PEDIATRIC ONCOLOGY

Treatment of Breast Cancer in Young Adults

Megan E. Tesch, MD; and Ann H. Partridge, MD, MPH

overview

Although breast cancer is rare and understudied in adults age 40 and younger, recent epidemiologic data show an increasing incidence of breast cancer among young women in the United States and ongoing inferior long-term outcomes. Given breast cancers arising at a young age are more likely to present at advanced stages and to have aggressive biology, multimodal treatments are often indicated. Elevated local recurrence risks and greater propensity for germline cancer predisposition mutations can impact local therapy choices. Recently, escalated systemic therapy regimens for triple-negative breast cancer incorporating immunotherapy, de-escalated anti-HER2 therapy, and emerging targeted agents, including CDK4/6 inhibitors and PARP inhibitors, for early-stage disease may be employed in younger and older patients alike, with some special considerations. Prognostic genomic signatures can spare low-risk young women with hormone receptor–positive breast cancer adjuvant chemotherapy, but management of intermediate-risk patients remains controversial. Ovarian function suppression and extended endocrine therapy are improving outcomes in hormone receptor–positive breast cancer, but treatment adherence is a particular problem for young patients. Young women may also face greater challenges in long-term survivorship, including impaired fertility, difficulties in psychosocial adjustment, and other treatment-related comorbidities. Consideration of these age-specific issues through dedicated multidisciplinary strategies is necessary for optimal care of young women with breast cancer.

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on April 18, 2022, and published at ascopubs.org on May 17, 2022: DOI https://doi.org/10.1200/EDBK_360970

Breast cancer is relatively rare in young adults, accounting for less than 5% of cases; yet, it is still the most common malignancy diagnosed in women age 40 and younger.[1] Although the incidence of breast cancer among women age 50 and older has stabilized, breast cancer rates continue to rise in younger women, with an estimated 12,000 cases diagnosed in this age group annually in the United States.[2] Breast cancer is the leading cause of cancer-related deaths in women under age 40, and although they have improved over time, survival rates for young women with breast cancer remain lower than those for older women.[3,4]

The reasons for the poorer outcomes experienced by young women with breast cancer are complex and likely multifactorial. Compared with older women, young women are more likely to present with symptoms and at a more advanced stage, in part because of diagnostic delays and lack of reliable screening.[5,6] Breast cancers arising in young women tend to have more unfavorable pathologic features (e.g., high grade, lymphovascular invasion) and aggressive subtypes, including luminal B, HER2, and triple-negative.[7,8] A number of studies have shown a particularly high prevalence of triple-negative tumors among young African American women, more than double that of White women, which likely contributes to the worse prognosis seen in this racial group.[1,9–12] Hereditary breast cancer predisposition is more common in young women, adding other challenges in terms of managing future cancer risks.[13–15] In addition, young women with breast cancer face a variety of concerns unique to or accentuated by their stage of life at diagnosis, including fertility, body image, sexual dysfunction, and social and vocational role functioning, all of which contribute to the increased risk of psychological distress seen in this age group, both at diagnosis and in long-term follow-up.[16]

Young women are often underrepresented in randomized trials evaluating novel therapies and prognostic tools to guide treatment decisions in breast cancer.[17–19] Hesitancy to extrapolate data from studies in primarily older populations may result in young women being excluded from treatment options that might otherwise be standard or put them at risk for overtreatment based solely on their age. Fortunately, in recent years, there has been increasing attention in research and clinical practice, including international guidelines dedicated to young women, to inform these issues.[20] It is therefore imperative that the treatment of young women with breast cancer be tailored to their disease biology and unique host issues, with incorporation of multidisciplinary strategies at diagnosis and in survivorship to optimize both survival and quality-of-life outcomes in this population (Fig. 1).

LOCOREGIONAL THERAPY FOR EARLY-STAGE DISEASE

Although young age at breast cancer diagnosis is a risk factor for local recurrence, available evidence

PRACTICAL APPLICATIONS

- Young age alone is not a contraindication to breast-conserving surgery but should be followed by adjuvant radiation with tumor bed boost to improve local control.
- Similarly to older women, systemic therapy decisions for young women are based on patient and tumor characteristics, predicting the risk of recurrence and potential responsiveness to treatment, including genomic risk profile as appropriate.
- Endocrine therapy options have expanded for young women with hormone receptor–positive breast cancer, but attention to menopausal side effects, fertility concerns and other issues that impact treatment adherence is warranted.
- Young women should be referred early for genetic testing and fertility preservation as appropriate, given the potential impacts on treatment planning and survivorship.
- Psychosocial support is important for young women with breast cancer, who are at greater risk for distress and poor quality of life than older women.

demonstrates that mastectomy in young women is not associated with improved survival compared with breast-conserving surgery.[21–25] Moreover, improvements in adjuvant radiation and systemic therapies have translated into declining rates of locoregional recurrence in young women. In a contemporary population-based cohort from the Netherlands comprising 1,000 women younger than age 35, 5-year rates of local or regional recurrence were substantially lower than previously, at 3.5% and 3.7%, respectively, and were not influenced by surgery type.[26] Nevertheless, an increasing number of young women are opting not only for mastectomy but also for contralateral prophylactic mastectomy.[27,28] Although the reasons for this trend are not well understood, proposed explanations include increased use of breast magnetic resonance imaging, esthetic considerations, wider availability of reconstructive options, increased use of genetic testing, and fears of cancer recurrence that are often overestimated.[29–32] Skin-sparing and nipple-sparing techniques with immediate breast reconstruction improve cosmetic results after mastectomy and have local recurrence rates comparable to conventional mastectomy without reconstruction.[33–35] Oncoplastic repair techniques may be particularly important in young women undergoing breast-

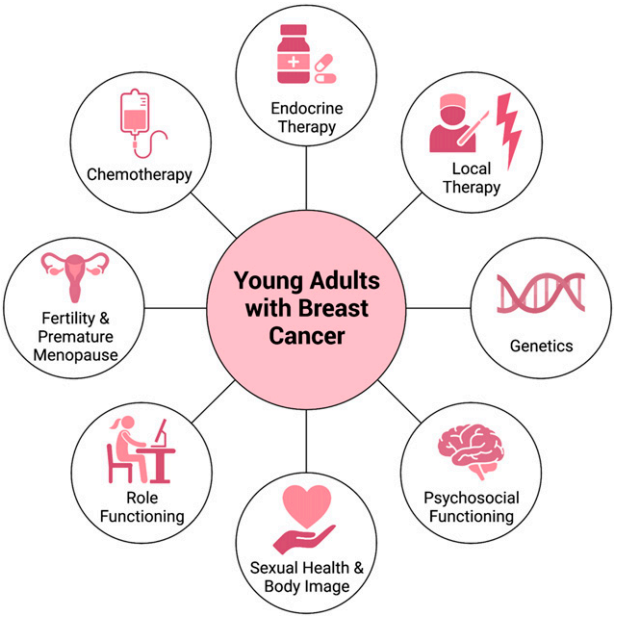

FIGURE 1. Multidisciplinary Considerations in the Treatment of Young Adults With Breast Cancer

conserving surgery, because young age is a predictor for long-term asymmetry between the treated and nontreated breasts.[36,37]

