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Breast Cancer Prevention (PDQ®)–Health Professional Version

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Who Is at Risk?

Besides female sex, advancing age is the biggest risk factor for breast cancer. Reproductive factors that increase exposure to endogenous estrogen, such as early menarche and late menopause, increase risk, as does the use of combination estrogen-progesterone hormones after menopause. Nulliparity and alcohol consumption also are associated with increased risk.

Women with a family history or personal history of invasive breast cancer, ductal carcinoma *in situ* or lobular carcinoma *in situ*, or a history of breast biopsies that show benign proliferative disease have an increased risk of breast cancer. [1-4]

Increased breast density is associated with increased risk. It is often a heritable trait but is also seen more frequently in nulliparous women, women whose first pregnancy occurs late in life, and women who use postmenopausal hormones and alcohol.

Exposure to ionizing radiation, especially during puberty or young adulthood, and the inheritance of detrimental genetic mutations increase breast cancer risk.

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Overview

Note: The Overview section summarizes the published evidence on this topic. The rest of the summary describes the evidence in more detail.

Other PDQ summaries with information related to breast cancer prevention include the following:

- Breast Cancer Screening
- Breast Cancer Treatment
- Male Breast Cancer Treatment
- Breast Cancer Treatment During Pregnancy
- Levels of Evidence for Cancer Screening and Prevention Studies

Factors With Adequate Evidence of Increased Risk of Breast Cancer

Sex and age

Based on solid evidence, female sex and increasing age are

the major risk factors for the development of breast cancer.

Magnitude of Effect: Women have a lifetime risk of developing breast cancer that is approximately 100 times the risk for men. The short-term risk of breast cancer in a 70-year-old woman is about ten times that of a 30-year-old woman.

> **Study Design**: Many epidemiological trials.
>
> **Internal Validity**: Good.
>
> **Consistency**: Good.
>
> **External Validity**: Good.

Inherited risk

Based on solid evidence, women who have a family history of breast cancer, especially in a first-degree relative, have an increased risk of breast cancer.

Magnitude of Effect: Risk is doubled if a single first-degree relative is affected; risk is increased fivefold if two first-degree relatives are diagnosed.

> **Study Design**: Population studies, cohort studies, and case-control studies.
>
> **Internal Validity**: Good.
>
> **Consistency**: Good.
>
> **External Validity**: Good.

Based on solid evidence, women who inherit gene mutations associated with breast cancer have an increased risk.

Magnitude of Effect: Variable, depending on gene mutation, family history, and other risk factors affecting gene expression.

> **Study Design**: Cohort or case-control studies.
>
> **Internal Validity**: Good.
>
> **Consistency**: Good.
>
> **External Validity**: Good.

Breast density

Based on solid evidence, women with dense breasts have an increased risk of breast cancer. This is most often an inherent characteristic, to some extent modifiable by reproductive behavior, medications, and alcohol.[1]

Magnitude of Effect: Women with dense breasts have increased risk, proportionate to the degree of density. This increased relative risk (RR) ranges from 1.79 for women with slightly increased density to 4.64 for women with very dense breasts, compared with women who have the lowest breast density.[2]

Study Design: Cohort, case-control studies.

Internal Validity: Good.

Consistency: Good.

External Validity: Good.

Modifiable Factors With Adequate Evidence of Increased Risk of Breast Cancer

Menopausal hormone therapy (MHT)

Based on solid evidence, MHT is associated with an increased risk of developing breast cancer, especially hormone-sensitive cancers. Estrogen-progesterone use significantly increases breast cancer risk starting with 1 to 4 years of usage and increases with duration of use. For estrogen use alone, the breast cancer risk is less but also significant. The excess risk persists after cessation of MHT.

Study Design: Randomized controlled trials (RCTs), prospective studies and ecological observations.

Internal Validity: Good.

Consistency: Good.

External Validity: Good.

Combination hormone therapy

Based on solid evidence, combination hormone therapy (estrogen-progestin) is associated with an increased risk of developing breast cancer.

Magnitude of Effect: Approximately a 26% increase in incidence of invasive breast cancer; the number needed to produce one excess breast cancer is 237.

> **Study Design**: RCTs and ecological observations. Furthermore, cohort and ecological studies show that cessation of combination HT is associated with a decrease in rates of breast cancer.
>
> **Internal Validity**: Good.
>
> **Consistency**: Good.
>
> **External Validity**: Good.

Estrogen therapy

Based on solid evidence, estrogen therapy that began close to the time of menopause is associated with an increased risk of breast cancer. Estrogen therapy that began at or after menopause is associated with an increased risk of endometrial cancer and total cardiovascular disease, especially stroke.

Magnitude of Effect: The increased incidence of breast cancer associated with estrogen therapy that began at the time of menopause ranged from 17% to 33%, depending on duration of use. Breast cancer incidence in women who have undergone hysterectomy is 23% lower if estrogen use began many years after menopause.[3] There is a 39% increase in stroke (RR, 1.12; 95% confidence interval [CI], 1.1–1.77) and a 12% increase in cardiovascular disease (RR, 1.12; 95% CI, 1.01–1.24).[3]

> **Study Design**: RCTs and ecological observations.
>
> **Internal Validity**: Good.
>
> **Consistency**: Good, although in women who have undergone hysterectomy, estrogen use that began many years after menopause was associated with a decrease in breast cancer incidence.
>
> **External Validity**: Good.

Ionizing radiation

Based on solid evidence, exposure of the breast to ionizing

radiation is associated with an increased risk of developing breast cancer, starting 10 years after exposure and persisting lifelong. Risk depends on radiation dose and age at exposure, and is especially high if exposure occurs during puberty, when the breast develops.

Magnitude of Effect: Variable but approximately a sixfold increase overall.

> **Study Design**: Cohort or case-control studies.
>
> **Internal Validity**: Good.
>
> **Consistency**: Good.
>
> **External Validity**: Good.

Obesity

Based on solid evidence, obesity is associated with an increased breast cancer risk in postmenopausal women who have not used HT. It is uncertain whether weight reduction decreases the risk of breast cancer in women with obesity.

Magnitude of Effect: The Women's Health Initiative observational study of 85,917 postmenopausal women found body weight to be associated with breast cancer. Comparing women weighing more than 82.2 kg with those weighing less than 58.7 kg, the RR was 2.85 (95% CI, 1.81–4.49).

> **Study Design**: Case-control and cohort studies.
>
> **Internal Validity**: Good.
>
> **Consistency**: Good.
>
> **External Validity**: Good.

Alcohol

Based on solid evidence, alcohol consumption is associated with increased breast cancer risk in a dose-dependent fashion. It is uncertain whether decreasing alcohol intake by heavy drinkers reduces the risk.

Magnitude of Effect: The RR for women consuming approximately four alcoholic drinks per day compared with

nondrinkers is 1.32 (95% CI, 1.19–1.45). The RR increases by 7% (95% CI, 5.5%–8.7%) for each drink per day.

Study Design: Case-control and cohort studies.

Internal Validity: Good.

Consistency: Good.

External Validity: Good.

Factors With Adequate Evidence of Decreased Risk of Breast Cancer

Early pregnancy

Based on solid evidence, women who have a full-term pregnancy before age 20 years have decreased breast cancer risk.

Magnitude of Effect: 50% decrease in breast cancer, compared with nulliparous women or women who give birth after age 35 years.

Study Design: Case-control and cohort studies.

Internal Validity: Good.

Consistency: Good.

External Validity: Good.

Breast-feeding

Based on solid evidence, women who breast-feed have a decreased risk of breast cancer.

Magnitude of Effect: The RR of breast cancer is decreased 4.3% for every 12 months of breast-feeding, in addition to 7% for each birth.[4]

Study Design: Case-control and cohort studies.

Internal Validity: Good.

Consistency: Good.

External Validity: Good.

Exercise

Based on solid evidence, physical exercise is associated with reduced breast cancer risk.

Magnitude of Effect: Average RR reduction association is 20% for both postmenopausal and premenopausal women and affects the risk of both hormone-sensitive and hormone-resistant cancers.

> **Study Design**: Prospective observational and retrospective studies.
>
> **Internal Validity**: Good.
>
> **Consistency**: Good.
>
> **External Validity**: Good.

