

Managing breast cancer in younger women: challenges and solutions

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Abstract: Breast cancer in young women is relatively rare compared to breast cancer occurring in older women. Younger women diagnosed with breast cancer also tend to have a more aggressive biology and consequently a poorer prognosis than older women. In addition, they face unique challenges such as diminished fertility from premature ovarian failure, extended survivorship periods and its attendant problems, and the psychosocial impact of diagnosis, while still raising families. It is therefore imperative to recognize the unique issues that younger women face, and plan management in a multidisciplinary fashion to optimize clinical outcomes. This paper discusses the challenges of breast cancer management for young women, as well as specific issues to consider in diagnosis, treatment, and follow-up of such patients.

Keywords: breast cancer, young women, diagnosis, treatment

Introduction

Early-onset breast cancer is relatively rare; however, it represents the commonest cause of cancer in women under age the of 40.¹ In the US, approximately 33,000 women under the age of 45 years are diagnosed with breast cancer every year, and it is the leading cause of cancer-related deaths in this age group.² Compared to older women with breast cancer, younger women tend to have a more aggressive biology and a poorer prognosis (Table 1). Younger women with breast cancer also face unique challenges such as premature ovarian failure, psychosocial issues with ongoing careers, and raising young families, as well as extended survivorship periods and its attendant complications as summarized in Figure 1. It is therefore imperative to recognize the unique issues that younger women face and plan management in a multidisciplinary fashion to optimize clinical outcomes.

Breast cancer screening

Screening for breast cancer should begin at age 40 for average-risk women.³ This includes annual mammography and clinical breast examination (CBE). Breast self-examination (BSE) is an additional option. For average-risk women under age 40, screening consists of CBE every 3 years with optional BSE; routine use of imaging is not recommended. Although no studies have documented improved breast cancer-related outcomes with BSE, given that routine imaging is not warranted, most malignancies in women under 40 will be detected by patients.⁴ Even for young women who do undergo annual mammography, cancers that develop are more likely to present as interval cancers.⁵⁻⁷ For this reason as well, CBE and BSE remain important screening modalities for young women. Increased breast density seen in younger women lowers

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Table 1 Breast cancer features in younger patients

Incidence	More common in older women. 4.5% incidence in women age <40 ¹³⁸
Presentation	More advanced in younger women, more diagnostic delays ^{10,11}
Biology	High frequency of HR-negative disease ²⁹
Genetics	As younger women are more likely to have inherited susceptibility, genetic testing is recommended for all patients ≤40 years
Prognosis	Inferior outcome in younger patients ^{45,57,58}
Unique considerations	Premature ovarian failure, reduced fertility, increased social stressors from raising young children and active workforce participation, prolonged survivorship period, bone loss

Abbreviation: HR, hormone receptor.

the sensitivity of mammography.⁸ Despite this, mammography is still an important screening tool. The incorporation of tomosynthesis, or three-dimensional mammography, will likely improve the sensitivity and specificity of mammography in women with dense breast tissue.⁹

Diagnostic evaluation of young women with breast complaints

Women, regardless of age, who present with symptoms, require diagnostic evaluation and a CBE. Because younger women do not undergo routine screening mammography, most will present with symptomatic and higher stage

breast cancer^{10,11} versus women diagnosed with a screening study. Young age and symptomatic presentation are both associated with delay in diagnosis and worse outcomes.^{10–12} The imaging modality selected for the diagnostic workup depends on the patient’s age and presenting symptoms.^{13–16} Masses should be evaluated by ultrasound with or without mammography, depending on the patient’s age, the clinical suspicion, and the nature of the mass. Pathologic nipple discharge concerning for ductal carcinoma in situ may mandate mammography even in younger women to evaluate for calcifications. Magnetic resonance (MR) is typically not indicated for evaluation of mammographic or ultrasound abnormalities; suspicious findings on conventional imaging or examination require standard evaluation, including biopsy, even in the setting of a negative MR. Negative imaging of any type does not negate the possibility of malignancy, and therefore even in the setting of normal imaging, suspicious palpable findings require biopsy for definitive diagnosis.