For many young women, local therapy decisions are influenced by the risk of or presence of a known genetic risk for new primary breast cancer; thus, it is crucial that genetic counseling and testing be offered to young patients as soon as possible after diagnosis. Guidelines recommend consideration of risk-reducing bilateral mastectomy among women harboring deleterious *BRCA1/2*, *PALB2*, *TP53*, and other germline mutations predisposing to breast cancer.[38] In addition, prophylactic bilateral salpingo-oopherectomy is recommended between the ages of 35 to 40 and at age 40 in *BRCA1* and *BRCA2* carriers, respectively, upon completion of childbearing. Nevertheless, risk-reducing surgeries should always be individualized to patient preferences, and alternative approaches are available, including annual breast cancer surveillance with magnetic resonance imaging.[39–41]

After breast-conserving surgery, adjuvant radiation is essential in young patients, given that their absolute risk of local recurrence is higher than that in older patients.[42] An additional radiation boost to the tumor bed further improves local control, with the greatest benefit seen in women younger than age 40 in the European Organisation for Research and Treatment of Cancer boost trial.[43] Alternative types of breast radiation, including partial breast radiation, are generally not recommended in younger women because of concerns about potentially inferior efficacy in this higher-risk population and exclusion of

women age 40 and younger from seminal trials.[44] Although the role of postmastectomy radiation in patients with one to three involved nodes remains disputable, limited data suggest a more pronounced benefit in young women.[45–47] Some young women with node-negative disease may also benefit from postmastectomy radiation if they have additional risk factors (e.g., tumor size ≥ 2 cm, lymphovascular invasion, close or positive margins).[48–53]

SYSTEMIC THERAPY FOR EARLY-STAGE DISEASE

Triple-Negative Breast Cancer

Neoadjuvant chemotherapy is favored for most young women with early-stage triple-negative breast cancer, assuming a tumor larger than 1 cm, given the prognostic value of pathologic response, enabling risk stratification and tailoring of adjuvant systemic therapies.[54,55] The threshold for adding platinum agents and immunotherapy to standard neoadjuvant anthracycline plus taxane-based chemotherapy regimens may be lower for young women with triple-negative breast cancer on account of their inferior prognosis overall compared with older women.[4] In addition, mature event-free survival results from the BrighTNess and KEYNOTE-522 phase 3 trials have shown improved long-term outcomes for patients with triple-negative breast cancer with addition of carboplatin and pembrolizumab, respectively, in the early-stage setting.[56,57] Younger women were well represented in both these studies, likely given the overrepresentation of triple-negative subtypes in this population.[7] In patients with triple-negative breast cancer with residual disease after neoadjuvant chemotherapy, adjuvant capecitabine had preserved disease-free survival (DFS) and overall survival (OS) benefits in patients aged ≤ 50 in subgroup analysis of the CREATE-X trial.[58]

Of additional relevance to young women, who are more likely to harbor *BRCA1/2* mutations, is the emerging use of adjuvant PARP inhibitors.[13–15] In the OLYMPIA trial, which randomized 1,836 patients with HER2-negative early-stage breast cancer and germline *BRCA1/2* mutations to 1 year of adjuvant olaparib or placebo, olaparib significantly improved invasive DFS (3-year rate, 85.9% vs. 77.1%; HR, 0.58; 99.5% CI, 0.41–0.82; $p < .001$) and OS (4-year rate, 89.8% vs. 86.4%; HR, 0.68; 98.5% CI, 0.47–0.97; $p = .009$), as presented recently at the European Society for Medical Oncology March 2022 Virtual Plenary.[59,60] The median age of trial participants was 43, with patients with triple-negative breast cancer comprising 82% of the study population and eligible for enrollment if they had high-risk clinicopathologic features or residual disease after neoadjuvant therapy.

HER2-Positive Breast Cancer

Compared with older women, young women with HER2-positive breast cancer have comparable outcomes when controlling for other known prognostic factors, and they derive equivalent benefit from adjuvant trastuzumab.[4,61,62] Thus, young patients with node-negative HER2-positive tumors measuring smaller than 2 cm may be effectively treated with the deintensified regimen of adjuvant weekly paclitaxel for 12 weeks plus trastuzumab for 1 year, which has demonstrated excellent long-term DFS and OS.[63] In addition, lower rates of chemotherapy-related amenorrhea with adjuvant weekly paclitaxel for 12 weeks plus trastuzumab for 1 year compared with standard alkylator-based chemotherapy regimens (only 9% of women age ≤ 40 reporting prolonged chemotherapy-related amenorrhea in the APT trial) may be desired.[64]

Neoadjuvant chemotherapy combined with HER2-directed therapy is preferred for young women with larger and/or node-positive HER2-positive tumors. Subcutaneous formulations of trastuzumab and trastuzumab plus pertuzumab, which have demonstrated similar pathologic complete response rates as the intravenous formulations of these therapies when combined with chemotherapy in the neoadjuvant setting, may be particularly attractive for young women who need to fit breast cancer treatment into complex personal and professional commitments.[65,66] In young women with residual disease after neoadjuvant therapy, adjuvant T-DM1 (ado-trastuzumab emtansine) was associated with superior 3-year invasive DFS compared with trastuzumab among the 296 patients younger than age 40 enrolled in the KATHERINE trial (86.5% vs. 74.9%; HR, 0.50; 95% CI, 0.29–0.86).[67]

Hormone Receptor–Positive Breast Cancer

Significant efforts have been made in recent years to improve risk stratification in hormone receptor (HR)-positive, HER2-negative breast cancer through use of prognostic genomic signatures such as the 21-gene recurrence score (Oncotype DX) and MammaPrint, with the goal of reserving chemotherapy for those likely to benefit and sparing those who are not. However, adoption of these tests in younger women has lagged behind older women, in part because of the minority of patients age40 and younger represented in validation studies (4%) and subgroup analyses in several of these studies finding differential chemotherapy benefits according to age.[68]

In the TAILORx trial, the addition of chemotherapy to endocrine therapy was associated with a lower 9-year rate of distant recurrence in node-negative patients age 50 and younger with recurrence scores 21–25 (difference, 6.4 ± 4.9%) and with recurrence scores 16–20 if clinical risk was high (difference, 6.5 ± 4.9%).[69,70] This contrasted with the main analysis, which showed endocrine therapy alone was effective for tumors with intermediate recurrence score. The lack of difference observed in distant relapse-free survival at 6 years by receipt of chemotherapy among node-negative patients age 40 and

younger with recurrence scores 11–25 enrolled in the Young Women's Breast Cancer Study, a prospective observational cohort, is also contradictory.[71] In the recent RxPONDER trial, the addition of chemotherapy to endocrine therapy in premenopausal women with one to three involved nodes and recurrence scores 0–25 was associated with an improved 5-year rate of invasive DFS (93.9% vs. 89.0%; HR, 0.60; 95% CI, 0.43–0.83; p = .002) and distant relapse-free survival (96.1% vs. 92.8%; HR, 0.58; 95% CI, 0.39–0.87; p = .0009), but not in postmenopausal women with these same characteristics.[18] In addition, women age 50 and younger with high clinical risk and low genomic risk on MammaPrint testing had an improvement in distant metastasis-free survival at 8 years with chemoendocrine therapy versus endocrine therapy in the recently updated MINDACT trial, (difference, 5.0%; SE, 2.8; 95% CI, −0.5 to 10.4), whereas no chemotherapy benefit was seen in the over 50 age group.[72]

It is important to note that only 13% to 15% of premenopausal women receiving endocrine therapy in these trials received ovarian function suppression (OFS), which raises the question of whether some, if not all, of the survival advantage young women derived from chemotherapy was as a result of its ovarian suppressive effects as opposed to direct cytotoxicity. It is well established that chemotherapy-related amenorrhea is a predictor for improved DFS and OS in premenopausal patients with HR-positive disease.[73,74] Given that the incidence of chemotherapy-related amenorrhea is higher in older premenopausal women, this could explain why a chemotherapy benefit was seen in patients ages 41–45 and 46–50 with intermediate recurrence scores but not in those age 40 and younger in a subgroup analysis of the TAILORx trial.[70,73] Thus, although adjuvant chemotherapy clearly benefits young women with high genomic risk and can be safely omitted in low clinical/genomic risk patients, current data support a more individualized approach for intermediate-risk patients, with consideration of other clinicopathologic risk factors and careful weighing of the risks and benefits of adjuvant chemotherapy, particularly when maximal endocrine therapy is planned. Further study of chemotherapy in the setting of optimal endocrine therapy including OFS is needed.