Interventions With Adequate Evidence of Decreased Risk of Breast Cancer

Selective estrogen receptor modulators (SERMs): Benefits

Based on solid evidence, tamoxifen and raloxifene reduce the incidence of breast cancer in postmenopausal women, and tamoxifen reduces the risk of breast cancer in high-risk premenopausal women. The effects observed for tamoxifen and raloxifene persist several years after active treatment is discontinued, with longer duration of effect noted for tamoxifen than for raloxifene.[5]

All fractures were reduced by SERMs, primarily noted with raloxifene but not with tamoxifen. Reductions in vertebral fractures (34% reduction) and small reductions in nonvertebral fractures (7%) were noted.[5]

Magnitude of Effect: Tamoxifen reduced the incidence of estrogen receptor–positive (ER-positive) breast cancer and ductal carcinoma *in situ* (DCIS) in high-risk women by about 30% to 50% over 5 years of treatment. The reduction in ER-positive invasive breast cancer was maintained for at least 16 years after starting treatment (11 years after tamoxifen cessation). Breast cancer mortality was not affected.[6]

Study Design: RCTs.

Internal Validity: Good.

Consistency: Good.

External Validity: Good.

Selective estrogen receptor modulators: Harms

Based on solid evidence, tamoxifen increases the risk of endometrial cancer, thrombotic vascular events (i.e., pulmonary embolism, stroke, and deep venous thrombosis), and cataracts. The endometrial cancer risk persists for 5 years after tamoxifen cessation but not the risk of vascular events or cataracts. Based on solid evidence, raloxifene also increases venous pulmonary embolism and deep venous thrombosis but not endometrial cancer.

Magnitude of Effect: Meta-analysis showed RR of 2.4 (95% CI, 1.5–4.0) for endometrial cancer and 1.9 (95% CI, 1.4–2.6) for venous thromboembolic events. Meta-analysis showed the hazard ratio (HR) for endometrial cancer was 2.18 (95% CI, 1.39–3.42) for tamoxifen and 1.09 (95% CI, 0.74–1.62) for raloxifene. Overall, HR for venous thromboembolic events was 1.73 (95% CI, 1.47–2.05). Harms were significantly higher in women over 50 years than in younger women.

Study Design: RCTs.

Internal Validity: Good.

Consistency: Good.

External Validity: Good.

Aromatase inhibitors or inactivators: Benefits

Based on solid evidence, aromatase inhibitors or inactivators (AIs) reduce breast cancer incidence in postmenopausal women who have an increased risk.

Magnitude of Effect: In postmenopausal women treated with adjuvant tamoxifen for hormone-sensitive breast cancer, subsequent therapy with AIs reduced the incidence of new primary breast cancers by 50% to 67%, compared with controls. In postmenopausal women at high risk of developing

breast cancer, 3 years of exemestane treatment reduced breast cancer incidence by 65%, compared with controls. A similar trial of 5 years of anastrozole treatment reduced breast cancer incidence by 53%, an effect persisting at 11 years.[7] After a median follow-up of 35 months, women aged 35 years and older who had at least one risk factor (age >60 years, a Gail 5-year risk >1.66%, or DCIS with mastectomy) and who took 25 mg of exemestane daily had a decreased risk of invasive breast cancer (HR, 0.35; 95% CI, 0.18–0.70) compared with controls. The absolute risk reduction was 21 cancers avoided out of 2,280 participants over 35 months. The number needed to treat was about 100.[8]

Study Design: Multiple RCTs.

Internal Validity: Good.

Consistency: Good.

External Validity: Good.

Aromatase inhibitors or inactivators: Harms

Based on fair evidence from a single RCT of 4,560 women over 35 months, exemestane is associated with hot flashes and fatigue compared with placebo.[8,9]

Magnitude of Effect: The absolute increase in hot flashes was 8% and the absolute increase in fatigue was 2%.

Study Design: One RCT.

Internal Validity: Good.

Consistency: Good.

External Validity: Good for women who meet inclusion criteria.

Prophylactic mastectomy: Benefits

Based on solid evidence, bilateral prophylactic mastectomy reduces the risk of breast cancer in women with a strong family history, and most women experience relief from anxiety about breast cancer risk. Based on strong evidence, bilateral prophylactic mastectomy reduces the risk of breast cancer in women with a strong family history of breast cancer or other

factors putting them at high risk (e.g., certain previous chest-wall radiation or previous personal history of breast cancer). Most women experience relief from anxiety about breast cancer risk after undergoing prophylactic mastectomy. Although some studies have suggested a survival benefit associated with contralateral prophylactic mastectomy, these results are generally attributed to selection bias, and there are no high-quality studies demonstrating a clear survival advantage. For more information, see Genetics of Breast and Gynecologic Cancers.

Magnitude of Effect: Breast cancer risk after bilateral prophylactic mastectomy in women at high risk may be reduced as much as 90%.

> **Study Design**: Evidence obtained from case-control and cohort studies.
>
> **Internal Validity**: Good.
>
> **Consistency**: Good.
>
> **External Validity**: Good.

Prophylactic oophorectomy or ovarian ablation: Benefits

Based on solid evidence, prophylactic oophorectomy in premenopausal women with a *BRCA* gene mutation is associated with decreased breast cancer incidence. Similar results are seen for oophorectomy or ovarian ablation in normal premenopausal women and in women with increased breast cancer risk resulting from thoracic irradiation.

Magnitude of Effect: Breast cancer incidence may be decreased by up to 50%.

> **Study Design**: Observational, case-control, and cohort studies.
>
> **Internal Validity**: Good.
>
> **Consistency**: Good.
>
> **External Validity**: Good.

Prophylactic oophorectomy or ovarian ablation: Harms

Based on solid evidence, castration may cause the abrupt onset of menopausal symptoms such as hot flashes, insomnia, anxiety, and depression. Long-term effects include decreased libido, vaginal dryness, and decreased bone mineral density.

Magnitude of Effect: Nearly all women experience some sleep disturbances, mood changes, hot flashes, and bone demineralization, but the severity of these symptoms varies greatly.

> **Study Design**: Observational, case-control, and cohort studies.
>
> **Internal Validity**: Good.
>
> **Consistency**: Good.
>
> **External Validity**: Good.

Estrogen use by women with previous hysterectomy: Benefits

Based on fair evidence, women who have undergone a previous hysterectomy and who are treated with conjugated equine estrogen have a lower incidence of breast cancer.[3]

Magnitude of Effect: After 6.8 years, breast cancer incidence was 23% lower in women treated with estrogen in an RCT (0.27% per year, with a median of 5.9 years of use, compared with 0.35% per year among those taking a placebo). However, the risk was 30% higher in women treated with estrogen in an observational study. The difference in these results may be explained by different screening behaviors of the women in these studies.

> **Study Design**: One RCT, observational studies.
>
> **Internal Validity**: Fair.
>
> **Consistency**: Poor.
>
> **External Validity**: Poor.

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Incidence and Mortality

Breast cancer is the most frequently diagnosed nonskin malignancy in U.S. women and is second only to lung cancer in cancer deaths in women.[1] Estimates for the U.S. population in 2025 are that 316,950 women will be diagnosed with breast cancer, with 42,170 deaths from this disease, and 2,800 men will be diagnosed with breast cancer, with 510 deaths from this disease.[1] Breast cancer incidence in women had been gradually increasing for many years until the early 2000s, when it decreased rapidly, coincident with a drop in postmenopausal hormone therapy use. However, since the initial decrease between 2000 and 2005, there has been a small but steady increase in incidence, approaching incidence rates seen before that decrease.[2]

According to data from the Surveillance, Epidemiology, and End Results (SEER) Program, breast cancer mortality rates declined by 44% from 1989 to 2022. However, mortality rates in Black women remain about 38% higher than in White women.[1] Incidence rates are now similar between Black and White women.

The major risk factor for breast cancer is advancing age. A 30-year-old woman has about a 1 in 175 chance of being diagnosed with breast cancer in the next 10 years, whereas a 70-year-old woman has a 1 in 9 chance over the same time period.[2]

Screening by mammography decreases breast cancer mortality by identifying cases for treatment at an earlier stage. However, screening also identifies more cases than would become symptomatic in a woman's lifetime, so screening increases breast cancer incidence. For more information, see the Overdiagnosis section in Breast Cancer Screening.