Genetic predisposition

First-degree relatives of women with breast cancer have nearly a twofold increased breast cancer risk compared to the general population, and this risk is much higher when the relative is diagnosed at a young age.^{17,18} Large twin studies have demonstrated nearly one-third of all breast cancer is attributed to hereditary factors.^{19,20} However, the susceptibility genes

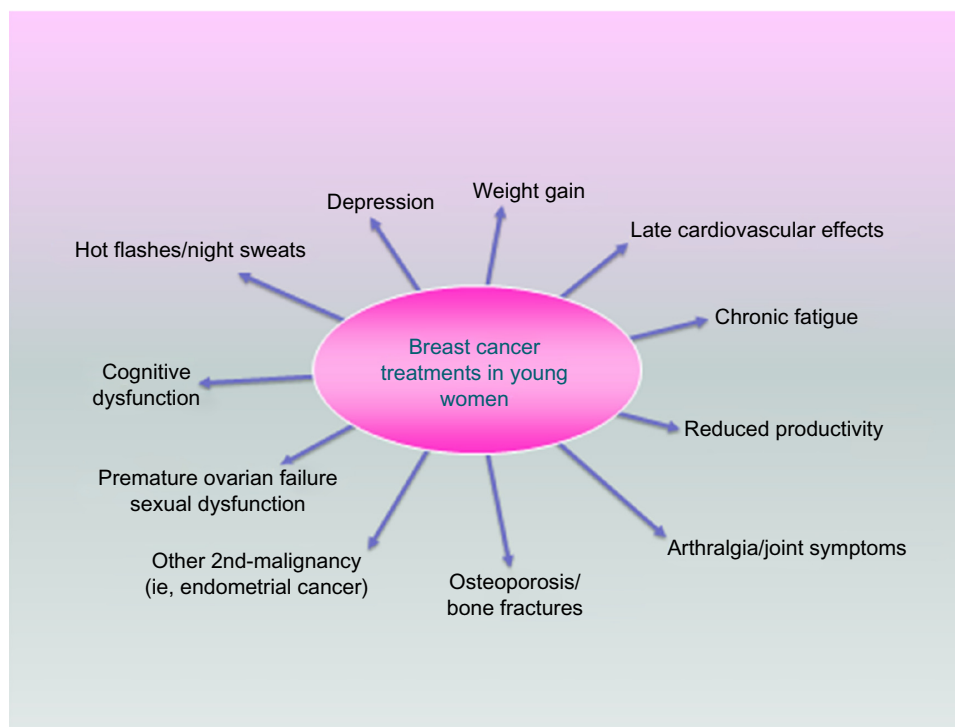


Figure 1 Breast cancer diagnosis and treatment effects on young women.

identified to date account for only 20%–30% of the excess familial risk.^{21,22} Consequently, the genetic etiology for the majority of families with an increased familial breast cancer risk remains unknown.

Young age at diagnosis is a feature of hereditary disease, and it is currently recommended that all women diagnosed with breast cancer less than 40 years of age be referred for genetics assessment. A higher proportion of young women with breast cancer have germline mutations, compared to their older counterparts, with most studies evaluating the prevalence of *BRCA1*, *BRCA2*, and *TP53* mutations.^{23–25} Furthermore, a greater proportion of young women, especially black women, have triple-negative disease, and among these women there is also an increased frequency of germline mutations, notably in *BRCA1*, *BRCA2*, and *PALB2* genes.²⁶ Identification of germline mutations has the potential to impact a woman's medical care, and to be informative for at-risk family members.

Multiple gene panels, with concurrent analysis of genes with varied levels of breast cancer risk, are now commonly used in clinical practice. Maxwell et al²⁷ evaluated the use of a 22-gene panel among a cohort of young women with breast cancer, classifying the results into clinically actionable and unclear actionability, based on the available data of the risks associated with each gene. Only 2.5% of this cohort of 278 patients was identified with clinically actionable gene variants compared to 8.6% of patients with variants for which clinical data are deficient.²⁷ The current lack of clinical validity for many genes makes translating clinical genetic testing results into improved patient care difficult, with the potential for overtreatment. Some investigators have advocated that genetic testing for breast cancer risk should only be offered after the clinical validity is established for the genes to be analyzed.²⁸ Until additional cancer susceptibility genes are discovered and clinical validation of recently discovered genes is performed, clinicians will need to continue to rely on the family cancer history to help guide medical care for the majority of young women diagnosed with breast cancer.