Neoadjuvant chemotherapy is indicated for young women with HR-positive disease that is inoperable or when downstaging of the breast tumor or axillary nodal disease preoperatively is desired, particularly when tumor characteristics are suggestive of chemotherapy responsiveness (e.g., low estrogen receptor expression, high grade). Although chemotherapy infrequently yields a pathologic complete response in this breast cancer subtype, women age 40 and younger with HR-positive/HER2-negative tumors were more likely to achieve a pathologic complete response than those ages 41–50 and age 50 and older in a pooled analysis of eight German neoadjuvant trials (pathologic complete response, 11% vs. 8.4% vs. 5.8%; p < .001).[75] In contrast, neoadjuvant endocrine therapy is not recommended in young women outside of clinical trials, given that limited data suggest worse response rates relative to neoadjuvant chemotherapy.[76–78]

For decades, tamoxifen for 5 years has been the standard adjuvant endocrine therapy in young women, conferring substantial reductions in breast cancer recurrence and mortality, regardless of age.[79] However, the range of adjuvant endocrine strategies in young women has expanded in the last few years to include the addition of OFS to tamoxifen or aromatase inhibitors and extension of tamoxifen to 10 years. The SOFT trial, which randomly assigned 3,066 premenopausal patients to 5 years of tamoxifen alone, tamoxifen-OFS, or exemestane-OFS, demonstrated that adding OFS to tamoxifen improved 8-year DFS (83.2% vs. 78.9%; HR, 0.76; 95% CI, 0.62–0.93; p = .009) and OS (93.3% vs. 91.5%; HR, 0.67; 95% CI, 0.48–0.92; p = .01).[80] In subgroup analysis, the OS benefit was limited to women who had received prior chemotherapy with correspondingly higher-risk clinicopathologic features (e.g., age < 40, larger tumors, node positive), with particular benefit seen in women younger than age 35. In contrast, tamoxifen alone was associated with excellent long-term outcomes in low-risk patients who did not receive chemotherapy (e.g., small tumors, node negative), with 12-year DFS and OS rates of 95.8% and 95.8%, respectively, in a recent update of the SOFT trial presented at the 2021 San Antonio Breast Cancer Symposium.[81] In a joint analysis of the SOFT and TEXT trials, exemestane-OFS was associated with a small DFS improvement compared with tamoxifen-OFS, but no difference in OS.[80] Similar findings were seen in a recent Early Breast Cancer Trialists' Collaborative Group meta-analysis including these trials, demonstrating that aromatase inhibitor OFS reduced the 10-year rate of breast cancer recurrence compared with tamoxifen-OFS (17.5% vs. 14.7%; risk ratio, 0.79; 95% CI, 0.69–0.90; p = .0005), but not breast cancer mortality (7.2% vs. 6.8%; risk ratio, 1.01; 95% CI, 0.82–1.24; p = .94).[82] Collectively, these data support the use of tamoxifen monotherapy in low-risk young women, whereas escalation to OFS plus aromatase inhibitor or tamoxifen as tolerated is indicated for those at higher risk of relapse (e.g., higher stage, age < 35).

It is important to note that ovarian suppression is not always successfully achieved with gonadotropin-releasing hormone agonists. At least 17% of patients in the SOFT-EST substudy had estradiol levels incompletely suppressed to postmenopausal levels on aromatase inhibitors after 12 months of treatment with triptorelin, which was mainly seen in the small population of women younger than age 35.[83] Despite the fact that standard estradiol assays lack sensitivity and accuracy at very low estradiol concentrations, hormone levels should be monitored regularly (e.g., every 6 months) while patients are receiving gonadotropin-releasing hormone agonists, especially if there are concerns about suboptimal OFS, such as breakthrough vaginal bleeding. Monthly administration of gonadotropin-releasing hormone

agonists is generally preferred in women age 40 and younger, given their stronger ovarian reserve; however, there are some data to support the safety and efficacy as it pertains to estradiol suppression of 3-monthly gonadotropin-releasing hormone agonist formulations in young women.[84,85] Surgical OFS via bilateral salpingo-oopherectomy can also be considered, but medical OFS is often favored in younger patients to avoid premature menopause and to allow future family planning.

Even after 5 years of adjuvant endocrine therapy, patients with HR-positive tumors have a persistent risk of recurrence and death caused by breast cancer for at least 30 years after diagnosis, and this risk may be particularly high in young women.[86–88] The extension of tamoxifen from 5 to 10 years was associated with absolute reductions in disease recurrence and breast cancer mortality of 3.7% and 2.8%, respectively, after 15 years of follow-up in the ATLAS trial.[89] Although premenopausal patients represented only 8% of trial participants, extended-duration tamoxifen is appropriate in this population when clinicopathologic risk factors for late recurrence are present (e.g., larger tumors, node positive, high grade). No studies have investigated extended OFS-based treatment, whereas those investigating extended treatment with an aromatase inhibitor excluded premenopausal women. Of note, though, in the MA.17 trial evaluating 5 years of letrozole after 5 years of tamoxifen, the greatest DFS benefit was seen in premenopausal patients at diagnosis who became definitely postmenopausal at the time of randomization (HR, 0.26; 95% CI, 0.13–0.55), making this a reasonable treatment option in this subgroup of patients.[90] Currently, however, no studies have directly evaluated the optimal hormone therapy after 5 years of OFS plus aromatase inhibitor or tamoxifen in women who remain premenopausal and warrant extended therapy.[91,92]

Targeted agents have begun to be incorporated into adjuvant treatment of HR-positive breast cancer. The addition of the CDK4/6 inhibitor abemaciclib to endocrine therapy resulted in absolute improvements in 3-year invasive DFS of 5.4% (HR, 0.70 vs. placebo; 95% CI, 0.59–0.82; $p < .0001$) and distant DFS of 4.2% (HR, 0.69 vs. placebo; 95% CI, 0.57–0.83; $p < .0001$).[93] A trend toward greater benefit was seen in the 44% of premenopausal patients included, but, importantly, only 22% of the study population received OFS.[94] Patients with germline *BRCA1/2* mutations and high-risk HR-positive disease are eligible for adjuvant olaparib, based on the results of the OLYMPIA trial, as discussed earlier.[59]

SYSTEMIC THERAPY FOR ADVANCED DISEASE

Current treatment recommendations for young women with advanced breast cancer are largely extrapolated from data gathered on older women. Consensus guidelines consistently stress that young age by itself is not a reason to prescribe more intensive and combination chemotherapy regimens over the sequential use of monotherapy.[20] OFS should be employed together with other treatment options if the disease is endocrine responsive, and bilateral salpingo-oopherectomy may be offered to ensure optimal estradiol suppression, although survival is equivalent for medical and surgical OFS in this setting.[95] Clinical trial participation is encouraged at each treatment juncture for young women with advanced breast cancer.

