(1):8](http://pubmed.ncbi.nlm.nih.gov/16388558?dopt=Abstract)
  + vitamin E 600 units every other day did not prevent cancer either (Women's Health Study trial [mdc15998891pJAMA 2005 Jul 6;294(1):56](http://pubmed.ncbi.nlm.nih.gov/15998891?dopt=Abstract) [full-text](http://jama.jamanetwork.com/article.aspx?articleid=201172)), editorial can be found in [mdc15998897pJAMA 2005 Jul 6;294(1):105](http://pubmed.ncbi.nlm.nih.gov/15998897?dopt=Abstract) , commentary can be found in [mnh16240470paph18581817pa9h18581817pbyh18581817pafh18581817phch18581817pnyh18581817ppbh18581817pcxh18581817pmdc16240470pJ Fam Pract 2005 Oct;54(10):838](http://pubmed.ncbi.nlm.nih.gov/16240470?dopt=Abstract) , [mdc16287949pJAMA 2005 Nov 16;294(19):2432](http://pubmed.ncbi.nlm.nih.gov/16287949?dopt=Abstract) , [mnh16388558tmdc16388558tACP J Club 2006 Jan-Feb;144(1):8](http://pubmed.ncbi.nlm.nih.gov/16388558?dopt=Abstract) , [17213053Evid Based Med 2006 Feb;11(1):11](http://pubmed.ncbi.nlm.nih.gov/17213053?dopt=Abstract)

Prophylactic mastectomy

* Currently, no randomized trials have evaluated the effects of bilateral or contralateral prophylactic mastectomy to reduce breast cancer incidence or mortality. While cohort studies have evaluated the effects of prophylactic mastectomy, such studies are limited due to a high risk of confounding factors and selection bias because women who chose prophylactic mastectomy may be different from those who chose surveillance. Therefore, it is important that women and their clinicians fully understand the risks and potential, but unproven, benefits before considering surgery.
* Society of Surgical Oncology Breast Disease Working Group statement on prophylactic mastectomy
  + bilateral and contralateral prophylactic mastectomy rates are increasing
  + breast surgeons assist with accurate assessment of breast cancer risk based on
    - genetic factors such as gender, age, genetic mutations in high or moderate penetrance genes, genetic polymorphisms, and family history of breast cancer
    - nongenetic factors such as
      * history of therapeutic radiation
      * lobular carcinoma in situ or atypical hyperplasia on breast biopsy
      * history of benign breast condition
      * increased mammographic breast density
      * increased bone mineral density
      * body mass index (BMI) > 30 kg/m2
      * high estrogen or insulin levels
      * history of > 5 years combined (estrogen and progestin) hormone replacement therapy
      * age > 35 years at first birth or nulliparity
      * alcohol consumption > 1 drink/day
      * first menstruation at age < 12 years
  + bilateral prophylactic mastectomy
    - performed in women with increased risk but without history of breast cancer
    - reported to reduce risk of primary breast cancer by 90% to nearly 100%
      * risk reduction varies by surgical technique
      * greatest risk reduction in healthy women with hereditary predisposition for breast or ovarian cancer
      * commonly combined with bilateral salpingo-oophorectomy in*BRCA* 1/2 mutation carriers and combination further improves risk reduction
    - no evidence for improved survival in women with average risk for breast cancer
  + contralateral prophylactic mastectomy
    - performed in women who have had, or will have, a mastectomy to treat breast cancer
    - reported to reduce risk of contralateral breast cancer by 91%-100%
    - potential overall survival benefit in women with
      * better prognosis from index cancer
      * low expected mortality from causes unrelated to breast cancer
      * high expected rate of contralateral breast cancer
  + considerations with prophylactic mastectomies include
    - changes in body image, quality of life, and sexuality
    - reported 6%-10% rates of occult malignancy (mostly carcinomas in situ)
    - common postoperative complications include infection, wound healing, and bleeding
    - reconstruction increases the risk of postoperative complications and may delay onset of systemic therapy
    - alternatives to prophylactic mastectomy include endocrine therapy for chemoprevention, bilateral salpingo-oophorectomy, and optimized screening for women at increased risk
  + Reference - [cxh120547773pmdc27933411pAnn Surg Oncol 2017 Feb;24(2):375](http://pubmed.ncbi.nlm.nih.gov/27933411?dopt=Abstract)
* **bilateral prophylactic mastectomy might be associated with reduced breast cancer incidence and breast cancer mortality in women at risk for breast cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cochrane Review[chhCD002748Cochrane Database Syst Rev 2018 Apr 5;(4):CD002748](http://www.ncbi.nlm.nih.gov/pubmed?term=29620792%5buid%5d%20AND%20CD002748%5bpg%5d)