Biology of early-onset breast cancer

Differences in pathologic characteristics between younger and older women with breast cancers have been observed in multiple studies. The Prospective study of Outcomes in Sporadic and Hereditary breast cancer is the largest to investigate factors affecting breast cancer prognosis in patients ≤ 40 years; however, there is no comparison to older women due to the observational nature of the study.²⁹ Although only 30% of the patients had screen-detected cancers, 50% of the patients

in this multicenter study presented with nodal involvement. One-third of them were hormone receptor (HR) negative, 20% had triple-negative breast cancer, and almost 60% had poorly differentiated tumors. In addition, although majority of patients received chemotherapy in addition to endocrine therapy, 10% of those with HR-positive breast cancer developed a late relapse between years 5 and 8. At a median follow-up of 5 years, the overall survival was 82%, with the majority of deaths due to breast cancer. Another large study using the California Cancer Registry also found that 20% of adolescents and young adults with breast cancer had triple-negative disease and 54% had high-grade tumors.³⁰ Numerous other studies have also suggested more biologically aggressive cancers in younger women.^{10,31–37}

Gene expression profiling has subdivided triple-negative-breast cancer (TNBC) patients into clinically relevant subtypes now being used to design clinical trials.³⁸ A comprehensive study on TNBC samples revealed several biomarkers, including *TP53*, *PIK3CA*, *AKT1*, *PTEN*, and *HER2* mutations that may be therapeutically relevant in the future.³⁹ Clinical trials investigating agents targeted at such aberrations are underway. For example, a recent open-label Phase II trial investigating enzalutamide, an androgen receptor (AR) antagonist, in AR-positive advanced TNBC patients, reported a 16-week clinical benefit rate of 35%.⁴⁰ TNBC cases that were strongly AR-positive exhibited lower proliferation rates than those that were not AR-positive.³⁹ These AR-positive tumors tend to be rich in genes regulated by the hormonal pathway.

TNBC is an immunogenic form of breast cancer due to the frequency of mutations causing neoantigens, and the association between high rates of tumor infiltrating lymphocytes and improved response to chemotherapy and survival seen in that subset of breast cancer.^{41,42} Novel immune checkpoint inhibitors, such as the PDL1 and PD1 inhibitors, appear to have activity in TNBC patients as well. Two studies utilizing these agents in the advanced TNBC setting reported durable clinical benefits in patients with PDL1-positive TNBC.^{43,44} Thus, new predictive markers in TNBC may prove to be therapeutically relevant in the future.

Several groups have also found gene expression profile differences between breast cancers occurring in younger versus older women. In the largest study evaluating age-related biological differences in breast cancer, Azim et al⁴⁵ found that genes enriched in processes related to immature mammary cell populations (*RANKL*, *c-kit*, *BRCA1*, mammary stem cells, and luminal progenitors cells) and growth factor signaling (*MAPK*, *PI3K*) were predominant in younger women.

Analysis of clinically annotated microarray data from 784 breast cancer patients also revealed that young women ≤ 45 years had lower mRNA expression of *ER α* , *ER β* , and PR, but higher expression of *HER2* and *EGFR* as opposed to women ≥ 65 years.⁴⁶ In women < 40 years, gene expression profiling further showed lower expression of *ER α* and *ER β* compared with women 40–50 years. In addition, gene sets unique to younger women included those related to biologically relevant and potentially actionable processes such as immune function, mTOR/rapamycin pathway, hypoxia, *BRCA1*, stem cells, apoptosis, histone deacetylase, and multiple oncogenic signaling pathways.

Differences in biology in young women also differ by race. In a large Surveillance, Epidemiology, and End Result (SEER) study involving over 126,000 women aged ≤ 49 years with breast cancer, we have previously reported that a higher proportion of blacks versus whites developed breast cancer under age 40. A higher proportion of blacks also presented with HR negative, more advanced stage, and higher grade tumors.⁴⁷ In the Carolina Breast Cancer Study, the prevalence of basal-like breast cancer was highest (39%) among black premenopausal women compared with other groups of patients (14%–16%).⁴⁸ This has also been observed in other studies in the US.^{49,50}

Prognosis

A recent study showed an increase in the incidence of young women aged 25–39 years diagnosed with metastatic breast cancer from 1.53 to 2.90 per 100,000 from 1976 to 2009.⁵¹ Several reasons such as stage migration, improved surveillance, and population-based changes in breast cancer risk factors may be implicated. This increase is particularly concerning as young age is an independent adverse factor for poor prognosis among women with breast cancer.^{1,52–56} The clinical outcome is worsened for very young women under age 35, with the hazard of death increasing by every 1 year decrease in age.⁵⁷ It is also apparent that the effect of age on outcome is modified by breast cancer subtype. A study by Sheridan et al⁵⁸ showed that within the HR-positive subtype, younger age carried a worse prognosis than older age. This has also been confirmed in Azim et al's⁴⁵ study, where they found an inferior relapse-free survival with young age in the HR-positive/HER2-negative subtype in a subgroup analysis.