BREAST CANCER DURING PREGNANCY

It is currently estimated that 1 in 3,000 pregnancies are complicated by breast cancer.[96] The treatment of breast cancer during pregnancy is complex because the potential benefits of any therapy for the mother must be balanced against the risks to the fetus, but comprehensive guidelines are available.[97,98] Although pregnant women are more likely to be diagnosed with breast cancer in advanced stages, their prognosis is similar to that of nonpregnant women when adjusting for tumor characteristics and treatment.[99–103] Moreover, termination of pregnancy has not been shown to improve survival.[104]

Mastectomy is often performed during pregnancy, given that radiation is contraindicated, but breast-conserving surgery is also an option if timing allows radiation to be administered after delivery without significant delay.[105] When initiated after the first trimester and completion of fetal organogenesis, chemotherapy has been safely administered, although there are still risks.[106–109] Prematurity, intrauterine growth restriction, and low birth weight are potential sequelae of chemotherapy in the second and third trimesters, but many healthy babies have been born after in utero exposure to chemotherapy.[104,109] Both trastuzumab and endocrine therapy are contraindicated during pregnancy because of the risk of oligohydramnios and teratogenicity, respectively.[110,111]

SUPPORTIVE CARE AND SURVIVORSHIP

Studies have consistently shown that young women with breast cancer report greater psychosocial morbidity and poorer quality of life than older women.[16,112,113] The unique life stage during which young women are diagnosed is an important contributor to how their breast cancer experience differs from that of older women. Young women are often at a time in their lives when they fill multiple active roles that can be disrupted by a breast cancer diagnosis and treatment, such as completing education, developing careers, seeking or maintaining relationships, and parenting young children.[114–117] They face the risk of becoming amenorrheic with breast cancer treatment, either temporarily or permanently, resulting in potential infertility, vasomotor symptoms, vaginal dryness, loss of libido, fatigue, and exposure to long-term risks of premature menopause.[16,73,118,119] The growing number of young women pursuing bilateral mastectomy for unilateral breast cancer

have an increased risk for not only postoperative complications but also long-term psychosocial consequences, including poor body image, worse sexual well-being, and anxiety.[120–123] In the context of their longer life expectancies, young breast cancer survivors face decades of potentially increased risk of other comorbidities, including cardiotoxicity, secondary cancers, and osteoporosis and fractures.[124–126] Young women with breast cancer are also at higher risk for cognitive problems, depression, feelings of isolation, and fears of cancer recurrence.[16,112,127–130]

Fertility- and pregnancy-related issues are often a priority for young patients with breast cancer, and these concerns can substantially impact decisions regarding and adherence to anticancer therapies.[131] The risk of infertility from chemotherapy varies according to age, ovarian reserve, type of chemotherapy, and the duration and dose administered.[73] Although an imperfect surrogate for ovarian function, chemotherapy-related amenorrhea rates after 2 years ranged from 4% to 20% across the most frequently used modern chemotherapy regimens (e.g., doxorubicin/cyclophosphamide-paclitaxel, docetaxel/cyclophosphamide, docetaxel/carboplatin/trastuzumab) among women age 40 and younger.[118] Before starting chemotherapy, women should be advised regarding the possibility of infertility and referred to a reproductive endocrinologist to discuss fertility preservation options if interested in future childbearing. Embryo and oocyte cryopreservation are the most well-established and successful techniques for fertility preservation.[132] Temporary ovarian suppression with gonadotropin-releasing hormone agonists during chemotherapy can be used after cryopreservation procedures, in patients with cost or access barriers to these strategies, or in those interested in ovarian preservation only, but it is not a replacement for proven fertility preservation methods.[132] In a meta-analysis of individual patient-level data, a concurrent gonadotropin-releasing hormone agonist during chemotherapy was associated with a significant reduction in premature ovarian insufficiency (30.9% vs. 14.1%; adjusted OR, 0.38; 95% CI, 0.26–0.57; $p < .001$) and a higher chance of pregnancy after breast cancer treatment (10.3% vs. 5.5%; incidence rate ratio, 1.83; 95% CI, 1.06–3.15; $p = .030$), though more data on pregnancy and live birth rates are needed.[133,134] Importantly, there is a risk of pregnancy despite amenorrhea during chemotherapy, endocrine therapy, or anti-HER2 therapy, and young women should be counseled regarding the need for reliable nonhormonal contraception if sexually active with men.[20]

Available data to date suggest that pregnancy in breast cancer survivors does not appear to compromise survival.[135–137] In a recent meta-analysis including more than 112,000 patients with breast cancer, of whom 7,505 had a subsequent pregnancy, those with a pregnancy had better DFS (HR, 0.66; 95% CI, 0.49–0.89) and OS (HR, 0.56; 95% CI, 0.45–0.68) than those without a pregnancy, which persisted when correcting for potential confounders.[135] This observation is likely explained in part by a "healthy mother" selection bias (i.e., healthy breast cancer survivors are more likely to become pregnant). The ideal time to wait between diagnosis and conception remains an open question, but experts recommend an individualized approach that takes into account patients' age, risk of relapse, and time of systemic therapy completion.[97] Timing is of particular importance for women with HR-positive disease who require 5 to 10 years of adjuvant endocrine therapy. In this subset of patients, the IBCSG48-14/BIG8-13 (POSITIVE) study is currently evaluating the safety of temporary endocrine therapy interruption to allow pregnancy.[138]

Young women are less likely to be adherent to endocrine therapy than older women, which may be a contributing factor to the inferior survival observed in this subgroup.[4,61,139] In the SOFT/TEXT trials, 20% of women younger than age 35 stopped all protocol-assigned therapy early, and nonadherence was significantly higher in this age group than among patients age 35 and older for medical OFS (23% vs. 17%; $p = .009$) and oral endocrine therapy (25% vs. 21%; $p = .01$) at 4 years after initiation.[140] The addition of OFS to tamoxifen was associated with greater menopausal symptoms, depression, insomnia, and osteoporosis.[141] Patients who received tamoxifen experienced more vasomotor symptoms, whereas those who received exemestane had more bone/joint pain, vaginal dryness, and sexual dysfunction.[142] In addition, there were more bone fractures with aromatase inhibitors than with tamoxifen in the Early Breast Cancer Trialists' Collaborative Group meta-analysis (6.4% vs. 5.1%; risk ratio, 1.27; 95% CI, 1.04–1.54; $p = .017$).[82] For this reason, use of adjuvant bisphosphonates should be considered in premenopausal patients who have low bone density while receiving OFS plus an aromatase inhibitor and/or to confer a modest DFS benefit, provided they have completed childbearing.[143] To improve endocrine therapy compliance in young breast cancer survivors, efforts to mitigate side effects are crucial, and excellent reviews are available on this topic.[144,145]

Given the complex medical and psychosocial issues faced by young women with breast cancer, they derive particular benefit from a multidisciplinary treatment approach. Adequate psychosocial support is necessary during the highly stressful and emotional time after diagnosis, when young women are making local and systemic therapy decisions. Patients' partners, children, and other family members may also benefit from psychosocial interventions.[146,147] In survivorship, rehabilitation strategies are important to improve all aspects of quality of life, including physical, psychological, social, and vocational well-being.[148] Healthy lifestyle changes as they relate to areas such as diet and exercise should be systematically promoted, given the potential breast cancer protective effects and other health benefits.[149,150] In addition, young women can be directed to support

organizations (e.g., Young Survival Coalition; www.youngsurvival.org) that provide tailored informational resources and a sense of community for young women with breast cancer.