studySummary2

* + based on Cochrane review of observational studies Cochrane Review
  + systematic review of 61 observational studies evaluating prophylactic mastectomy in 15,077 women at risk of breast cancer in at least 1 breast
  + 21 studies included only women choosing bilateral prophylactic mastectomy
  + bilateral mastectomy associated with
    - reduced incidence of breast cancer in individual studies, particularly in women with breast cancer susceptibility gene (*BRCA*) 1/2 mutations
    - reduced breast cancer mortality in individual studies
    - reduced level of emotional concern about developing breast cancer in 1 study
    - decreased satisfaction with body image and sexual feelings in individual studies
    - increased additional unanticipated surgeries in individual studies, especially in women having reconstruction after risk-reducing mastectomy
  + inconsistent evidence for association between contralateral prophylactic mastectomy and breast cancer mortality, but limited evidence suggests possible association with reduced breast cancer incidence
  + CochraneCD002748The Cochrane database of systematic reviews20180405Cochrane Database Syst Rev4CD002748CD002748 Reference - [chhCD002748Cochrane Database Syst Rev 2018 Apr 5;(4):CD002748](http://www.ncbi.nlm.nih.gov/pubmed?term=29620792%5buid%5d%20AND%20CD002748%5bpg%5d)
* **risk-reducing bilateral mastectomy associated with 90%-100% reduction in breast cancer incidence in women at high risk or with *BRCA1/2* mutation (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[JAMA 2019 Aug 20;322(7):666](http://pubmed.ncbi.nlm.nih.gov/31429902?dopt=Abstract)

Oncologic\_Diseaserisk-reducing bilateral mastectomy associated with 90%-100% reduction in breast cancer incidence in women at high risk or with BRCA1 or BRCA2 mutation (JAMA 2019 Aug 20)10/15/2019 11:07:57 AMstudySummary2risk-reducing bilateral mastectomy associated with 90%-100% reduction in breast cancer incidence in women at high risk or with BRCA1 or BRCA2 mutation (JAMA 2019 Aug 20)10/15/2019 11:07:57 AMOncologic\_Disease

* + Systematic Reviewbased on systematic review of mostly observational studies
  + systematic review of 73 observational studies, 15 randomized trials, 14 diagnostic accuracy studies, and 1 systematic review evaluating risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer in 92,712 women
  + 6 observational studies evaluated risk-reducing mastectomy and breast cancer incidence in 2,546 women at high risk or carrying *BRCA1/2* mutation
    - risk-reducing bilateral mastectomy associated with 90%-100% reduction in breast cancer incidence compared to no risk-reducing mastectomy
    - breast cancer-specific mortality reported to be reduced 81%-100% after risk-reducing mastectomy in modeling analysis in 1 study with 639 women
  + 12 observational studies evaluated complications and psychological outcomes associated with risk-reducing mastectomy in high-risk women and *BRCA1/2* mutation carriers
    - ≥ 50% women had surgical complications
    - complications included necrosis, pain, infection, hematoma, and implant problems
    - some women had worse psychological symptoms and body image after surgery, but most returned to baseline over time
  + PubMed31429902JAMAJAMA201908203227666-685666Reference - [JAMA 2019 Aug 20;322(7):666](http://pubmed.ncbi.nlm.nih.gov/31429902?dopt=Abstract)
* **contralateral prophylactic mastectomy may decrease risk of metachronous contralateral breast cancer and recurrence, but may not improve overall survival or breast cancer-specific mortality in women with unilateral breast cancer who have elevated familial or genetic risk (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[24950272Ann Surg 2014 Dec;260(6):1000](http://pubmed.ncbi.nlm.nih.gov/24950272?dopt=Abstract)