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Etiology and Pathogenesis of Breast Cancer

Breast cancer develops when a series of genetic mutations occurs.[1] Some cancer-associated mutations are inherited, but most are somatic mutations that occur as random events during a woman's lifetime. Initially, mutations do not change the histological appearance of the tissue, but accumulated mutations will result in hyperplasia, dysplasia, carcinoma *in situ*, and eventually, invasive cancer.[2] The longer a woman lives, the more somatic mutations occur, and the more likely it is that these mutations will produce populations of cells that may eventually become malignancies. Estrogen and progestin hormones, whether endogenous or exogenous, stimulate growth and proliferation of breast cells, perhaps via growth factors such as transforming growth factor-alpha.[3] The stimulation by these hormones can promote the development and proliferation of breast cancer cells.

International variation in breast cancer rates may be explained by differences in genetics, reproductive factors, diet, exercise, and screening behavior. The relative importance of these factors was demonstrated in a study of breast cancer incidence of Japanese immigrants to the United States. Whereas Japanese women in Japan had a low breast cancer incidence, Japanese women in the United States had a much higher breast cancer incidence, similar to that of American women, within two generations of migration.[4-6]

References

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Endogenous Estrogen

Endogenous estrogen plays a role in the development of breast cancer. Women whose menarche occurred at or before age 11 years have about a 20% greater chance of developing breast cancer than do women whose menarche occurred at or after age 14 years.[1-3] Women who experience late menopause also have an increased risk. Women who develop breast cancer tend to have higher endogenous estrogen and androgen levels.[3-7]

Conversely, women who experience premature menopause have a lower risk of breast cancer. Following ovarian ablation, breast cancer risk may be reduced as much as 75% depending on age, weight, and parity, with the greatest reduction for young, thin, nulliparous women.[8-11] The removal of one ovary also reduces the risk of breast cancer but to a lesser degree.[12]

Other hormonal changes also influence breast cancer risk. For more information, see the sections on Early Pregnancy and Breast-feeding in the Factors With Adequate Evidence of Decreased Risk of Breast Cancer section.

The interaction of endogenous estrogen levels, insulin levels, and obesity—all of which affect breast cancer risk—are poorly understood but suggest strategies for interventions to decrease that risk. It is likely that reproductive risk factors interact with predisposing genotypes. For example, in the Nurses' Health Study,[13] the associations between age at first birth, menarche, and menopause and the development of breast cancer were observed only among women without a family history of breast cancer in a mother or sister.

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Inherited Risk

Breast cancer risk increases in women with a positive family history, particularly if first-degree relatives are affected.[1] The following risk assessment models, derived from databases, cohort, and case-control studies, quantitate this risk:

- Breast Cancer Risk Assessment Tool [Gail Model].
- Breast Cancer Surveillance Consortium [BCSC] Risk Calculator.
- Breast Cancer Referral Screening Tool [B-RST].
- Hall Detailed Breast Risk Calculator.
- IBIS Breast Cancer Risk Calculator Tool.

Specific abnormal alleles are associated with approximately 5% of breast cancers. For more information, see Genetics of Breast and Gynecologic Cancers. Mutations in *BRCA* genes are inherited in an autosomal dominant fashion and are highly penetrant in causing cancer, often at a younger age.[2-4] Family history and mutation location within the *BRCA1* or *BRCA2* gene may contribute to the risk of cancer development among those with an inherited predisposition to breast cancer.[5] The lifetime risk of breast cancer is 55% to 65% for *BRCA1* mutation carriers and 45% to 47% for *BRCA2* mutation carriers.[6,7] In comparison, the lifetime risk of breast cancer is 13% in the general population.[8]

Some women inherit a susceptibility to mutagens or growth factors, which increase breast cancer risk.[9,10] For more information, see the Ionizing Radiation Exposure section.

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Increased Breast Density

Widespread use of screening mammograms has demonstrated great variability in breast tissue density. Women with a greater proportion of dense tissue have a higher incidence of breast cancer. Mammographic density also confounds the identification of cancers by mammograms. The extent of increased risk was described in a report of three nested case-control studies in screened populations with 1,112 matched case-control pairs. Compared with women with density comprising less than 10% of breast tissue, women with

density in 75% or more of their breast had an increased risk of breast cancer (odds ratio [OR], 4.7; 95% confidence interval [CI], 3.0–7.4), whether the cancer was detected by screening (OR, 3.5; 95% CI, 2.0–6.2) or detected less than 12 months after a negative screening examination (OR, 17.8; 95% CI, 4.8–65.9). Increased risk of breast cancer, whether detected by screening or other means, persisted for at least 8 years after study entry and was greater in younger women than in older women. For women younger than the median age of 56 years, 26% of all breast cancers and 50% of cancers detected less than 12 months after a negative screening test were identified in women with mammographic breast density of 50% or more. [1,2]

Compared with women who have the lowest breast density, women with dense breasts have increased risk, proportionate to the degree of density. This increased relative risk ranges from 1.79 for women with slightly increased breast density to 4.64 for women with very dense breasts.[3] There is no increased risk of breast cancer mortality among women with dense breast tissue.[4]

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Factors With Adequate Evidence of Increased Risk of Breast Cancer

Menopausal Hormone Therapy (MHT)

MHT has been used to alleviate hot flashes and other symptoms associated with menopause. Single-agent estrogen is associated with an increased incidence of uterine cancer, but estrogen-progesterone use is not. Women with intact uteri are prescribed the combination, with oral progesterone given continuously or intermittently, or intrauterine progesterone delivered locally by intrauterine device (IUD). Estrogen therapy that began close to the time of menopause is associated with an increased risk of developing breast cancer. Estrogen therapy that began at or after menopause is associated with an increased risk of developing endometrial cancer and total cardiovascular disease, especially stroke.[1] Women who have undergone hysterectomy often take unopposed estrogen.

In 1997, 51 epidemiological studies were reanalyzed, encompassing more than 150,000 women, and it was found that MHT was associated with increased breast cancer risk.[2]

The Heart and Estrogen/Progestin Replacement Study, published in 2002, extended these findings by randomly assigning 2,763 women, with coronary heart disease (median age, 67), to receive either estrogen-progestin or placebo.[3] At 6.8 years of follow-up, breast cancer incidence was higher for hormone users (relative risk [RR], 1.27; 95% confidence interval [CI], 0.84–1.94).

The Women's Health Initiative (WHI), also published in 2002, randomly assigned over 16,000 women aged 50 to 79 years with intact uteri to receive either estrogen-progesterone or placebo.[4] The WHI was terminated early because the risk for coronary heart disease was unchanged, but the risk for stroke was increased with MHT. The incidence of invasive breast cancer was also increased in women who had taken MHT (hazard ratio, 1.24; 95% CI, 10.2–1.50). In addition to the randomized trial, the WHI conducted an observational study that examined women aged 50 to 79 years and found an

increased risk of breast cancer, especially for those starting MHT at menopause. The WHI also randomly assigned 10,739 women who had undergone hysterectomy and were aged 50 to 79 years to receive either estrogen or placebo. Estrogen use was associated with an increased risk of stroke, so the trial was stopped early. After the publication of the WHI results, MHT use dropped worldwide, and breast cancer risk declined in countries where MHT usage had been high.

In 2003, the Cancer Surveillance System of Puget Sound reported results of a population-based survey of 965 women with breast cancer and 1,007 controls.[5] This study showed a 1.7-fold increased risk of invasive breast cancer with estrogen-progesterone use, but not with estrogen use alone.

While the association between estrogen-progesterone MHT and breast cancer risk was consistently observed, questions arose about the use of estrogen-only in women who had undergone hysterectomy, especially about the timing of therapy in relation to menopause and the participation in screening activities by MHT users.