CONCLUSIONS

Young women with breast cancer represent a vulnerable population because of their increased risk for poorer prognosis and psychosocial distress. Special consideration of the unique medical and life-stage challenges that young women encounter from diagnosis through treatment and into survivorship is integral and best addressed in a multidisciplinary setting, with early maximization of supportive services. As ongoing advances are made to improve survival outcomes for young patients with breast cancer by tailoring treatments to their disease biology and recurrence risk, attention must also be paid to avoiding long-term complications, whenever possible, to optimize both quantity and quality of life for young survivors.

AFFILIATION

Dana-Farber Cancer Institute, Boston, MA

CORRESPONDING AUTHOR

Ann H. Partridge, MD, MPH, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02115; Twitter: @AnnPartridgeMD; email: ann_partridge@dfci.harvard.edu.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/EDBK_360970.

REFERENCES

1. DeSantis CE, Ma J, Gaudet MM, et al. Breast cancer statistics, 2019. CA Cancer J Clin. 2019;69:438-451.
2. Ellington TD, Miller JW, Henley SJ, et al. Trends in breast cancer incidence, by race, ethnicity, and age among women aged ≥20 years — United States, 1999–2018. MMWR Morb Mortal Wkly Rep. 2022;71:43–47.
3. Guo F, Kuo YF, Shih YCT, et al. Trends in breast cancer mortality by stage at diagnosis among young women in the United States. Cancer. 2018;124:3500-3509.
4. Kim HJ, Kim S, Freedman RA, et al. The impact of young age at diagnosis (age <40 years) on prognosis varies by breast cancer subtype: a U.S. SEER database analysis. Breast. 2022;61:77-83.
5. Partridge AH, Hughes ME, Ottesen RA, et al. The effect of age on delay in diagnosis and stage of breast cancer. Oncologist. 2012;17:775-782.
6. Zabicki K, Colbert JA, Dominguez FJ, et al. Breast cancer diagnosis in women ≤ 40 versus 50 to 60 years: increasing size and stage disparity compared with older women over time. Ann Surg Oncol. 2006;13:1072-1077.
7. Azim HA Jr, Partridge AH. Biology of breast cancer in young women. Breast Cancer Res. 2014;16:427.
8. Guzmán-Arocho YD, Rosenberg SM, Garber JE, et al. Clinicopathological features and BRCA1 and BRCA2 mutation status in a prospective cohort of young women with breast cancer. Br J Cancer. 2022;126:302-309.
9. Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA. 2006;295:2492-2502.
10. Keegan TH, DeRouen MC, Press DJ, et al. Occurrence of breast cancer subtypes in adolescent and young adult women. Breast Cancer Res. 2012;14:R55.
11. Sweeney C, Bernard PS, Factor RE, et al. Intrinsic subtypes from PAM50 gene expression assay in a population-based breast cancer cohort: differences by age, race, and tumor characteristics. Cancer Epidemiol Biomarkers Prev. 2014;23:714-724.
12. Shavers VL, Harlan LC, Stevens JL. Racial/ethnic variation in clinical presentation, treatment, and survival among breast cancer patients under age 35. Cancer. 2003;97:134-147.
13. Tung N, Lin NU, Kidd J, et al. Frequency of germline mutations in 25 cancer susceptibility genes in a sequential series of patients with breast cancer. J Clin Oncol. 2016;34:1460-1468.
14. Haffty BG, Choi DH, Goyal S, et al. Breast cancer in young women (YBC): prevalence of BRCA1/2 mutations and risk of secondary malignancies across diverse racial groups. Ann Oncol. 2009;20:1653-1659.
15. Malone KE, Daling JR, Neal C, et al. Frequency of BRCA1/BRCA2 mutations in a population-based sample of young breast carcinoma cases. Cancer. 2000;88:1393-1402.
16. Howard-Anderson J, Ganz PA, Bower JE, et al. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. J Natl Cancer Inst. 2012;104:386-405.
17. Cardoso F, van't Veer LJ, Bogaerts J, et al; MINDACT Investigators. 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med. 2016;375:717-729.
18. Kalinsky K, Barlow WE, Gralow JR, et al. 21-Gene assay to inform chemotherapy benefit in node-positive breast cancer. N Engl J Med. 2021;385:2336-2347.
19. Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. N Engl J Med. 2015;373:2005-2014.
20. Paluch-Shimon S, Cardoso F, Partridge AH, et al. ESO-ESMO 4th International Consensus Guidelines for Breast Cancer in Young Women (BCY4). Ann Oncol. 2020;31:674-696.

21. Botteri E, Bagnardi V, Rotmensz N, et al. Analysis of local and regional recurrences in breast cancer after conservative surgery. Ann Oncol. 2010;21:723-728.
22. de Bock GH, van der Hage JA, Putter H, et al. Isolated loco-regional recurrence of breast cancer is more common in young patients and following breast conserving therapy: long-term results of European Organisation for Research and Treatment of Cancer studies. Eur J Cancer. 2006;42:351-356.
23. van der Sangen MJ, van de Wiel FM, Poortmans PM, et al. Are breast conservation and mastectomy equally effective in the treatment of young women with early breast cancer? Long-term results of a population-based cohort of 1,451 patients aged ≤ 40 years. Breast Cancer Res Treat. 2011;127:207-215.
24. Mahmood U, Morris C, Neuner G, et al. Similar survival with breast conservation therapy or mastectomy in the management of young women with early-stage breast cancer. Int J Radiat Oncol Biol Phys. 2012;83:1387-1393.
25. Quan ML, Paszat LF, Fernandes KA, et al. The effect of surgery type on survival and recurrence in very young women with breast cancer. J Surg Oncol. 2017;115:122-130.
26. Aalders KC, Postma EL, Strobbe LJ, et al. Contemporary locoregional recurrence rates in young patients with early-stage breast cancer. J Clin Oncol. 2016;34:2107-2114.
27. Kummerow KL, Du L, Penson DF, et al. Nationwide trends in mastectomy for early-stage breast cancer. JAMA Surg. 2015;150:9-16.
28. Kurian AW, Lichtensztajn DY, Keegan THM, et al. Use of and mortality after bilateral mastectomy compared with other surgical treatments for breast cancer in California, 1998-2011. JAMA. 2014;312:902-914.
29. Hawley ST, Jagsi R, Morrow M, et al. Social and clinical determinants of contralateral prophylactic mastectomy. JAMA Surg. 2014;149:582-589.
30. Montgomery LL, Tran KN, Heelan MC, et al. Issues of regret in women with contralateral prophylactic mastectomies. Ann Surg Oncol. 1999;6:546-552.
31. Rosenberg SM, Tracy MS, Meyer ME, et al. Perceptions, knowledge, and satisfaction with contralateral prophylactic mastectomy among young women with breast cancer: a cross-sectional survey. Ann Intern Med. 2013;159:373-381.
32. Sorbero ME, Dick AW, Beckjord EB, et al. Diagnostic breast magnetic resonance imaging and contralateral prophylactic mastectomy. Ann Surg Oncol. 2009;16:1597-1605.
33. Agha RA, Al Omran Y, Wellstead G, et al. Systematic review of therapeutic nipple-sparing versus skin-sparing mastectomy. BJS Open. 2018;3:135-145.
34. De La Cruz L, Moody AM, Tappy EE, et al. Overall survival, disease-free survival, local recurrence, and nipple-areolar recurrence in the setting of nipple-sparing mastectomy: a meta-analysis and systematic review. Ann Surg Oncol. 2015;22:3241-3249.
35. Lanitis S, Tekkis PP, Sgourakis G, et al. Comparison of skin-sparing mastectomy versus non-skin-sparing mastectomy for breast cancer: a meta-analysis of observational studies. Ann Surg. 2010;251:632-639.
36. Losken A, Hart AM, Chatterjee A. Updated evidence on the oncoplastic approach to breast conservation therapy. Plast Reconstr Surg. 2017;140(5S Advances in Breast Reconstruction):14S-22S.
37. Immink JM, Putter H, Bartelink H, et al. Long-term cosmetic changes after breast-conserving treatment of patients with stage I-II breast cancer and included in the EORTC 'boost versus no boost' trial. Ann Oncol. 2012;23:2591-2598.
38. NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (Version 1.2022). 2022. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf. Accessed March 2, 2022.
39. Kriege M, Brekelmans CT, Boetes C, et al; Magnetic Resonance Imaging Screening Study Group. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med. 2004;351:427-437.
40. Warner E, Hill K, Causer P, et al. Prospective study of breast cancer incidence in women with a BRCA1 or BRCA2 mutation under surveillance with and without magnetic resonance imaging. J Clin Oncol. 2011;29:1664-1669.
41. Warner E, Messersmith H, Causer P, et al. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. Ann Intern Med. 2008;148:671-679.
42. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet. 2011;378:1707-1716.
43. Bartelink H, Maingon P, Poortmans P, et al; European Organisation for Research and Treatment of Cancer Radiation Oncology and Breast Cancer Groups. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol. 2015;16:47-56.
44. Correa C, Harris EE, Leonardi MC, et al. Accelerated partial breast irradiation: executive summary for the update of an ASTRO evidence-based consensus statement. Pract Radiat Oncol. 2017;7:73-79.
45. EBCTCG (Early Breast Cancer Trialists' Collaborative Group). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014;383:2127–2135.
46. Garg AK, Oh JL, Oswald MJ, et al. Effect of postmastectomy radiotherapy in patients <35 years old with stage II-III breast cancer treated with doxorubicin-based neoadjuvant chemotherapy and mastectomy. Int J Radiat Oncol Biol Phys. 2007;69:1478-1483.
47. Quan ML, Osman F, McCready D, et al. Postmastectomy radiation and recurrence patterns in breast cancer patients younger than age 35 years: a population-based cohort. Ann Surg Oncol. 2014;21:395-400.
48. Abi-Raad R, Boutrus R, Wang R, et al. Patterns and risk factors of locoregional recurrence in T1-T2 node negative breast cancer patients treated with mastectomy: implications for postmastectomy radiotherapy. Int J Radiat Oncol Biol Phys. 2011;81:e151-e157.
49. Truong PT, Olivotto IA, Speers CH, et al. A positive margin is not always an indication for radiotherapy after mastectomy in early breast cancer. Int J Radiat Oncol Biol Phys. 2004;58:797-804.