Treatment

Locoregional treatment – surgery

Young women with breast cancer have similar surgical options as older women. These include breast conserva-

tion therapy (BCT) (partial mastectomy with radiation) or mastectomy. Although young age at diagnosis is associated with a higher risk of local recurrence and more aggressive phenotypes, data suggest no survival gains with mastectomy compared to BCT, and there does not appear to be a survival advantage with contralateral prophylactic mastectomy either.^{59–63} Therefore, young age alone is not a contraindication to BCT. Despite this, bilateral mastectomies are on the rise in women of all ages.^{61–63} This is likely due to patient and physician perception of improved outcomes and due to improved reconstruction techniques and cosmesis. Immediate and immediate-delayed reconstruction are now preferred, and many women are candidates for nipple sparing procedures with immediate or immediate-delayed reconstruction. Nipple sparing procedures are increasingly being offered as data supports the oncologic safety, and these procedures are associated with better self-image.^{64,65}

Locoregional treatment – radiotherapy

After partial mastectomy, adjuvant whole breast radiation has been shown to reduce the risk of ipsilateral breast tumor recurrence, as well as improve breast cancer survival.^{66,67} Adjuvant radiation is especially important for young women in this setting, as their absolute risk of local recurrence is higher than for older women, and as a result, younger women have a greater absolute benefit from adjuvant radiation.⁶⁷

For young women with early-stage breast cancer, there are important considerations with regards to treatment volume. Accelerated partial breast irradiation (APBI) may not be an appropriate option for young women. Although results from the NSABP B-39 trial,⁶⁸ comparing whole and partial breast radiation, are pending, there are several published consensus statements describing APBI selection criteria. All include a minimum patient age in their criteria, ranging from 45 to 60 years as the suggested minimum age.^{69–71} This is based on the existing published literature on APBI which primarily includes women over 50, the concern for increased risk of multifocal and multicentric disease in younger women, and the known higher local recurrence rates seen in young women who receive whole breast radiation. NSABP B-39 trial included women over 18 years old, and we await the results from this trial.

Other considerations with regards to dose and fractionation include the use of boost and hypofractionation. In the European Organization for Research and Treatment of Cancer trial, use of boost reduced the 20-year cumulative incidence of ipsilateral breast tumor recurrence from 16.4% to 12.0% (hazard ratio: 0.65, $P < 0.0001$).⁷² The benefit of a boost

was found to be greatest for young women. The absolute risk reduction was 4.4% in the entire cohort, and 11.6% for women under 40. Hypofractionated whole-breast schedules have been found to be as effective as standard fractionation for certain populations. However, majority of these data were obtained in women over 50 years old, and therefore the American Society for Radiation Oncology guidelines on fractionation support the use of hypofractionation only for women over 50, who also meet the other specified criteria.⁷³ Until further evidence is available for younger women, the standard of care for these women includes delivery of whole-breast radiation with standard fractionation.

For women with locally advanced breast cancer, randomized trials have demonstrated a locoregional recurrence and survival benefit to postmastectomy radiation for women with large primary tumors >5 cm, invasion of the skin or chest wall, or lymph node involvement.^{74–76} Retrospective analysis of 107 stage II or III patients aged ≤35 years treated with or without adjuvant radiation following mastectomy showed that patients who received postmastectomy radiation compared with those who did not had a better 5-year local control and overall survival rates.⁷⁷ Since young age and/or premenopausal status are risk factors for locoregional recurrence after mastectomy, some young women with node negative disease may benefit from postmastectomy radiation if they have additional risk factors.^{78–80}

For most breast cancer scenarios, young women have a higher risk of local and regional recurrence, and therefore derive an even greater absolute benefit from adjuvant radiation than older women. Given their young age and potential for long-term survival, special care must be taken during radiation treatment planning to minimize radiation exposure to adjacent organs in order to reduce the risk of late effects and secondary malignancies.