The United Kingdom Million Women Study [6] recruited 1,084,110 women aged 50 to 64 years between 1996 and 2001. This study obtained information about MHT use, along with other health information, and followed them for breast cancer incidence and death. One-half of the women had used MHT. At 2.6 years of follow up, there were 9,364 invasive breast cancers, and at 4.1 years, there were 637 breast cancer deaths. At recruitment, current MHT users were more likely than were never-users to develop breast cancer (adjusted RR, 1.66; 95% CI, 1.58–1.75; $P < .0001$) and to die from the disease (adjusted RR, 1.22; 95% CI, 1.00–1.48; $P = .05$). Past MHT users had no increased risk of incident breast cancer (odds ratio [OR], 1.01; 95% CI, 0.94–1.09) or fatal breast cancer (OR, 1.05; 95% CI, 0.82–1.34). Incidence was increased for current users of estrogen (RR, 1.30; 95% CI, 1.21–1.40; $P < .0001$), combined MHT (RR, 2.00; 95% CI, 1.88–2.12; $P < .0001$), and tibolone (RR, 1.45; 95% CI, 1.25–1.68; $P < .0001$). The magnitude of the associated risk was greater for combined MHT than for other types of MHT ($P < .0001$). Tibolone is approved for use to

manage menopausal symptoms or to prevent osteoporosis in many countries. However, it is not approved for use in Canada or the United States.

A population-based survey of 965 women with breast cancer and 1,007 controls was conducted by the Cancer Surveillance System of Puget Sound. It showed that combined MHT users had a 1.7-fold increased risk of invasive breast cancer, whereas estrogen-only users did not.[5]

In 2019, the Collaborative Group on Hormonal Factors in Breast Cancer reported results of a meta-analysis of 24 prospective and 34 retrospective studies of MHT and breast cancer risk, encompassing 143,887 women who developed breast cancer and 424,972 controls. Overall, MHT users had higher breast cancer risk, especially for hormone-sensitive tumors.[7]

Table 1. Breast Cancer Risk Among Menopausal Hormone Therapy Users[a]

	Years 1–4 of Use	Years 5–14 of Use
Estrogen-progesterone	RR, 1.60 (95% CI, 1.52–1.62)	RR, 2.08 (95% CI, 2.02–2.15)
Estrogen-only	RR, 1.17 (95% CI, 1.10–1.26)	RR, 1.33 (95% CI, 1.28–1.37)

CI = confidence interval; RR = relative risk.

[a][7]

The associations between MHT and breast cancer were weaker for women starting MHT after age 60 years and for women with obesity. Women with obesity had minimal risk from estrogen MHT that began after age 60 years. In summary, women of average weight who used 5 years of MHT starting at 50 years have an increased risk of breast cancer

incidence of 1 in 50 users for estrogen-progesterone, 1 in 70 users for estrogen plus intermittent progesterone, and 1 in 200 users for estrogen-only products.

This meta-analysis, confirming and expanding the understanding of estrogen-progesterone risk of breast cancer, also resolves the question of estrogen use in women who have undergone hysterectomy. If the estrogen use began at menopause, it is associated with an increase in breast cancer risk, but not if it began many years later. These findings, as well as the documented increase in stroke risk with estrogen therapy, should be considered when reviewing options to treat.

In 2022, an evidence review concluded that the use of combined estrogen and progestin for the primary prevention of chronic disease (i.e., cardiovascular disease, cancer, osteoporosis, and fracture) in postmenopausal women with an intact uterus was associated with some benefits. However, this combination therapy was also associated with an increased risk of harms. Therefore, it has no net benefit. Moreover, the systematic review concluded with moderate certainty that the use of estrogen alone for the primary prevention of chronic diseases in postmenopausal women who had a hysterectomy also has no net benefit.[8]

Ionizing Radiation Exposure

A well-established relationship exists between exposure to ionizing radiation and subsequent breast cancer.[9] Excess breast cancer risk has been observed in association with atomic bomb exposure, frequent fluoroscopy for tuberculosis, and radiation therapy for acne, tinea, thymic enlargement, postpartum mastitis, and lymphoma. Risk is higher for the young, especially around puberty. An estimate of the risk of breast cancer associated with medical radiology puts the figure at less than 1% of all breast cancer cases.[10] However, it has been theorized that certain populations, such as *AT* heterozygotes, are at an increased risk of breast cancer from radiation exposure.[11] A large cohort study of women who carry mutations of *BRCA1* or *BRCA2* concluded that chest x-

rays, especially before age 20 years increased their risk of breast cancer beyond already increased levels (RR, 1.54; 95% CI, 1.1–2.1).[12]

Women treated for Hodgkin lymphoma with mantle radiation by age 16 years have a subsequent risk up to 35% of developing breast cancer by age 40 years.[13-15] Higher radiation doses (median dose, 40 Gy in breast cancer cases) and treatment between the ages of 10 and 16 years are associated with higher risk.[13] Unlike the risk for secondary leukemia, the risk of treatment-related breast cancer does not abate with duration of follow-up, persisting more than 25 years after treatment.[13,15,16] In these studies, most patients (85%–100%) who developed breast cancer did so either within the field of radiation or at the margin.[13,14,16] A Dutch study examined 48 women who developed breast cancer at least 5 years after treatment for Hodgkin disease and compared them with 175 matched female Hodgkin disease patients who did not develop breast cancer. Patients treated with chemotherapy and mantle radiation were less likely to develop breast cancer than were those treated with mantle radiation alone, possibly because of chemotherapy-induced ovarian suppression (RR, 0.06; 95% CI, 0.01–0.45).[17] Another study of 105 radiation-associated breast cancer patients and 266 age-matched and radiation-matched controls showed a similar protective effect for ovarian radiation.[15] These studies suggest that reduction of ovarian hormones limits the proliferation of breast tissue with radiation-induced mutations.[15]

The question arises whether breast cancer patients treated with lumpectomy and radiation therapy (L-RT) are at higher risk for second breast malignancies or other malignancies than are those treated by mastectomy. Outcomes of 1,029 L-RT patients were compared with outcomes of 1,387 patients who underwent mastectomies. After a median follow-up of 15 years, there was no difference in the risk of second malignancies.[18] Further evidence from three RCTs is also reassuring. One report of 1,851 women randomly assigned to undergo total mastectomy, lumpectomy alone, or L-RT showed rates of contralateral breast cancer to be 8.5%, 8.8%, and

9.4%, respectively.[19] Another study of 701 women randomly assigned to undergo radical mastectomy or breast-conserving surgery followed by radiation therapy demonstrated the rate of contralateral breast carcinomas per 100 woman-years to be 10.2 versus 8.7, respectively.[20] The third study compared 25-year outcomes of 1,665 women randomly assigned to undergo radical mastectomy, total mastectomy, or total mastectomy with radiation. There was no significant difference in the rate of contralateral breast cancer according to treatment group, and the overall rate was 6%.[21]

Obesity

Obesity is associated with increased breast cancer risk, especially among postmenopausal women who do not use hormone therapy (HT). The WHI observed 85,917 women aged 50 to 79 years and collected information on weight history and known risk factors for breast cancer.[22,23] Height, weight, and waist and hip circumferences were measured. With a median follow-up of 34.8 months, 1,030 of the women developed invasive breast cancer. Among the women who never used HT, increased breast cancer risk was associated with weight at entry, body mass index (BMI) at entry, BMI at age 50 years, maximum BMI, adult and postmenopausal weight change, and waist and hip circumferences. Weight was the strongest predictor, with a RR of 2.85 (95% CI, 1.81–4.49) for women weighing more than 82.2 kg, compared with those weighing less than 58.7 kg.

The association between obesity, diabetes, and insulin levels with breast cancer risk have been studied but not clearly defined. The British Women's Heart and Health Study of women aged 60 to 79 years compared 151 women who had a diagnosis of breast cancer with 3,690 women who did not. The age-adjusted OR was 1.34 (95% CI, 1.02–1.77) for each unit increase in log(e) insulin level among nondiabetic women. The association was observed, after adjustment for confounders and for potential mediating factors, for both pre- and postmenopausal breast cancers. In addition, fasting glucose level, homeostatic model assessment score (the product of fasting glucose and insulin levels divided by 22.5), diabetes,

and a history of gestational glycosuria or diabetes were also associated with breast cancer.[24]

Alcohol

Alcohol consumption increases the risk of breast cancer. A British meta-analysis included individual data from 53 case-control and cohort studies.[25] Compared with the RR of breast cancer for women who reported no alcohol consumption, the RR of breast cancer was 1.32 (95% CI, 1.19–1.45; $P < .001$) for women consuming 35 g to 44 g of alcohol per day and 1.46 (95% CI, 1.33–1.61; $P < .001$) for those consuming at least 45 g of alcohol per day. The RR of breast cancer increases by about 7% (95% CI, 5.5%–8.7%; $P < .001$) for each 10 g of alcohol (i.e., one drink) consumed per day. These findings persist after stratification for race, education, family history, age at menarche, height, weight, BMI, breast-feeding, oral contraceptive use, menopausal hormone use and type, and age at menopause.