50. Wallgren A, Bonetti M, Gelber RD, et al; International Breast Cancer Study Group Trials I through VII. Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. J Clin Oncol. 2003;21:1205-1213.

51. Yildirim E, Berberoglu U. Can a subgroup of node-negative breast carcinoma patients with T1-2 tumor who may benefit from postmastectomy radiotherapy be identified? Int J Radiat Oncol Biol Phys. 2007;68:1024-1029.

52. Cassidy RJ, Liu Y, Kahn ST, et al. The role of postmastectomy radiotherapy in women with pathologic T3N0M0 breast cancer. Cancer. 2017;123:2829-2839.

53. Wu SP, Tam M, Shaikh F, et al. Post-mastectomy radiation therapy in breast cancer patients with nodal micrometastases. Ann Surg Oncol. 2018;25:2620-2631.

54. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014;384:164-172.

55. Yau C, Osdoit M, van der Noordaa M, et al; I-SPY 2 Trial Consortium. Residual cancer burden after neoadjuvant chemotherapy and long-term survival outcomes in breast cancer: a multicentre pooled analysis of 5161 patients. Lancet Oncol. 2022;23:149-160.

56. Geyer CE, Sikov WM, Huober J, et al. Long-term efficacy and safety of addition of carboplatin with or without veliparib to standard neoadjuvant chemotherapy in triple-negative breast cancer: 4-year follow-up data from BrighTNess, a randomized phase III trial. Ann Oncol. 2022;33:384-394.

57. Schmid P, Cortes J, Dent R, et al; KEYNOTE-522 Investigators. Event-free survival with pembrolizumab in early triple-negative breast cancer. N Engl J Med. 2022;386:556-567.

58. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med. 2017;376:2147-2159.

59. Tutt ANJ, Garber JE, Kaufman B, et al; OlympiA Clinical Trial Steering Committee and Investigators. Adjuvant olaparib for patients with *BRCA1*- or *BRCA2*-mutated breast cancer. N Engl J Med. 2021;384:2394-2405.

60. Tutt ANJ, Garber J, Gelber RD, et al. VP1-2022: Pre-specified event driven analysis of overall survival (OS) in the OlympiA phase III trial of adjuvant olaparib (OL) in germline BRCA1/2 mutation (gBRCAm) associated breast cancer. Ann Oncol. 2022;33:566-568.

61. Partridge AH, Hughes ME, Warner ET, et al. Subtype-dependent relationship between young age at diagnosis and breast cancer survival. J Clin Oncol. 2016;34:3308-3314.

62. Partridge AH, Gelber S, Piccart-Gebhart MJ, et al. Effect of age on breast cancer outcomes in women with human epidermal growth factor receptor 2-positive breast cancer: results from a herceptin adjuvant trial. J Clin Oncol. 2013;31:2692-2698.

63. Tolaney SM, Guo H, Pernas S, et al. Seven-year follow-up analysis of adjuvant paclitaxel and trastuzumab trial for node-negative, human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol. 2019;37:1868-1875.

64. Ruddy KJ, Guo H, Barry W, et al. Chemotherapy-related amenorrhea after adjuvant paclitaxel-trastuzumab (APT trial). Breast Cancer Res Treat. 2015;151:589-596.

65. Ismael G, Hegg R, Muehlbauer S, et al. Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I-III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial. Lancet Oncol. 2012;13:869-878.

66. Tan AR, Im SA, Mattar A, et al; FeDeriCa study group. Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection plus chemotherapy in HER2-positive early breast cancer (FeDeriCa): a randomised, open-label, multicentre, non-inferiority, phase 3 study. Lancet Oncol. 2021;22:85-97.

67. von Minckwitz G, Huang CS, Mano MS, et al; KATHERINE Investigators. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med. 2019;380:617-628.

68. Villarreal-Garza C, Ferrigno AS, De la Garza-Ramos C, et al. Clinical utility of genomic signatures in young breast cancer patients: a systematic review. NPJ Breast Cancer. 2020;6:46.

69. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med. 2018;379:111-121.

70. Sparano JA, Gray RJ, Ravdin PM, et al. Clinical and genomic risk to guide the use of adjuvant therapy for breast cancer. N Engl J Med. 2019;380:2395-2405.

71. Poorvu PD, Gelber SI, Rosenberg SM, et al. Prognostic impact of the 21-gene recurrence score assay among young women with node-negative and node-positive ER-positive/HER2-negative breast cancer. J Clin Oncol. 2020;38:725-733.

72. Piccart M, van 't Veer LJ, Poncet C, et al. 70-Gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. Lancet Oncol. 2021;22:476-488.

73. Walshe JM, Denduluri N, Swain SM. Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. J Clin Oncol. 2006;24:5769-5779.