Systemic treatment – endocrine

The Early Breast Cancer Trialists' Collaborative Group's (EBCTCG) meta-analyses demonstrated that 5 years of adjuvant tamoxifen improved the annual breast cancer death rate by one-third and recurrence risk by 50% for all women with HR-positive cancers irrespective of age.⁸¹ However, approximately 10% of those with HR-positive cancers will develop a late relapse beyond year 5; therefore, there has been interest in extending adjuvant endocrine therapy to prevent later relapses. In the Adjuvant Tamoxifen: Longer Against Shorter trial, women with early stage breast cancer were randomly assigned to continue tamoxifen to 10 years or stop at 5.⁸² Allocation to 10 years was associated with

reductions in the risk of recurrence, improvements in breast cancer specific survival, and overall survival. Similarly, in the UK adjuvant Tamoxifen-To offer more? trial, 10 years of adjuvant tamoxifen reduced late breast cancer recurrences and mortality among women with HR-positive cancers.⁸³ The group that continued tamoxifen to year 10 had further reductions in recurrence, from year 7 onward, as well as breast cancer mortality after year 10. Based on these and other studies, the American Society for Clinical Oncology clinical practice guideline now recommends treatment with adjuvant tamoxifen for 10 years in women with stage I–III HR-positive cancers. While these results were not restricted to young women, in clinical practice, young patients who are believed to have a worse prognosis are generally being considered for 10 rather than 5 years of tamoxifen.

An alternative form of endocrine manipulation involves ovarian suppression (OS). Although, the prognosis for premenopausal women who have chemotherapy-induced amenorrhea (CIA) is better than for those who do not have CIA, the prognostic value of therapeutic OS remains unclear.^{84–86} The Suppression of Ovarian Function (SOFT) trial was designed to determine the utility of dual endocrine blockade by adding OS to tamoxifen and also to determine the benefit of an aromatase inhibitor with OS for premenopausal patients.⁸⁷ Premenopausal women were assigned to either 5 years of tamoxifen, tamoxifen plus OS, or exemestane plus OS. At 5 years, 90.9% of those who received exemestane with OS were free from breast cancer, versus 88.4% in the tamoxifen plus OS arm, versus 86.4% in the tamoxifen alone group. In the subgroup of women younger than 35 years, the rate of freedom from breast cancer at 5 years was 83.4% for those assigned to exemestane plus OS, 78.9% for those assigned to tamoxifen plus OS, and 67.7% for patients assigned to tamoxifen alone. Similarly, the Tamoxifen and Exemestane Trial (TEXT) was designed to compare exemestane plus OS versus tamoxifen plus OS also in premenopausal women.⁸⁸ In the combined analysis of both SOFT and TEXT trials, the 5-year rate of freedom from breast cancer was 92.8% in those receiving exemestane plus OS, versus 88.8% for those assigned to receive tamoxifen plus OS. The symptom burden of OS with either tamoxifen or exemestane is higher than tamoxifen alone and different depending on what drug is given in combination with OS. Patients who receive tamoxifen have more vasomotor symptoms, while those who receive exemestane have more arthralgia, sexual dysfunction, and vaginal dryness.⁸⁹ These side effects need to be discussed with individual patients prior to electing treatment. Results from these studies show that even in premenopausal women

with early stage breast cancer, the outcomes in those with HR-positive cancers is very good in general; however, there is still a need to define who merits more aggressive therapy. In addition, further tools and research are needed on compliance, management of menopausal symptoms, bone loss, cognitive problems, and sexual dysfunction, and careful monitoring of late side effects such as secondary malignancies.

Systemic treatment – chemotherapy

The preferred chemotherapy regimens remain the same for all patients with early stage breast cancer irrespective of age. In general, for most high-risk breast cancer patients, combination regimens including anthracyclines and taxanes are employed. The EBCTCG meta-analyses, evaluated the benefits of adjuvant polychemotherapy on outcomes in younger versus older women.⁸¹ Anthracycline-based chemotherapy combinations had a larger impact in reducing the annual breast cancer death rate for women younger than 50 years (38% reduction) versus 20% for those aged 50–69 years. In addition, there was also a threefold age-related benefit for polychemotherapy versus no chemotherapy for women <50 years versus women 50–69 years with larger benefits for recurrences than mortality. The 5-year improvements from chemotherapy were approximately twofold for HR-negative versus HR-positive cancers, but the 15-year improvements were less dependent on HR status, likely due to differences in timing of recurrences with HR-negative versus HR-positive cancers. Preferred National Comprehensive Cancer Network (NCCN) guidelines for adjuvant chemotherapy for high-risk HR-breast cancer patients include several regimens such as doxorubicin plus cyclophosphamide followed by paclitaxel or docetaxel plus cyclophosphamide.