studySummary2

* + based on systematic review of observational studies Systematic Review
  + systematic review of 14 observational studies (9 cohort studies, 1 case-control study, 3 case series, and 1 convenience sample) evaluating contralateral prophylactic mastectomy in 159,152 women with unilateral breast cancer
    - 8.2% had contralateral prophylactic mastectomy, patient follow-up ranged from 4 to 18 years
    - 4 studies only included patients with elevated familial or genetic risk (family history of breast cancer and/or *BRCA* mutation carriers)
  + comparing contralateral prophylactic mastectomy to no mastectomy in patients with elevated familial or genetic risk
    - contralateral prophylactic mastectomy associated with
      * decreased risk of metachronous contralateral breast cancer (relative risk [RR] 0.04, 95% CI 0.02-0.09) in analysis of 4 studies with 2,418 patients
      * decreased risk of distant or metastatic recurrence (RR 0.71, 95% CI 0.53-0.94) in analysis of 2 studies with 918 patients
    - no significant differences in
      * overall survival (RR 1.09, 95% CI 0.97-1.24) in analysis of 3 studies with 1,936 patients
      * breast cancer-specific mortality (RR 0.66, 95% CI 0.27-1.64) in analysis of 2 studies with 918 patients
  + contralateral prophylactic mastectomy associated with significant improvement in all outcomes in overall analyses
  + PubMed24950272Annals of surgery20141201Ann Surg260610001000 Reference - [24950272Ann Surg 2014 Dec;260(6):1000](http://pubmed.ncbi.nlm.nih.gov/24950272?dopt=Abstract)
  + **contralateral prophylactic mastectomy associated with reduced breast cancer mortality in women < 50 years old with early-stage estrogen receptor-negative breast cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**
    - based on observational study
    - analysis of Surveillance, Epidemiology, and End Results (SEER) database including 107,106 women with breast cancer who had mastectomy, including 8,902 who had contralateral prophylactic mastectomy
    - 5-year adjusted breast cancer survival was higher with vs. without contralateral prophylactic mastectomy (88.5% vs. 83.7%)
    - significant reduction in breast cancer-specific mortality occurred in women aged 18-49 years with stages II-III estrogen receptor-negative breast cancer
    - Reference - [20185801J Natl Cancer Inst 2010 Mar 17;102(6):401](http://pubmed.ncbi.nlm.nih.gov/20185801?dopt=Abstract)[full-text](http://jnci.oxfordjournals.org/content/102/6/401.long)
* cross-sectional survey of perceptions, knowledge, and satisfaction with contralateral prophylactic mastectomy in young women with breast cancer can be found in [mnh24042365pmdc24042365pAnn Intern Med 2013 Sep 17;159(6):373](http://pubmed.ncbi.nlm.nih.gov/24042365?dopt=Abstract) , editorial can be found in [mnh24042370pmdc24042370pAnn Intern Med 2013 Sep 17;159(6):428](http://pubmed.ncbi.nlm.nih.gov/24042370?dopt=Abstract)
* case report of primary invasive breast cancer after prophylactic bilateral subcutaneous mastectomy can be found in [16079000World J Surg Oncol 2005 Aug 4;3:52](http://pubmed.ncbi.nlm.nih.gov/16079000?dopt=Abstract)[full-text](http://www.wjso.com/content/3/1/52)

Hysterectomy and oophorectomy

* **oophorectomy may not reduce risk of breast cancer in women with *BRCA1/2* mutation (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[JAMA 2019 Aug 20;322(7):666](http://pubmed.ncbi.nlm.nih.gov/31429902?dopt=Abstract)

Oncologic\_Diseaseoophorectomy may not reduce risk of breast cancer in women with BRCA1 or BRCA2 mutation (JAMA 2019 Aug 20)10/15/2019 11:11:45 AMstudySummary2oophorectomy may not reduce risk of breast cancer in women with BRCA1 or BRCA2 mutation (JAMA 2019 Aug 20)10/15/2019 11:11:45 AMOncologic\_Disease