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Factors With Adequate Evidence of Decreased Risk of Breast Cancer

Early Pregnancy

Childbirth is followed by an increase in risk of breast cancer for several years, and then a long-term reduction in risk, which is greater for younger women.[1-3] In one study, women who experienced a first full-term pregnancy before age 20 years were half as likely to develop breast cancer as nulliparous women or women whose first full-term pregnancy occurred at age 35 years or older.[4,5]

The effect of childbirth on breast cancer risk was demonstrated by the International Premenopausal Breast Cancer Collaborative Group, which undertook a pooled analysis of individual-level data from about 890,000 women from 15 prospective cohort studies. When compared with

nulliparous women, parous women had an increased risk of developing both estrogen receptor–positive (ER–positive) and estrogen receptor–negative (ER–negative) breast cancer for up to 20 years after childbirth. However, after about 24 years, the risk of developing ER–positive breast cancer decreased, but the risk of developing ER–negative breast cancer remained elevated. Thus, the association between parity and breast cancer risk is complex and appears to be influenced by the time period after childbirth, as well as tumor phenotype.[6]

Breast-feeding

Breast-feeding is associated with a decreased risk of breast cancer.[7] A reanalysis of individual data from 47 epidemiological studies in 30 countries of 50,302 women with breast cancer and 96,973 controls revealed that breast cancer incidence was lower in parous women who had ever breast-fed than in parous women who had not. It was also proportionate to duration of breast-feeding.[8] The relative risk (RR) of breast cancer decreased by 4.3% (95%, confidence interval [CI], 2.9%–5.8%; $P < .0001$) for every 12 months of breast-feeding in addition to a decrease of 7.0% (95% CI, 5.0%–9.0%; $P < .0001$) for each birth.

Exercise

Many studies have shown an associated benefit between physical exercise and breast cancer risk. A French study of 59,308 women, averaging 8.5 years postmenopause, found that recreational activity greater than 12 metabolic equivalent task (MET) h/wk was associated with decreased risk of invasive breast cancer (hazard ratio [HR], 0.9; 95% CI, 0.83–0.99).[9] The Nurses' Health Study included 95,396 postmenopausal women and found that women who exercised more than 27 MET h/wk (equivalent to 1 h/d of brisk walking) had decreased breast cancer incidence compared with those who had fewer than 3 MET h/wk (HR, 0.85; 95% CI, 0.78–0.93; $P < .001$ for trend). There was no difference in the association between exercise and breast cancer risk for hormone-positive or hormone-negative cancers.[10] Two meta-analyses yielded the same conclusions. One meta-analysis included 38 prospective trials performed from 1987 to 2014. The summary RR was 0.88 (95%

CI, 0.85–0.90); results were similar for hormone-positive or hormone-negative cancers.[11] Another meta-analysis reviewed 139 studies encompassing 236,955 women with 3,963 controls. Women who exercised had a significant decrease in breast cancer (odds ratio, 0.78; 95% CI, 0.76–0.81), with a similar effect size for premenopausal and postmenopausal women.[12]

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Interventions With Adequate Evidence of Benefit

Selective Estrogen Receptor Modulators (SERMs)

Tamoxifen

Tamoxifen is used to treat metastatic breast cancer and to suppress local recurrences and new primary breast cancers after surgical excision of breast cancer.[1] Tamoxifen also maintains bone density among postmenopausal women with breast cancer.[2-6] Adverse effects include hot flashes, venous thromboembolic events, and endometrial cancer.[7-9]

The Breast Cancer Prevention Trial (BCPT) randomly assigned

13,388 patients at elevated risk of breast cancer to receive tamoxifen or placebo.[10,11] The study was closed early because the incidence of breast cancer for the tamoxifen group was 49% lower than for the control group (85 vs. 154 invasive breast cancer cases and 31 vs. 59 *in situ* cases at 4 years). Tamoxifen-treated women also had fewer fractures (47 vs. 71) but more endometrial cancer (33 vs. 14 cases) and thrombotic events (99 vs. 70), including pulmonary emboli (17 vs. 6).[11]

An update of the BCPT results after 7 years of follow-up confirmed and extended those results.[12] Benefits and risks of tamoxifen were not significantly different from those in the original report, with persistent benefit of fewer fractures and persistent increased risk of endometrial cancer, thrombosis, and cataract surgery. No overall mortality benefit was observed after 7 years of follow-up (relative risk [RR], 1.10; 95% confidence interval [CI], 0.85–1.43).

Three other trials of tamoxifen for primary prevention of breast cancer have been completed.[13-15]

- A study in the United Kingdom [13] enrolled 2,471 women at increased breast cancer risk because of a family history of breast and/or ovarian cancer. Risk of estrogen receptor–positive (ER-positive) breast cancer was significantly reduced in the tamoxifen arm (hazard ratio [HR], 0.61; 95% CI, 0.43–0.86), an effect noted predominantly in the posttreatment period. Overall, tamoxifen was associated with decreased breast cancer risk at 13 years (HR, 0.78; 95% CI, 0.58–1.04) but not at 6 years (RR, 1.06).[16]
- An Italian study [14] focused on 5,408 women who had undergone hysterectomy and who were described as low to normal risk. After nearly 4 years of follow-up, no protective effect of tamoxifen was observed. Longer follow-up and subgroup analysis in this trial found a protective effect of tamoxifen among women at high risk for hormone receptor–positive breast cancer (RR, 0.24; 95% CI, 0.10–0.59) and among women who were taking HT during the trial (RR, 0.43; 95% CI, 0.20–0.95).[17,18]

- The International Breast Cancer Intervention Study (IBIS-I) randomly assigned 7,152 women aged 35 to 70 years who were at an increased risk of breast cancer to receive tamoxifen (20 mg/day) or placebo for 5 years.[15] After a median follow-up of 50 months, fewer tamoxifen-treated women had developed invasive or *in situ* breast cancer (absolute rate, 4.6 vs. 6.75 per 1,000 woman-years; risk reduction, 32%; 95% CI, 8%–50%). The RR reduction in ER-positive invasive breast cancer was 31%; there was no reduction in estrogen receptor–negative (ER-negative) cancers. The nonsignificant increase in all-cause mortality in the tamoxifen group (25 vs. 11; $P = .028$) was attributed to chance. The beneficial effect of tamoxifen on breast cancer persisted beyond active treatment; 46 months after the 5-year treatment, fewer women in the tamoxifen arm developed breast cancer (142 vs. 195 cases; RR, 0.73; 95% CI, 0.58–0.91).[19]

A meta-analysis of these primary prevention tamoxifen trials showed a 38% reduction in the incidence of breast cancer without statistically significant heterogeneity.[9] Incidence rates of ER-positive tumors were reduced by 48%. Rates of endometrial cancer were increased (consensus RR, 2.4; 95% CI, 1.5–4.0), as were venous thromboembolic events (RR, 1.9; 95% CI, 1.4–2.6). None of these primary prevention trials was designed to detect differences in breast cancer mortality.

The Cochrane Database of Systematic Reviews found that tamoxifen administered at the standard dose of 20 mg/day for 5 years is effective in decreasing breast cancer incidence, but the increased risk of toxicity has limited its broad use.[20] This finding warrants further investigation because the clinical implications of the lower dose, whether it may prevent cancer or improve mortality, was not studied.