Systemic treatment – biologic therapy

Patients who have HER2+ breast cancer receive trastuzumab as part of their (neo)adjuvant systemic treatment based on improvements in overall survival seen in large randomized trials.^{90–93} Young patients also derive similar benefits from adjuvant trastuzumab as older patients.¹² Pertuzumab is a humanized monoclonal antibody directed at HER2 and is approved in combination with trastuzumab and chemotherapy for treatment of HER2+ breast cancers in the neoadjuvant and advanced settings based on several studies.^{94–96}

Unique considerations

Fertility preservation

Among the unique concerns for young women with breast cancer are treatment-induced ovarian failure and infertility.

The risk of infertility varies according to age, reproductive reserve, chemotherapy agent, duration of treatment, and dose administered.⁹⁷ Alkylating agents are among those with the highest gonadotoxic properties.⁹⁸ The true rates of infertility after breast cancer treatments have been difficult to ascertain as there is no consensus on what constitutes infertility. Different surrogates used in different studies include amenorrhea, estradiol, anti-Mullerian hormone, inhibin B, and follicle count.^{99,100}

Young women who are desirous of future childbearing should be properly counseled by an oncofertility specialist on options for fertility preservation prior to chemotherapy. Existing reproductive options include embryo and oocyte cryopreservation, cryopreservation of ovarian tissue, or OS with luteinizing hormone releasing hormone (LHRH) agonists.^{101–103} The POEMS study randomized 257 premenopausal women with HR-negative breast cancer to receive standard chemotherapy with or without goserelin to determine if goserelin reduced ovarian failure.¹⁰⁴ The ovarian failure rate was 8% in the intervention group versus 22% in the chemotherapy group. In addition, 22 patients in the goserelin group achieved at least 1 pregnancy versus 12 in the standard group, although more women in the goserelin group attempted pregnancy. While these data are encouraging, the use in those with HR-positive cancer is cautioned, as this study only included those with HR-negative cancer. Although less of an issue with LHRH agonists that are administered during chemotherapy, practical barriers limiting fertility preservation are cost, insurance, absence of a male partner, and chemotherapy timing issues.

Retrospective studies have suggested no worsening of breast cancer outcomes in patients who become pregnant.^{105–108} POSITIVE (Pregnancy Outcome and Safety of Interrupting Therapy for women with endocrine responsive Breast Cancer) is an ongoing trial, designed to evaluate the safety and outcomes of women with HR-positive cancers who interrupt endocrine therapy for childbearing. This trial seeks to enroll women under age 42 who have received 18–30 months of endocrine therapy and who then stop endocrine therapy temporarily to attempt pregnancy.¹⁰⁹ Guidelines also recommend avoiding pregnancy within 6 months of systemic therapy completion, due to teratogenicity.^{110,111}

Pregnancy-associated breast cancer

The incidence of pregnancy at the time of breast cancer diagnosis is approximately 1.5%, and breast cancer is the most common pregnancy-associated malignancy in women.^{112–114} A confirmed diagnosis of malignancy should prompt

diagnostic mammography in addition to ultrasound with uterine shielding.¹¹⁵ Fine needle aspiration may be difficult to interpret in the setting of pregnancy-related proliferative changes;¹¹⁶ core biopsy is preferred. The pathologist should be alerted to the patient's gravid state. Staging should be directed by signs and symptoms and by clinical stage as for the nonpregnant patient. Computed tomography, plain X-ray, and nuclear medicine studies expose the fetus to radiation, and so risks and benefits of this exposure need to be weighed. Nuclear medicine studies are typically avoided due to a lack of safety data, and breast MR, which requires gadolinium contrast, is not safe during pregnancy.^{117,118}