* + Systematic Review based on systematic review of mostly observational studies
  + systematic review of 73 observational studies, 15 randomized trials, 14 diagnostic accuracy studies, and 1 systematic review evaluating risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer in 92,712 women
  + 3 observational studies controlled for potential biases in evaluation of association between salpingo-oophorectomy or oophorectomy alone and breast cancer incidence in 5,502 women with *BRCA1/2* mutation
  + no significant association found between oophorectomy and breast cancer risk or cancer-specific mortality
  + surgical complications reported in 4% in 1 study with 159 women having salpingo-oophorectomy
  + PubMed31429902JAMAJAMA201908203227666-685666Reference - [JAMA 2019 Aug 20;322(7):666](http://pubmed.ncbi.nlm.nih.gov/31429902?dopt=Abstract)
* **hysterectomy with bilateral salpingo-oophorectomy (BSO) in postmenopausal women associated with reduced risk of breast cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cohort Study[24807324Obstet Gynecol 2014 Jun;123(6):1247](http://pubmed.ncbi.nlm.nih.gov/24807324?dopt=Abstract)

studySummary2

* + based on cohort study Cohort Study
  + 66,802 postmenopausal women evaluated for association between hysterectomy with or without BSO and cancer risk, compared with no surgery
  + women stratified by age to 3 categories: < 45 years, 45-54 years, and ≥ 55 years
  + 8,621 cancers diagnosed during median follow-up of 13.9 years
  + hysterectomy with BSO performed at all age groups combined associated with reduced risk of
    - all cancers (adjusted relative risk [RR] 0.9, 95% CI 0.85-0.96)
    - breast cancer (adjusted RR 0.8, 95% CI 0.73-0.88)
  + hysterectomy with BSO performed at ≥ 55 years old not associated with reduced risk of all cancers
  + hysterectomy without BSO associated with reduced risk of
    - all cancers if performed at < 45 years old (adjusted RR 0.88, 95% CI 0.8-0.97)
    - breast cancer if performed < 45 years old (adjusted RR 0.8, 95% CI 0.69-0.94)
  + PubMed24807324Obstetrics and gynecology20140601Obstet Gynecol123612471247 Reference - [24807324Obstet Gynecol 2014 Jun;123(6):1247](http://pubmed.ncbi.nlm.nih.gov/24807324?dopt=Abstract)
* **bilateral oophorectomy associated with increased risk of all-cause mortality but decreased risk of breast and ovarian cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cohort Study[19384117Obstet Gynecol 2009 May;113(5):1027](http://pubmed.ncbi.nlm.nih.gov/19384117?dopt=Abstract)

studySummary2

* + based on prospective cohort study Cohort Study
  + 29,380 female patients in Nurses' Health Study who underwent hysterectomy for benign disease were followed for 24 years
  + bilateral oophorectomy associated with increased
    - total mortality (hazard ratio [HR] 1.12, 95% CI 1.03-1.21)
    - fatal and nonfatal coronary heart disease (HR 1.17, 95% CI 1.02-1.35)
    - lung cancer (HR 1.26, 95% CI 1.02-1.56)
    - total cancer mortality (HR 1.17, 95% CI 1.04-1.32)
  + bilateral oophorectomy associated with decreased
    - breast cancer (HR 0.75, 95% CI 0.68-0.84)
    - ovarian cancer (HR 0.04, 95% CI 0.01-0.09)
    - all cancers (HR 0.9, 95% CI 0.84-0.96)
  + PubMed19384117Obstetrics and gynecology20090501Obstet Gynecol113510271027 Reference - [19384117Obstet Gynecol 2009 May;113(5):1027](http://pubmed.ncbi.nlm.nih.gov/19384117?dopt=Abstract)
* see [Hysterectomy](https://dpa-pde-oxford.shinyapps.io/procedure/hysterectomy) for additional information

Other prevention strategies

* inconsistent evidence for association between use of bisphosphonates for osteoporosis and decreased risk of breast cancer in postmenopausal women
  + **bisphosphonates may reduce risk of breast cancer in women (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[mnh22622199pcxh108066663pmdc22622199pClin Breast Cancer 2012 Aug;12(4):276](http://pubmed.ncbi.nlm.nih.gov/22622199?dopt=Abstract)