Women with a history of ductal carcinoma *in situ* (DCIS) are at increased risk of contralateral breast cancer. The National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-24 addressed the management of these patients. Women were randomly assigned to receive lumpectomy and radiation therapy either with or without adjuvant tamoxifen. At 6 years,

the tamoxifen-treated women had fewer invasive and *in situ* breast cancers (8.2% vs. 13.4%; RR, 0.63; 95% CI, 0.47–0.83). The risk of contralateral breast cancer was also lower in women treated with tamoxifen (RR, 0.49; 95% CI, 0.26–0.87). [21]

Low-dose tamoxifen

The above-referenced clinical trials assessed tamoxifen use at a dose of 20 mg per day taken for 5 years. Because of the toxicity associated with tamoxifen and low adherence rates, several recent studies have examined the effects of lower-dose tamoxifen. In a double-blind, placebo-controlled, randomized controlled trial, researchers at the Karolinska Institutet found that a lower dose of 2.5 mg was similarly effective in reducing breast density as was a 20 mg dose. This effect was most pronounced in premenopausal women. In addition, vasomotor symptoms declined as the dose of tamoxifen decreased. The authors postulated that decreased mammographic density may be a surrogate for response to tamoxifen therapy and that adherence may improve with less severe symptoms.[22]

The TAM-01 randomized, placebo-controlled, double-blind study examined the use of low-dose (5 mg) tamoxifen as a strategy to prevent invasive breast cancer.[23] The study enrolled 500 women aged 75 years and younger with hormone-sensitive (67%) or unknown breast intraepithelial neoplasia, including atypical ductal hyperplasia, lobular carcinoma *in situ*, and DCIS (69%); 60% of the women were postmenopausal. Patients in the treatment group received tamoxifen 5 mg per day for 3 years. Of those with DCIS, 45% received radiation therapy. The following results were reported:

- After a median follow-up of 9.7 years, there were 25 breast cancers in the tamoxifen group (41 invasive cancers) and 41 in the placebo group (59 invasive) (HR, 0.58; 95% CI, 0.35–0.95; log-rank P = .03).
- For contralateral breast cancers, there were 6 events in the tamoxifen group and 16 in the placebo group (HR, 0.36;

95% CI, 0.14–0.92; *P* = .025). During the 3-year treatment period, there were 12 serious adverse events with tamoxifen and 16 with placebo. There was one deep vein thrombosis and one stage I endometrial cancer with tamoxifen treatment and one pulmonary embolism with placebo. A limitation of this study is the small sample size.

- Post-hoc sub-group analyses suggested possible clinically important differences in effects by menopausal status. The study was also not powered to assess differences in effect by DCIS versus non-DCIS breast disease. However, particularly in the United States, DCIS is typically managed differently than atypia.

Raloxifene

Raloxifene hydrochloride (Evista) is a SERM that has antiestrogenic effects on breast and estrogenic effects on bone, lipid metabolism, and blood clotting. Unlike tamoxifen, it has antiestrogenic effects on the endometrium.[24] The Multiple Outcomes of Raloxifene Evaluation (MORE) trial was a randomized, double-blind trial that evaluated 7,705 postmenopausal women with osteoporosis from 1994 to 1998 at 180 clinical centers in the United States. Vertebral fractures were reduced. The effect on breast cancer incidence was a secondary end point. After a median follow-up of 47 months, the risk of invasive breast cancer was decreased in the raloxifene-treated women (RR, 0.25; 95% CI, 0.17–0.45).[25] As with tamoxifen, raloxifene reduced the risk of ER-positive breast cancer but not ER-negative breast cancer and was associated with an excess risk of hot flashes and thromboembolic events. No excess risk of endometrial cancer or hyperplasia was observed.[26]

An extension of the MORE trial was the Continuing Outcomes Relevant to Evista (CORE) trial, which studied about 80% of MORE participants in their randomly assigned groups for an additional 4 years. Although there was a median 10-month gap between the two studies, and only about 55% of women were adherent to their assigned medications, the raloxifene group continued to experience a lower incidence of invasive ER-positive breast cancer. The overall reduction in invasive breast

cancer during the 8 years of MORE and CORE was 66% (HR, 0.34; 95% CI, 0.22–0.50); the reduction for ER-positive invasive breast cancer was 76% (HR, 0.24; 95% CI, 0.15–0.40).[27]

The Raloxifene Use for the Heart trial was a randomized, placebo-controlled trial to evaluate the effects of raloxifene on incidence of coronary events and invasive breast cancer. As in the MORE and CORE studies, raloxifene reduced the risk of invasive breast cancer (HR, 0.56; 95% CI, 0.38–0.83).[28]

The Study of Tamoxifen and Raloxifene (STAR) (NSABP P-2) compared tamoxifen and raloxifene in 19,747 high-risk women who were monitored for a mean of 3.9 years. Invasive breast cancer incidence was approximately the same for both drugs, but there were fewer noninvasive cancers in the tamoxifen group. Adverse events of uterine cancer, venous thromboembolic events, and cataracts were more common in tamoxifen-treated women, and there was no difference in ischemic heart disease events, strokes, or fractures.[29] Treatment-associated symptoms of dyspareunia, musculoskeletal problems, and weight gain occurred less frequently in tamoxifen-treated women, whereas vasomotor flushing, bladder control symptoms, gynecologic symptoms, and leg cramps occurred less frequently in those receiving raloxifene.[30]

Table 2. Incidence of Outcomes Per 1,000 Women

	Tamoxifen	Raloxifene	RR, 95% CI
Invasive breast cancer	4.3	4.41	1.02, 0.82–1.28
Noninvasive breast cancer	1.51	2.11	1.4, 0.98–2.00

Uterine cancer	2.0	1.25	0.62, 0.35–1.08
VTE	3.8	2.6	0.7, 0.68–0.99
Cataracts	12.3	9.72	0.79, 0.68–0.92
Incidence of Symptoms (0–4 scale)			
Favor Tamoxifen			
Dyspareunia	0.68	0.78	*P* < .001
Musculoskeletal problems	1.10	1.15	*P* = .002
Weight gain	0.76	0.82	*P* < .001
Favor Raloxifene			
Vasomotor symptoms	0.96	0.85	*P* < .001
Bladder control symptoms	0.88	0.73	*P* < .001
Leg cramps	1.10	0.91	*P* < .001
Gynecologic problems	0.29	0.19	*P* < .001

CI = confidence interval; RR = relative risk; VTE = venous

thromboembolism.

Aromatase Inhibitors or Inactivators (AIs)

Another class of agents used to treat women with hormone-sensitive breast cancer may also prevent breast cancer. These drugs interfere with aromatase, the adrenal enzyme that allows estrogen production in postmenopausal women. Anastrozole and letrozole inhibit aromatase activity, whereas exemestane inactivates the enzyme. Side effects for all three drugs include fatigue, arthralgia, myalgia, decreased bone mineral density, and increased fracture rate.

Women with a previous diagnosis of breast cancer have a lower risk of recurrence and of new breast cancers when treated with AIs, as shown in the following studies:

1. In the Arimidex, Tamoxifen, Alone or in Combination trial, which compared anastrozole with tamoxifen as adjuvant therapy for primary breast cancer, the rate of locoregional and distant recurrence was lower for anastrozole when compared with tamoxifen (7.1% vs. 8.5%) but higher for the combination (9.1%).[31] Anastrozole was also more effective in reducing the incidence of new contralateral breast cancer (0.4% vs. 1.1% vs. 0.9%).
2. In another trial, 5,187 women who received 5 years of adjuvant tamoxifen were randomly assigned to receive either letrozole or placebo.[32] After only 2.5 years of median follow-up, the study was terminated because previously defined efficacy end points had been reached. Patients treated with letrozole had a lower incidence of locoregional and distant cancer recurrence and a lower incidence of new contralateral breast cancer (14 vs. 26).
3. Another placebo-controlled trial of 1,918 women with breast cancer examined the effect of extending letrozole treatment for an additional 5 years in women who had received adjuvant tamoxifen followed by 5 years of letrozole.[33] At a median of 6.3 years from study entry, the extended letrozole group had an improved 5-year

disease-free survival rate of 95% (95% CI, 93%–96%) compared with 91% (95% CI, 89%–93%) for the control group (HR, 0.66) but no difference in overall survival. The difference in new contralateral breast cancer diagnoses was statistically significant: 21% (95% CI, 10%–32%) for the extended letrozole group compared with 49% (32%–67%) for the control group (HR, 0.42). Women treated with letrozole had an increased risk of bone pain (18% vs. 14%), bone fracture (14% vs. 9%), and new-onset osteoporosis (11% vs. 6%).

4. A trial randomly assigned 4,742 women who had received 2 years of adjuvant tamoxifen to either continue the tamoxifen or switch to exemestane.[34] After 2.4 years of median follow-up, the exemestane group had a decreased risk of local or metastatic recurrence and a decreased incidence of new contralateral breast cancer (9 vs. 20).