74. Zhou Q, Yin W, Du Y, et al. Prognostic impact of chemotherapy-induced amenorrhea on premenopausal breast cancer: a meta-analysis of the literature. Menopause. 2015;22:1091-1097.

75. Loibl S, Jackisch C, Lederer B, et al. Outcome after neoadjuvant chemotherapy in young breast cancer patients: a pooled analysis of individual patient data from eight prospectively randomized controlled trials. Breast Cancer Res Treat. 2015;152:377-387.

76. Alba E, Calvo L, Albanell J, et al; GEICAM. Chemotherapy (CT) and hormonotherapy (HT) as neoadjuvant treatment in luminal breast cancer patients: results from the GEICAM/2006-03, a multicenter, randomized, phase-II study. Ann Oncol. 2012;23:3069-3074.

77. Kim HJ, Noh WC, Lee ES, et al. Efficacy of neoadjuvant endocrine therapy compared with neoadjuvant chemotherapy in pre-menopausal patients with oestrogen receptor-positive and HER2-negative, lymph node-positive breast cancer. Breast Cancer Res. 2020;22:54.

78. Korde LA, Somerfield MR, Carey LA, et al. Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO guideline. J Clin Oncol. 2021;39:1485-1505.

79. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet. 2011;378:771-784.

80. Francis PA, Pagani O, Fleming GF, et al; SOFT and TEXT Investigators and the International Breast Cancer Study Group. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. N Engl J Med. 2018;379:122-137.

81. Regan MM, Walley BA, Fleming GF, et al. Abstract GS2-05: Randomized comparison of adjuvant aromatase inhibitor exemestane (E) plus ovarian function suppression (OFS) vs tamoxifen (T) plus OFS in premenopausal women with hormone receptor-positive (HR+) early breast cancer (BC): update of the combined TEXT and SOFT trials. Cancer Res. 2022;82:4s (suppl; abstr GS2-05).

82. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in premenopausal women with oestrogen receptor-positive early-stage breast cancer treated with ovarian suppression: a patient-level meta-analysis of 7030 women from four randomised trials. Lancet Oncol. 2022;23:382-392.

83. Bellet M, Gray KP, Francis PA, et al. Twelve-month estrogen levels in premenopausal women with hormone receptor-positive breast cancer receiving adjuvant triptorelin plus exemestane or tamoxifen in the Suppression of Ovarian Function Trial (SOFT): the SOFT-EST substudy. J Clin Oncol. 2016;34:1584-1593.

84. Masuda N, Iwata H, Rai Y, et al. Monthly versus 3-monthly goserelin acetate treatment in pre-menopausal patients with estrogen receptor-positive early breast cancer. Breast Cancer Res Treat. 2011;126:443-451.

85. Noguchi S, Kim HJ, Jesena A, et al. Phase 3, open-label, randomized study comparing 3-monthly with monthly goserelin in pre-menopausal women with estrogen receptor-positive advanced breast cancer. Breast Cancer. 2016;23:771-779.

86. Pan H, Gray R, Braybrooke J, et al; EBCTCG. 20-Year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. N Engl J Med. 2017;377:1836-1846.

87. Yu KD, Wu J, Shen ZZ, et al. Hazard of breast cancer-specific mortality among women with estrogen receptor-positive breast cancer after five years from diagnosis: implication for extended endocrine therapy. J Clin Endocrinol Metab. 2012;97:E2201-E2209.

88. Pedersen RN, Esen BO, Mellemkjær L, et al. The incidence of breast cancer recurrence 10-32 years after primary diagnosis. J Natl Cancer Inst. 2022;114:391-399.

89. Davies C, Pan H, Godwin J, et al; Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet. 2013;381:805-816.

90. Goss PE, Ingle JN, Martino S, et al. Impact of premenopausal status at breast cancer diagnosis in women entered on the placebo-controlled NCIC CTG MA17 trial of extended adjuvant letrozole. Ann Oncol. 2013;24:355-361.

91. Sella T, Ruddy KJ, Carey LA, et al. Optimal endocrine therapy in premenopausal women: a pragmatic approach to unanswered questions. JCO Oncol Pract. 2022;18:211-216.

92. Sella T, Zheng Y, Rosenberg SM, et al. Abstract PD13-10: Extended adjuvant endocrine therapy in a longitudinal cohort of young breast cancer survivors. Cancer Res. 2022;82:4s (suppl; abstr PD13-10).

93. Harbeck N, Rastogi P, Martin M, et al; monarchE Committee Members. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol. 2021;32:1571-1581.

94. Johnston SRD, Harbeck N, Hegg R, et al; monarchE Committee Members and Investigators. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2−, node-positive, high-risk, early breast cancer (monarchE). J Clin Oncol. 2020;38:3987-3998.

95. Taylor CW, Green S, Dalton WS, et al. Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: an intergroup study. J Clin Oncol. 1998;16:994-999.

96. Cottreau CM, Dashevsky I, Andrade SE, et al. Pregnancy-associated cancer: a U.S. population-based study. J Womens Health (Larchmt). 2019;28:250-257.

97. Peccatori FA, Azim HA, Jr., Orecchia R, et al; ESMO Guidelines Working Group. Cancer, pregnancy and fertility: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24(Suppl 6):vi160-vi170.

98. Amant F, Deckers S, Van Calsteren K, et al. Breast cancer in pregnancy: recommendations of an international consensus meeting. Eur J Cancer. 2010;46:3158-3168.

99. Amant F, von Minckwitz G, Han SN, et al. Prognosis of women with primary breast cancer diagnosed during pregnancy: results from an international collaborative study. J Clin Oncol. 2013;31:2532-2539.

100. Litton JK, Warneke CL, Hahn KM, et al. Case control study of women treated with chemotherapy for breast cancer during pregnancy as compared with nonpregnant patients with breast cancer. Oncologist. 2013;18:369-376.

101. Middleton LP, Amin M, Gwyn K, et al. Breast carcinoma in pregnant women: assessment of clinicopathologic and immunohistochemical features. Cancer. 2003;98:1055-1060.

102. Iqbal J, Amir E, Rochon PA, et al. Association of the timing of pregnancy with survival in women with breast cancer. JAMA Oncol. 2017;3:659-665.

103. Liao Q, Deng D, Xie Q, et al. Clinical characteristics, pregnancy outcomes and ovarian function of pregnancy-associated breast cancer patients: a retrospective age-matched study. BMC Cancer. 2022;22:152.

104. Cardonick E, Dougherty R, Grana G, et al. Breast cancer during pregnancy: maternal and fetal outcomes. Cancer J. 2010;16:76-82.

105. Kal HB, Struikmans H. Radiotherapy during pregnancy: fact and fiction. Lancet Oncol. 2005;6:328-333.

106. Giacalone PL, Laffargue F, Bénos P. Chemotherapy for breast carcinoma during pregnancy: a French national survey. Cancer. 1999;86:2266-2272.

107. Berry DL, Theriault RL, Holmes FA, et al. Management of breast cancer during pregnancy using a standardized protocol. J Clin Oncol. 1999;17:855-861.

108. Ring AE, Smith IE, Jones A, et al. Chemotherapy for breast cancer during pregnancy: an 18-year experience from five London teaching hospitals. J Clin Oncol. 2005;23:4192-4197.

109. Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol. 2012;13:887-896.

110. Andrikopoulou A, Apostolidou K, Chatzinikolaou S, et al. Trastuzumab administration during pregnancy: an update [published correction appears in *BMC Cancer*. 2021;21:1340]. BMC Cancer. 2021;21:463.

111. Isaacs RJ, Hunter W, Clark K. Tamoxifen as systemic treatment of advanced breast cancer during pregnancy—case report and literature review. Gynecol Oncol. 2001;80:405-408.