studySummary2

* + - based on systematic review limited by clinical heterogeneity Systematic Review
    - systematic review of 4 observational studies (2 cohort and 2 case-control studies) comparing users of bisphosphonates to nonusers for prevention of breast cancer in 507,369 women
      * breast cancer in 15,363 women
      * bisphosphonate use in 84,931 women
    - analyses limited by variation in type of bisphosphonates used and unclear dosing and frequency of use
    - use of bisphosphonates associated with reduced risk of breast cancer
      * overall (risk ratio 0.85, 95% CI 0.74-0.98) in analysis of 4 studies, results limited by significant heterogeneity
      * in subgroup analysis of women with invasive breast cancer (risk ratio 0.68, 95% CI 0.59-0.8)
    - longer duration of bisphosphonate use associated with greater reduction in breast cancer risk
    - PubMed22622199Clinical breast cancer20120801Clin Breast Cancer124276276 Reference - [mnh22622199pcxh108066663pmdc22622199pClin Breast Cancer 2012 Aug;12(4):276](http://pubmed.ncbi.nlm.nih.gov/22622199?dopt=Abstract)
  + **bisphosphonates not associated with reduced risk of breast cancer in postmenopausal women (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Randomized Trial[mdc25111880pJAMA Intern Med 2014 Oct 1;174(10):1550](http://pubmed.ncbi.nlm.nih.gov/25111880?dopt=Abstract)

studySummary2

* + - based on secondary analysis of 2 randomized trials
      * 6,459 women aged 55-81 years randomized to [alendronate](https://dpa-pde-oxford.shinyapps.io/drug-monograph/alendronate) vs. placebo and followed for mean of 3.8 years
      * 7,765 women aged 65-89 years randomized to IV [zoledronic acid](https://dpa-pde-oxford.shinyapps.io/drug-monograph/zoledronic-acid) annually vs. placebo and followed for mean of 2.8 years

Randomized Trial

* + - no significant difference in postmenopausal breast cancer incidence in pooled analyses, or in individual trials
    - PubMed25111880JAMA internal medicine20141001JAMA Intern Med1741015501550 Reference - [mdc25111880pJAMA Intern Med 2014 Oct 1;174(10):1550](http://pubmed.ncbi.nlm.nih.gov/25111880?dopt=Abstract) , correction can be found in JAMA Intern Med 2014 Nov 1;174(11):1875
* **longer duration of breastfeeding associated with reduced risk for breast cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Meta-analysis[mnh12133652p t caph6994818t c pa9h6994818t c pbyh6994818t c pafh6994818t c pbeh6994818t c phch6994818t c pnyh6994818t c pnxh6994818t c pbth6994818t c ppbh6994818t c pcxh6994818t c pmdc12133652p t cLancet 2002 Jul 20;360(9328):187](http://pubmed.ncbi.nlm.nih.gov/12133652?dopt=Abstract)

studySummary2

* + based on meta-analysis of 47 studies comparing 50,302 women with breast cancer and 96,973 controls Meta-analysis
  + PubMed12133652Lancet (London, England)20020720Lancet3609328187187 Reference - [mnh12133652p t caph6994818t c pa9h6994818t c pbyh6994818t c pafh6994818t c pbeh6994818t c phch6994818t c pnyh6994818t c pnxh6994818t c pbth6994818t c ppbh6994818t c pcxh6994818t c pmdc12133652p t cLancet 2002 Jul 20;360(9328):187](http://pubmed.ncbi.nlm.nih.gov/12133652?dopt=Abstract) , commentary can be found in [mnh12531604p tmdc12531604p tLancet 2003 Jan 11;361(9352):176](http://pubmed.ncbi.nlm.nih.gov/12531604?dopt=Abstract) , Evidence-Based Medicine 2003 Mar-Apr;8(2):63
* see also [Hereditary Breast and Ovarian Cancer (HBOC) Syndromes](https://dpa-pde-oxford.shinyapps.io/condition/hereditary-breast-and-ovarian-cancer-hboc-syndromes)