Aromatase inhibitors or inactivators also have been shown to prevent breast cancer in women at increased risk, as shown in the following studies:

1. An RCT of primary prevention of breast cancer compared exemestane with placebo in 4,560 women with at least one risk factor (age >60 years, a Gail 5-year risk >1.66%, or a history of DCIS with mastectomy). After 35 months of median follow-up, invasive breast cancer was diagnosed less frequently in the exemestane group (11 vs. 32; HR, 0.35; 95% CI, 0.18–0.70; number needed-to-treat, about 100 for 35 months). Compared with the placebo group, the exemestane-treated women had more hot flashes (increase, 8%) and fatigue (increase, 2%) but no difference in fractures or cardiovascular events.[35]
2. The International Breast Cancer Intervention Study II (IBIS-II) randomly assigned 3,864 postmenopausal women who were at increased risk of developing breast cancer to receive either daily anastrozole (1 mg) or placebo for 5 years.[36] After a median follow-up of 5 years, fewer breast cancers (invasive and DCIS) occurred in the anastrozole-treated group than in the placebo

group (HR, 0.47; 95% CI, 0.32–0.68). The risk of hormone receptor–positive, but not hormone receptor–negative, breast cancer was reduced. Additional follow-up, up to a median of 131 months, showed continued benefit for women treated with anastrozole, who had a 49% reduction in breast cancer (HR, 0.51; 95% CI, 0.39–0.66). No difference in breast cancer mortality was observed.[37] Women treated with anastrozole were more likely than those taking placebo to have musculoskeletal symptoms, including arthralgias (51% vs. 46%), joint stiffness (7% vs. 5%), carpal tunnel syndrome (3% vs. 2%); hypertension (5% vs. 3%); vasomotor symptoms (57% vs. 49%); and dry eyes (4% vs. 2%).

Prophylactic Mastectomy

A retrospective cohort study evaluated the impact of bilateral prophylactic mastectomy on breast cancer incidence among women at high and moderate risk on the basis of family history.[38] *BRCA* mutation status was not known. Subcutaneous, rather than total, mastectomy was performed in 90% of these women. After a median follow-up of 14 years postsurgery, the risk reduction for the 425 moderate-risk women was 89%; for the 214 high-risk women, it was 90% to 94%, depending on the method used to calculate expected rates of breast cancer. The risk reduction for breast cancer mortality was 100% for moderate-risk women and 81% for high-risk women. Because the study used family history as a risk indicator rather than genetic testing, breast cancer risk may be overestimated.

Contralateral prophylactic mastectomy (CPM) refers to the surgical removal of the opposite uninvolved breast in women who present with unilateral breast cancer. Women who undergo CPM therefore generally undergo bilateral mastectomy for the treatment of unilateral breast cancer, and rates of this procedure among women with unilateral disease (DCIS and early-stage invasive breast cancer) was reported to have increased from 1.9% in 1998 to 11.2% in 2011 based on data from the U.S. National Cancer Data Base.[39]

Some observational studies have suggested that CPM is associated with reduced breast cancer mortality, but these results are generally attributed to selection bias. As of yet, there is no high-quality evidence that CPM is associated with improvements in overall survival. However, some women with unilateral breast cancer, who have a high risk of developing contralateral breast cancer, may reasonably choose CPM to reduce the risk of a new primary cancer in the opposite breast. [40]

Prophylactic Oophorectomy

Ovarian ablation and oophorectomy are associated with decreased breast cancer risk in average-risk women and in women with increased risk resulting from thoracic irradiation. For more information, see the Endogenous Estrogen section. Observational studies of women with high breast cancer risk resulting from *BRCA1* or *BRCA2* gene mutations showed that prophylactic oophorectomy to prevent ovarian cancer was also associated with a 50% decrease in breast cancer incidence. [41-43] These studies are confounded by selection bias, family relationships between patients and controls, indications for oophorectomy, and inadequate information about hormone use. A prospective cohort study had similar findings, with a greater breast cancer risk reduction in *BRCA2* mutation carriers than in *BRCA1* carriers.[44]

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Factors and Interventions With Inadequate Evidence of an Association

Hormonal Contraceptives

Oral contraceptives have been associated with a small increased risk of breast cancer in current users that diminishes over time.[1] A well-conducted case-control study did not observe an association between breast cancer risk and

oral contraceptive use for ever use, duration of use, or recent use.[2]

Another case-control study found no increased risk of breast cancer associated with the use of injectable or implantable progestin-only contraceptives in women aged 35 to 64 years.[3]

A nationwide prospective cohort study in Denmark found that women who currently or recently used hormonal contraceptives had a higher risk of breast cancer than did women who had never used hormonal contraceptives. Moreover, the risk of breast cancer increased with longer duration of hormonal contraceptive use. However, in absolute terms, the effect of oral contraceptives on breast cancer risk was very small; approximately one extra case of breast cancer may be expected for every 7,690 women using hormonal contraception for 1 year.[4]

Environmental Factors

Occupational, environmental, or chemical exposures have all been proposed as causes of breast cancer. Meta-analyses, describing up to 134 environmental chemicals, their sources, and biomarkers of their exposures, suggest that some may be associated with cancer.[5,6] Epidemiological and animal data summarized by the National Academy of Medicine [7] and the Interagency Breast Cancer and Environmental Research Coordinating Committee [8] for a wide range of metals, chemicals, and consumer products indicated that there may be biological plausibility for an association between breast cancer risk and environmental factors. However, the data were largely inconclusive as to whether or not definitive associations exist between specific exposures and increased breast cancer risk, particularly at levels relevant to the general population.

Clearly determining whether specific environmental exposures influence the risk of breast cancer in humans poses important challenges. People are exposed to a variable, difficult-to-measure mix of environmental factors over a lifetime;

additionally, cancer can take decades to develop after a potential exposure, making accurate recall challenging. Therefore, teasing out the effects of any individual substance on breast cancer risk is not easy. Because so many factors must be considered, any observed associations can be easily confounded by the analytical problems of multiplicities, measurement challenges, and recall and publication bias. [9,10] Additionally, although a specific environmental exposure might be determined to have the *potential* to be harmful as observed in an animal model or other toxicological studies using high-dose exposures, this does not necessarily mean that the substance, under conditions in which the general human population is exposed, leads to adverse health outcomes. The ultimate risk to human health depends not only on the intrinsic toxic potential of the substance, but also on the dose or amount the population is exposed to and the timing or length of time of the exposure. Overall, available human studies evaluating potential associations between breast cancer and specific environmental exposures are not conclusive.

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Factors and Interventions With Adequate Evidence of Little or No Association

Abortion

Abortion has been proposed as a risk factor for breast cancer. Findings from observational studies have varied; some studies showed an association, while other studies did not. Observational studies that support this association were less rigorous and potentially biased because of differential recall by women on a socially sensitive issue.[1-4] For example, the impact of recall or reporting bias was demonstrated in a study

that compared regions with different social attitudes on abortion.[5] The Committee on Gynecologic Practice of the American College of Obstetricians and Gynecologists has concluded that “more rigorous recent studies demonstrate no causal relationship between induced abortion and a subsequent increase in breast cancer risk.”[6] Studies that used prospectively recorded data regarding abortion, thereby avoiding recall bias, largely showed no association with the subsequent development of breast cancer.[7-12]

Diet

There is little evidence that dietary modifications of any kind have an impact on the incidence of breast cancer.

Very few randomized trials in humans compare cancer incidence for different diets. Most studies are observational—including post hoc analyses of randomized trials—and are subject to biases that may be so large as to render the observation difficult to interpret. In particular, *P* values and confidence intervals (CIs) do not have the same interpretation as when calculated for the primary end point in a randomized trial.