112. Champion VL, Wagner LI, Monahan PO, et al. Comparison of younger and older breast cancer survivors and age-matched controls on specific and overall quality of life domains. Cancer. 2014;120:2237-2246.

113. Marschner N, Trarbach T, Rauh J, et al; TMK-Group (Tumour Registry Breast Cancer). Quality of life in pre- and postmenopausal patients with early breast cancer: a comprehensive analysis from the prospective MaLife project. Breast Cancer Res Treat. 2019;175:701-712.

114. Raque-Bogdan TL, Hoffman MA, Ginter AC, et al. The work life and career development of young breast cancer survivors. J Couns Psychol. 2015;62:655-669.

115. Keesing S, Rosenwax L, McNamara B. A dyadic approach to understanding the impact of breast cancer on relationships between partners during early survivorship. BMC Womens Health. 2016;16:57.

116. Schmitt F, Piha J, Helenius H, et al. Multinational study of cancer patients and their children: factors associated with family functioning. J Clin Oncol. 2008;26:5877-5883.

117. Moore CW, Rauch PK, Baer L, et al. Parenting changes in adults with cancer. Cancer. 2015;121:3551-3557.

118. Poorvu PD, Hu J, Zheng Y, et al. Treatment-related amenorrhea in a modern, prospective cohort study of young women with breast cancer. NPJ Breast Cancer. 2021;7:99.

119. Rosenberg SM, Tamimi RM, Gelber S, et al. Treatment-related amenorrhea and sexual functioning in young breast cancer survivors. Cancer. 2014;120:2264-2271.

120. Bresser PJ, Seynaeve C, Van Gool AR, et al. Satisfaction with prophylactic mastectomy and breast reconstruction in genetically predisposed women. Plast Reconstr Surg. 2006;117:1675-1682,discussion 1683-1684.

121. Dominici L, Hu J, Zheng Y, et al. Association of local therapy with quality-of-life outcomes in young women with breast cancer. JAMA Surg. 2021;156:e213758.

122. Miller ME, Czechura T, Martz B, et al. Operative risks associated with contralateral prophylactic mastectomy: a single institution experience. Ann Surg Oncol. 2013;20:4113-4120.

123. Rosenberg SM, Dominici LS, Gelber S, et al. Association of breast cancer surgery with quality of life and psychosocial well-being in young breast cancer survivors. JAMA Surg. 2020;155:1035-1042.

124. Lee Chuy K, Yu AF. Cardiotoxicity of contemporary breast cancer treatments. Curr Treat Options Oncol. 2019;20:51.

125. Kirova YM, De Rycke Y, Gambotti L, et al; Institut Curie Breast Cancer Study Group. Second malignancies after breast cancer: the impact of different treatment modalities. Br J Cancer. 2008;98:870-874.

126. Gnant M, Mlineritsch B, Luschin-Ebengreuth G, et al; Austrian Breast and Colorectal Cancer Study Group (ABCSG). Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. Lancet Oncol. 2008;9:840-849.

127. Lebel S, Beattie S, Arès I, et al. Young and worried: age and fear of recurrence in breast cancer survivors. Health Psychol. 2013;32:695-705.

128. Thewes B, Butow P, Bell ML, et al; FCR Study Advisory Committee. Fear of cancer recurrence in young women with a history of early-stage breast cancer: a cross-sectional study of prevalence and association with health behaviours. Support Care Cancer. 2012;20:2651-2659.

129. Gould J, Grassau P, Manthorne J, et al. 'Nothing fit me': nationwide consultations with young women with breast cancer. Health Expect. 2006;9:158-173.

130. Rosedale M. Survivor loneliness of women following breast cancer. Oncol Nurs Forum. 2009;36:175-183.

131. Ruddy KJ, Gelber SI, Tamimi RM, et al. Prospective study of fertility concerns and preservation strategies in young women with breast cancer. J Clin Oncol. 2014;32:1151-1156.

132. Oktay K, Harvey BE, Partridge AH, et al. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol. 2018;36:1994-2001.

133. Lambertini M, Moore HCF, Leonard RCF, et al. Gonadotropin-releasing hormone agonists during chemotherapy for preservation of ovarian function and fertility in premenopausal patients with early breast cancer: a systematic review and meta-analysis of individual patient-level data. J Clin Oncol. 2018;36:1981-1990.

134. Chen H, Xiao L, Li J, et al. Adjuvant gonadotropin-releasing hormone analogues for the prevention of chemotherapy-induced premature ovarian failure in premenopausal women. Cochrane Database Syst Rev. 2019;3:CD008018.

135. Lambertini M, Blondeaux E, Bruzzone M, et al. Pregnancy after breast cancer: a systematic review and meta-analysis. J Clin Oncol. 2021;39:3293-3305.

136. Azim HA, Jr., Santoro L, Pavlidis N, et al. Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. Eur J Cancer. 2011;47:74-83.

137. Lambertini M, Ameye L, Hamy AS, et al. Pregnancy after breast cancer in patients with germline *BRCA* mutations. J Clin Oncol. 2020;38:3012-3023.

138. Partridge AH, Niman SM, Ruggeri M, et al. Who are the women who enrolled in the POSITIVE trial: a global study to support young hormone receptor positive breast cancer survivors desiring pregnancy. Breast. 2021;59:327-338.

139. Hershman DL, Kushi LH, Shao T, et al. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. J Clin Oncol. 2010;28:4120-4128.

140. Saha P, Regan MM, Pagani O, et al; International Breast Cancer Study Group. Treatment efficacy, adherence, and quality of life among women younger than 35 years in the International Breast Cancer Study Group TEXT and SOFT adjuvant endocrine therapy trials. J Clin Oncol. 2017;35:3113-3122.

141. Francis PA, Regan MM, Fleming GF, et al; International Breast Cancer Study Group. Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med. 2015;372:436-446.

142. Bernhard J, Luo W, Ribi K, et al. Patient-reported outcomes with adjuvant exemestane versus tamoxifen in premenopausal women with early breast cancer undergoing ovarian suppression (TEXT and SOFT): a combined analysis of two phase 3 randomised trials. Lancet Oncol. 2015;16:848-858.

143. Gnant M, Mlineritsch B, Stoeger H, et al; Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. Lancet Oncol. 2011;12:631-641.

144. Henry NL. Endocrine therapy toxicity: management options. Am Soc Clin Oncol Educ Book. 2014;34:e25-e30.

145. Franzoi MA, Agostinetto E, Perachino M, et al. Evidence-based approaches for the management of side-effects of adjuvant endocrine therapy in patients with breast cancer. Lancet Oncol. 2021;22:e303-e313.

146. Borstelmann NA, Rosenberg S, Gelber S, et al. Partners of young breast cancer survivors: a cross-sectional evaluation of psychosocial concerns, coping, and mental health. J Psychosoc Oncol. 2020;38:670-686.

147. Purc-Stephenson R, Lyseng A. How are the kids holding up? A systematic review and meta-analysis on the psychosocial impact of maternal breast cancer on children. Cancer Treat Rev. 2016;49:45-56.

148. Easley J, Miedema B. Rehabilitation after breast cancer: recommendations from young survivors. Rehabil Nurs. 2012;37:163-170.

149. Schmid D, Leitzmann MF. Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis. Ann Oncol. 2014;25:1293-1311.

150. Rock CL, Demark-Wahnefried W. Nutrition and survival after the diagnosis of breast cancer: a review of the evidence. J Clin Oncol. 2002;20:3302-3316.