Screening

* risk assessment for screening recommendations
  + for women without a strong family history suggesting inherited gene mutations, models to assess risk include the Gail model and the Breast Cancer Surveillance Consortium (BCSC) risk calculator
  + for women with a strong family history suggesting inherited gene mutations, models to assess risk include Tyrer-Cuzick, Claus, Ford, and Manual (for family history), and BRCAPRO or Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (based on likelihood of *BRCA* mutations)
  + indications for genetic evaluation and possible testing include a personal or family history suggestive of increased risk for mutation in *BRCA1* and *BRCA2* genes, or sufficient score on one of the risk stratification models to determine the need for genetic testing (including Ontario Family History Assessment Tool, Manchester Scoring System, Breast Cancer Genetics Referral Screening Tool, Pedigree Assessment Tool, and 7-question Family History Screening [FHS-7])
* screening recommendations from public health and professional organizations
  + for women at average risk
    - recommendations for mammography screening vary by age and organization
      * for women aged 40-49 years, recommendations vary
        + Canadian Task Force on Preventive Health Care (CTFPHC) does not recommend routine screening ([CTFPHC Weak recommendation, Moderate-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__CTFPHCGRADE))
        + United States Preventive Services Task Force (USPSTF) and American College of Physicians (ACP) recommend screening every 2 years if requested by informed patient ([USPSTF Grade C](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__SNIPPET-POINTER_1657691660))
        + National Comprehensive Cancer Network (NCCN), American College of Obstetricians and Gynecologists (ACOG), and American Cancer Society (ACS) recommend regular mammography screening

NCCN and ACOG recommend beginning at age 40 years ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

ACS recommends beginning at age 45 years ([ACS Strong recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACSGRADE)), annually for ages 45-49 with option to begin annual screening at age 40 years ([ACS Qualified recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACSGRADE))

* + - * + European Society for Medical Oncology (ESMO) states no consensus on role of screening ([26314782Ann Oncol 2015 Sep;26 Suppl 5:v8](http://pubmed.ncbi.nlm.nih.gov/26314782?dopt=Abstract))
      * for women aged 50-74 years, screening recommended with differences in frequency
        + USPSTF, CTFPHC, ESMO, and ACP recommend mammography screening every 2-3 years ([USPSTF Grade B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__SNIPPET-POINTER_1657691660) for women aged 50-74 years every 2 years; [CTFPHC Weak recommendation, Moderate-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__CTFPHCGRADE) for women aged 50-69 years every 2-3 years; [ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE) for women aged 50-69 years every 2 years)
        + ACS recommends annual mammography screening for women aged 50-54 years, with transition to biennial at age 55 and an option for continued annual screening ([ACS Qualified recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACSGRADE))
        + NCCN recommends annual mammography ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * for women ≥ 75 years old, recommendations vary as ACP does not recommend mammography screening, USPSTF states current evidence insufficient to assess benefits and harms ([USPSTF Grade I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__SNIPPET-POINTER_1657691660)), ACS and NCCN recommend continued screening as long as overall heath good and life expectancy ≥ 10 years ([ACS Qualified recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACSGRADE))
    - recommendations for screening with digital breast tomosynthesis (DBT) vary with the ACP recommending against screening with annual DBT, USPSTF concluding insufficient evidence to balance benefits and harms ([USPSTF Grade I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__SNIPPET-POINTER_1657691660)), and NCCN recommending consideration of annual DBT as an adjunct to mammography screening in women > 40 years old ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
    - recommendations for screening with clinical breast exam (CBE) vary across organizations
      * NCCN recommends annual CBE in women ≥ 40 years old ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * World Health Organization (WHO) states that, for women aged 50-69 years in limited resource settings with weak health systems where mammography screening is not cost-effective or feasible, CBE may be a promising screening approach ([WHO 2014 PDF](http://apps.who.int/iris/bitstream/10665/137339/1/9789241507936_eng.pdf?ua=1&ua=1))
      * USPSTF states current evidence is insufficient to assess additional benefits or harms of CBE when added to screening mammography for women ≥ 40 years old ([USPSTF Grade I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__SNIPPET-POINTER_1657691660))
      * CTFPHC and ACS do not recommend CBE, either alone or in conjunction with mammography, for women of any age ([CTFPHC Weak recommendation, Low-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__CTFPHCGRADE); [ACS Qualified recommendation](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ACSGRADE))
    - systematic breast self-exam is not recommended, but women should be aware of changes and discuss any with a clinician
    - screening with ultrasound and/or magnetic resonance imaging (MRI) not recommended
  + for women at increased risk
    - recommendations for screening differ by organization and level of risk
      * for women with known *BRCA*, *TP53*, or *PTEN* mutation or untested family member of known mutation carriers
        + USPSTF recommendations state earlier, more frequent, and/or more intensive breast cancer screening may reduce the risk of cancer or cancer-related death in asymptomatic women at increased risk for breast cancer due to mutations in *BRCA* genes
        + ACS recommends screening using mammography plus MRI every year starting at age 30 years
        + NCCN recommends