A summary of ecological studies published before 1975 showed a positive correlation between international age-adjusted breast cancer mortality rates and the estimated per capita consumption of dietary fat.[13] Results of case-control studies have been mixed. Twenty years later, a pooled analysis of results from seven cohort studies found no association between total dietary fat intake and breast cancer risk.[14]

A randomized, controlled, dietary modification study was undertaken among 48,835 postmenopausal women aged 50 to 79 years who were also enrolled in the Women's Health Initiative. The intervention promoted a goal of reducing total fat intake by 20% by increasing vegetable, fruit, and grain consumption. The intervention group reduced fat intake by approximately 10% for more than 8.1 years of follow-up, resulting in lower estradiol and gamma-tocopherol levels, but no persistent weight loss. The incidence of invasive breast

cancer was numerically, but not statistically lower in the intervention group, with a hazard ratio (HR) of 0.91 (95% CI, 0.83–1.01).[15] There was no difference in all-cause mortality, overall mortality, or the incidence of cardiovascular events.[16]

With regard to fruit and vegetable intake, a pooled analysis of eight cohort studies including more than 350,000 women with 7,377 incident breast cancers showed little or no association for various assumed statistical models.[17]

The Women's Healthy Eating and Living Randomized Trial [18] examined the effect of diet on the incidence of new primary breast cancers in women previously diagnosed with breast cancer. More than 3,000 women were enrolled and randomly assigned to an intense regimen of increased fruit and vegetable intake, increased fiber intake, and decreased fat intake, or a comparison group receiving printed materials on the “5-A-Day” dietary guidelines. After a mean of 7.3 years of follow-up, there was no reduction in new primary cancers, no difference in disease-free survival, and no difference in overall survival.

A randomized trial in Spain [19] assigned participants who were at high cardiovascular risk to one of three diets: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control Mediterranean diet (counseling to reduce dietary fat). The investigators reported a statistically significant reduction in major cardiovascular events, which was the trial’s primary end point.[20] The investigators also addressed other end points, including the incidence of breast cancer, although it is not specified how many were examined. Based on only 35 cases of invasive breast cancer (as compared with 288 major cardiovascular events), the respective rates of breast cancer were 8 of 1,476 (0.54%); 10 of 1,285 (0.78%); and 17 of 1,391 (1.22%) with respective average follow-up durations of 4.8, 4.3, and 4.2 years. The circumstances of the study make it difficult to determine the statistical significance of these differences.

Vitamins

The potential role of specific micronutrients for breast cancer risk reduction has been examined in clinical trials, with cardiovascular disease and cancer as outcomes. The Women's Health Study, a randomized trial with 39,876 women, found no difference in breast cancer incidence at 2 years between women assigned to take either beta carotene or placebo.[21] In this same study, no overall effect on cancer was seen in women taking 600 IU of vitamin E every other day.[22] The Women's Antioxidant Cardiovascular Study examined 8,171 women for incidence of total cancer and invasive breast cancer and found no effect for vitamin C, vitamin E, or beta carotene.[23] Two years later, a subset of 5,442 women were randomly assigned to take 1.5 mg of folic acid, 50 mg of vitamin B6, and 1 mg of vitamin B12, or placebo. After 7.3 years, there was no difference in the incidence of total invasive cancer or invasive breast cancer.[24]

Fenretinide [25] is a vitamin A analog that has been shown to reduce breast carcinogenesis in preclinical studies. A phase III Italian trial compared the efficacy of a 5-year intervention with fenretinide versus no treatment in 2,972 women, aged 30 to 70 years, with surgically removed stage I breast cancer or DCIS. At a median observation time of 97 months, there were no statistically significant differences in the occurrence of contralateral breast cancer (P = .642), ipsilateral breast cancer (P = .177), incidence of distant metastases, nonbreast malignancies, and all-cause mortality.[26]

Active and Passive Cigarette Smoking

The potential role of active cigarette smoking in the etiology of breast cancer has been studied for more than three decades, with no clear-cut evidence of an association.[27] Since the mid-1990s, studies of cigarette smoking and breast cancer have more carefully accounted for secondhand smoke exposure.[27,28] A recent meta-analysis suggests that there is no overall association between passive smoking and breast cancer and that study methodology (ascertainment of exposure after breast cancer diagnosis) may be responsible for the apparent risk associations seen in some studies.[29]

Underarm Deodorants/Antiperspirants

Despite warnings to women in lay publications that underarm deodorants and antiperspirants cause breast cancer, there is no evidence to support these concerns. A study based on interviews with 813 women who had breast cancer and 793 controls found no association between the risk of breast cancer and the use of antiperspirants, the use of deodorants, or the use of blade razors before these products were applied.[30] In contrast, a study of 437 breast cancer survivors found that women who used antiperspirants/deodorants and shaved their underarms more frequently had cancer diagnosed at a significantly younger age. It is likely that this finding could be explained by differences in endogenous hormones rather than shaving and antiperspirant/deodorant use. Early menarche and increased body hair are both associated with increased levels of endogenous hormones, known to be risk factors for breast cancer.[31]

Statins

Two well-conducted meta-analyses of randomized controlled trials (RCTs) [32] and RCTs plus observational studies [33] found no evidence that statin use either increases or decreases the risk of breast cancer.

Bisphosphonates

Oral and intravenous bisphosphonates for the treatment of hypercalcemia and osteoporosis have been studied for a possible beneficial effect on breast cancer prevention. Initial observational studies suggested that women who used these drugs for durations of approximately 1 to 4 years had a lower incidence of breast cancer.[34-37] These findings are confounded by the fact that women with osteoporosis have lower breast cancer risk than those with normal bone density. Additional evidence came from studies of women with a breast cancer diagnosis; the use of these drugs was associated with fewer new contralateral cancers.[38] With this background, two large randomized placebo-controlled trials were done. The Fracture Intervention Trial (FIT) treated 6,194 postmenopausal osteopenic women with either alendronate

or placebo and found no difference at 3.8 years in breast cancer incidence, with incidence of 1.8% and 1.5%, respectively (HR, 1.24; 95% CI, 0.84–1.83). The Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly-Pivotal Fracture Trial (HORIZON-PRT) examined 7,580 postmenopausal osteoporotic women with either intravenous zoledronate or placebo and found no difference at 2.8 years in breast cancer incidence, with incidence of 0.8% and 0.9%, respectively (HR, 1.15; 95% CI, 0.7–1.89).[39]

Working Night Shifts

Based on evidence from animal studies, the World Health Organization's International Agency for Research on Cancer (IARC) classified shift work that involves circadian disruption as a probable breast carcinogen.[40] In 2013, a meta-analysis of 15 epidemiological studies found only weak evidence of an increased incidence of breast cancer among women who had ever worked night shifts.[41] In 2016, the results from three recent prospective studies from the United Kingdom, involving nearly 800,000 women, were combined with results from seven other prospective studies and showed no evidence of any association between breast cancer incidence and night shift work. In particular, the confidence intervals for the incidence rate ratios were narrow, even for 20 years or more of night shift work (rate ratio, 1.01; 95% CI, 0.93–1.10). These results exclude a moderate association of breast cancer incidence with long duration of night shift work.[42]

The U.K. Generations Study was established in 2003 to address risk factors and causes of breast cancer. In a prospective cohort of 105,000 women, information was obtained by questionnaire on bedroom light levels at night at the time of study recruitment and at age 20 years. They followed women for an average of 6.1 years and observed 1,775 breast cancers. Adjusting for potentially confounding factors, including night shift work, they found no evidence that the amount of bedroom light at night was associated with breast cancer risk. For the highest-to-lowest levels of light at night, the HR of breast cancer incidence was 1.01 (95% CI, 0.88–1.15).[43]

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Latest Updates to This Summary (04/09/2025)

The PDQ cancer information summaries are reviewed

regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

Incidence and Mortality

Updated statistics with estimated new cases and deaths for 2025 (cited American Cancer Society as reference 1).

Revised text to state that according to data from the Surveillance, Epidemiology, and End Results (SEER) Program, breast cancer mortality rates declined by 44% from 1989 to 2022. However, mortality rates in Black women remain about 38% higher than in White women.

This summary is written and maintained by the PDQ Screening and Prevention Editorial Board, which is editorially independent of NCI. The summary reflects an independent review of the literature and does not represent a policy statement of NCI or NIH. More information about summary policies and the role of the PDQ Editorial Boards in maintaining the PDQ summaries can be found on the About This PDQ Summary and PDQ® Cancer Information for Health Professionals pages.

About This PDQ Summary

Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about breast cancer prevention. It is intended as a resource to inform and assist clinicians in the care of their patients. It does not provide formal guidelines or recommendations for making health care decisions.

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