Surgery is often the safest mode of treatment during early pregnancy as endocrine and cytotoxic therapies are contraindicated during the first trimester.¹¹⁹ For patients who undergo surgery early in pregnancy and who do not need adjuvant chemotherapy, radiation may be delayed many months although studies suggest worse outcomes with such delays.¹²⁰ Fetal radiation exposure is associated with birth defects, mental retardation, childhood malignancy, and other complications, and as the fetus grows its proximity to the breast increases, the potential for fetal radiation exposure increases.^{119,121} Therefore, radiation is contraindicated in the third trimester. Clinically node-negative women undergo axillary staging with a sentinel lymph node biopsy. Traditionally, radioisotope was avoided due to the risk of radiation exposure to the fetus. More recent data suggest that the dose to the fetus is small, and available data suggest no negative impact on pregnancy outcomes with the use of radioisotope.^{122,123} This method of sentinel node mapping may be preferred due to continued concerns about teratogenicity or maternal anaphylaxis with methylene blue and isosulfan blue dye, respectively, both of which are Pregnancy Class C drugs. A small series, however, has not demonstrated negative pregnancy outcomes with the use of blue dyes.¹²³ The potential risks and benefits of the sentinel node procedure need to be discussed with patients preoperatively.

Fetal malformations are seen with first trimester exposure to chemotherapy.¹²⁴ Anthracycline-based regimens have the most available data and can be given during the second and third trimesters.^{125–127} Chemotherapy should be withheld ideally at least 3 weeks before confinement to avoid cytopenias at the time of delivery. Other systemic therapies such as endocrine therapy and trastuzumab are contraindicated during pregnancy.¹²⁸

Bone health

Young women with breast cancer are at higher risk of long-term side effects from cancer treatments and survivorship

due to the longer life expectancy. One particular area which has received a lot of recent attention is bone health. Although fragility fractures are more common in women over 50 years, several factors lead to bone compromise in younger women treated for breast cancer. Androgens and estrogens are regulators of bone growth, and consequently, estrogen deficiency is a key determinant in bone loss. Cancer treatments with chemotherapy can lead to estrogen deficiency via gonadal dysfunction, and also impair bone health via direct effects on bone metabolism or systemic steroids commonly used as supportive medications during chemotherapy. Radiation can impair bone integrity in the treated radiation field. Hormonal treatment designed to induce hypogonadism also leads to accelerated bone loss. In premenopausal women receiving endocrine therapy for breast cancer, changes in bone mineral density have been observed with tamoxifen, ovarian suppression, tamoxifen or aromatase inhibitors with ovarian suppression, and oophorectomy.^{129–131} Thresholds for pharmacologic intervention with bisphosphonates or RANK ligand inhibitors include a history of osteoporosis, fragility fractures, and osteopenia with additional risk factors. Several studies have confirmed that antiresorptive therapies maintain or increase bone mineral density in women or men treated with endocrine therapy.^{129,132–137} While this is encouraging, it remains unclear what impact these treatments have on the incidence of fractures in those at risk.

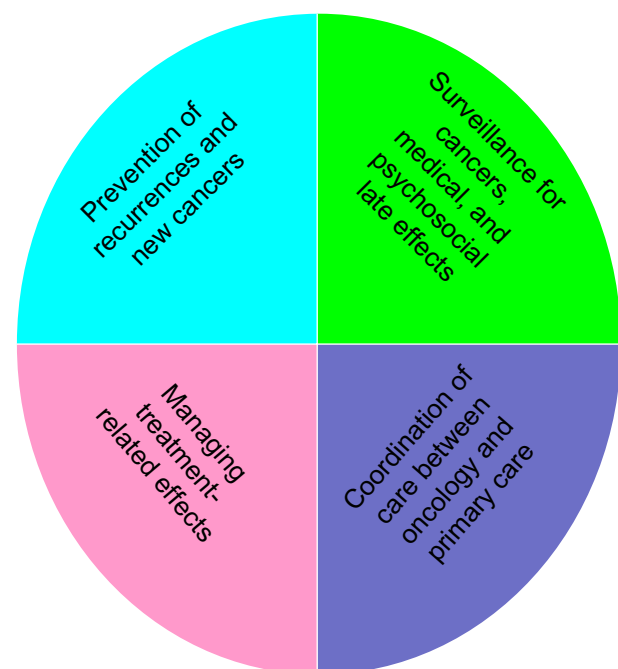


Figure 2 Essential components of a survivorship plan.

Conclusion

Young patients with breast cancer face unique management challenges that are best addressed in a multidisciplinary setting. Currently, treatment recommendations are made on tumor characteristics and not solely on age. Close attention to long-term side effects with optimal supportive care should be considered. A survivorship care plan involving a multidisciplinary team is essential for young patients (Figure 2). Younger patients are also underrepresented in clinical trials and should be encouraged to participate for a better understanding of early-onset breast cancer.

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The authors report no conflicts of interest in this work.

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