CBE, risk assessment, and risk-reduction counseling every 6-12 months from age 20 (TP53) or age 25 (BRCA and PTEN) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

annual MRI with contrast starting at age 20 (TP53), age 25 (BRCA), or age 30 (PTEN) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

annual mammography starting at age 30, but mammography may be started earlier if unable to perform MRI ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

* + - * for women with history of thoracic irradiation at young age; start 8-10 years after radiation therapy
        + for women currently < 25 years old, perform CBE, risk assessment, and risk-reduction counseling annually ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + for women currently ≥ 25 years old

perform CBE, risk assessment, and risk-reduction counseling every 6-12 months ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

perform MRI and mammography screening annually ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); consider adjunctive tomosynthesis annually ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

* + - * for women with lifetime risk > 20% due to models based on family history
        + starting at age increased risk determined, perform CBE, risk assessment, and risk-reduction counseling every 6-12 months ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + starting at age 10 years younger than earliest case in the family

perform mammography screening annually (but not before age 30 years) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); consider adjunctive tomosynthesis annually ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

recommend MRI annually (but not before age 25 years) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))

* + - * + ESMO recommends that for women with familial breast cancer, with or without proven *BRCA* mutations ([26314782Ann Oncol 2015 Sep;26 Suppl 5:v8](http://pubmed.ncbi.nlm.nih.gov/26314782?dopt=Abstract))

perform annual mammography screening plus or alternating with annual MRI every 6 months, beginning 10 years younger than earliest case in the family ([ESMO Grade A, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__ESMOGRADE))

no consensus on role of ultrasound in screening of women with increased risk

* + - * + ACS recommends screening using mammography plus MRI every year starting at age 30 years
      * for women with lifetime risk > 20% due to history of lobular carcinoma in situ (LCIS), atypical ductal hyperplasia (ADH), or atypical lobular hyperplasia (ALH), start at age at which high risk established
        + perform CBE, risk assessment, and risk-reduction counseling every 6-12 months ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + perform mammography screening annually (but not before age 30 years) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); consider adjunctive tomosynthesis annually ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + consider MRI annually (but not before age 25 years) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + ACS states that there is insufficient evidence to recommend for or against MRI screening as adjunct to mammography for women with LCIS, ADH, or ALH
      * for women ≥ 35 years old with 5-year risk of invasive breast cancer ≥ 1.7% by [Breast Cancer Risk Assessment Tool (Gail model)](https://www.cancer.gov/bcrisktool/); start at age indicated as increased risk
        + perform CBE, risk assessment, and risk-reduction counseling every 6-12 months ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + perform mammography screening annually ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE)); consider adjunctive tomosynthesis annually ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
      * for women with personal history of invasive breast cancer or ductal carcinoma in situ
        + perform annual mammography, do not screen reconstructed breast ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_0074d589/#GUID-E579FEA8-D57C-4429-80F8-CD049AFDB43E__NCCNGRADE))
        + ACS states that there is insufficient evidence to recommend for or against MRI screening as adjunct to mammography for women with history of breast cancer (including ductal carcinoma in situ)
* efficacy
  + mammography
    - screening associated with 15%-30% decrease in mortality from breast cancer but no significant difference in overall mortality
    - screening associated with 8%-10% false-positive callbacks for additional work-up
    - breast cancer may be overdiagnosed (breast cancer that will not cause death or symptoms in patient's lifetime) with mammography screening, but rate of overdiagnosis unclear
  + no completed randomized controlled trials of CBE vs. no other screening
  + 2 randomized controlled trials revealed no significant difference in breast cancer mortality, overall mortality, or stage at diagnosis between screening with breast self-exam vs. control
* shared decision making
  + benefits of screening include reduction in mortality due to breast cancer and earlier detection of breast cancer
  + potential harms include potential for false-positive results, false-negative results, unnecessary biopsies or treatment, chance of overdiagnosis, radiation exposure, and pain or discomfort from procedure
* see [Breast Cancer Screening](https://dpa-pde-oxford.shinyapps.io/prevention/breast-cancer-screening) for details