Journal of Multidisciplinary Healthcare

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Breast cancer in young women: special considerations in multidisciplinary care

This article was published in the following Dove Press journal:
Journal of Multidisciplinary Healthcare
29 September 2014
Number of times this article has been viewed

Chantal Reyna
Marie Catherine Lee

Comprehensive Breast Program, H Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

Abstract: Breast cancer is one of the most prevalent cancers in females, and 5%–7% of breast cancer cases occur in women under 40 years of age. Breast cancer in the young has gained increased attention with an attempt to improve diagnosis and prognosis. Young patients tend to have different epidemiology, presenting with later stages and more aggressive phenotypes. Diagnostic imaging is also more difficult in this age group. Multidisciplinary care generally encompasses surgeons, medical oncologists, radiation oncologists, radiologists, and social workers. Other special considerations include reconstruction options, fertility, genetics, and psychosocial issues. These concerns enlarge the already diverse multidisciplinary team to incorporate new expertise, such as reproductive specialists and genetic counselors. This review encompasses an overview of the current multimodal treatment regimens and the unique challenges in treating this special population. Integration of diagnosis, treatment, and quality of life issues should be addressed and understood by each member in the interdisciplinary team in order to optimize outcomes.

Keywords: diagnosis, interdisciplinary, quality of life, treatment, premenopausal, fertility preservation

Introduction

The care of young women with breast cancer has become a more recent focus with improvements in diagnosis, treatment, and survivorship. This population, usually defined as women diagnosed under the age of 40, requires individualized treatment plans. Because of the inherently multimodal treatment plans, breast cancer has been a model for multidisciplinary care planning, and typically involves surgeons, medical oncologists, radiation oncologists, radiologists, pathologists, geneticists, social workers, and plastic surgeons. Given the differences in epidemiology and management options, as well as the unique issues surrounding fertility, sexuality, and pregnancy, the multidisciplinary approach to treatment for these women frequently may also incorporate other areas of expertise.

Epidemiology

Around 5%–7% of breast cancers are diagnosed in women younger than 40, making it the most commonly diagnosed female cancer in the 25- to 39-year-old age group.[1–3] Overall, the incidence of breast cancer remains the highest in the non-Hispanic white population. When stratified by age, incidence rates are similar for non-Hispanic whites and African Americans between the ages of 30 and 49 years. However, in patients

Correspondence: Marie Catherine Lee
Moffitt Cancer Center, Comprehensive Breast Program, 12902 Magnolia Drive, Tampa, FL 33612, USA
Tel +1 813 745 8480
Fax +1 813 745 7287
Email m.catherine.lee@moffitt.org

younger than 40 years specifically, African American females have the highest relative incidence of breast cancer.[4,5]

In comparison to the older population, breast cancer in the young appears to have some marked differences. Young women tend to present at more advanced stages and their tumors tend to be higher grade, hormone receptor negative, have increased HER2/Neu overexpression, and more lymphovascular invasion.[2,6–9] A retrospective study of 700 breast tumors by Anders et al demonstrated that women younger than 45 years were less likely to have estrogen receptor-positive disease, and more likely to have grade 3 tumors, nodal metastasis, and larger primary breast tumors.[9] Multiple studies demonstrated the overrepresentation of triple-negative breast cancers (TNBC) in the young, particularly in African American females.[2,3,7]

Similar to tumor biology and presentation, diagnosis at a young age also impacts local recurrence and overall survival. An analysis of two trial groups, European Organization for Research and Treatment of Cancer (EORTC) and National Surgical Adjuvant Breast and Bowel Project (NSABP), indicated a higher risk of local recurrence in patients younger than 35 years.[2,10,11]

Overall survival is also affected; some studies showed higher mortality rates (up to 1.5-fold) for diagnosed women younger than 40 years.[1,12] A review of the Surveillance, Epidemiology, and End Results database (SEER) from 1998–2003 by Gnerlich et al indicated young patients with stage 1 or 2 breast cancer had a higher disease-specific mortality rate when adjusted for other factors.[8] It is unclear whether the survival difference is due to the aggressive phenotype of these tumors or more advanced stages at presentation.[13,14]

Breast cancer at a young age is associated with an increased risk for contralateral breast cancer (CBC).[15,16] Overall, patients younger than 50 years have a risk of CBC of 0.1% annually, or approximately 13% cumulative risk in a 10-year period.[17] Diagnosis before the age of 45 doubles the risk of having a CBC.[17] Radiation during the initial breast cancer diagnosis and family history have been implicated as risk factors for CBC in young patients.[15] Given this information, these patients should be followed closely with contralateral breast imaging after breast cancer treatment, despite their young age.

Diagnostic imaging

Although mammography has been the only imaging modality shown to decrease mortality in breast cancer, radiologic imaging is difficult in the younger population.[18,19] Usually, these patients present with breast symptoms. Routine mammographic screening is not recommended under the age of 40 due to decreased mammographic sensitivity, generally a result of breast density.[19] Poor sensitivity may lead to missed or misinterpreted lesions in women with dense breast tissue; for these reasons, screening mammography is neither cost effective nor beneficial in this population.[19–22]

Given the limitations of mammography in dense breast tissue, ultrasound and breast-specific magnetic resonance imaging (MRI) are frequently used in the diagnostic setting. Although screening is not recommended for women at average risk prior to age 40, it is important to note that annual breast MRI is currently recommended for screening of unaffected women starting at age 30 if they have a lifetime breast cancer risk at or exceeding 20%–25%. This is a fairly specific population, primarily comprised of women with known or suspected deleterious genetic mutations associated with breast cancer, or women previously treated with mantle radiation for the treatment of lymphoma.[23] Similar to ultrasound, MRI has a high sensitivity, but low specificity for breast cancer, which may lead to unnecessary biopsies. However, MRI has still been shown to be more sensitive than mammogram in the dense breast population.[24] It is important to note that the American Cancer Society specifically does not recommend the use of breast density alone to justify MRI for screening purposes.

Surgical approach

The overall surgical approach to the young adult is similar to the general breast cancer population; however, there are unique considerations given the general good health and potential longevity of these women, and early integration of multiple providers can markedly impact surgical, oncologic, and cosmetic outcomes. In the nonmetastatic setting, local–regional control of the breast still can be achieved with partial mastectomy and radiation (breast conserving therapy [BCT]) or mastectomy. This decision depends on tumor burden, cosmetic outcome, previous radiation, patient preference, and reconstructive options. Because most women in this age group have few comorbidities and low surgical risk, a discussion of breast reconstruction relative to the oncologic surgical plan should be addressed early in the treatment discussions.

In the general breast cancer population, the recurrence rate and the disease-free survival rates are similar between women receiving BCT or mastectomy.[25,26] Overall, triple negative breast cancers (TNBC) have higher local-regional and distant recurrence rates compared to other subtypes of

breast cancer. Two recent studies suggest that TNBC treated with BCT have a decreased local-regional recurrence rate compared to modified radical mastectomy without radiation, suggesting radiation may benefit in the local regional control in TNBC.[27,28] In very young patients (under 35 years old), BCT has been shown to have higher recurrence rates compared to older patients receiving BCT.[26,29,30] Voogd et al combined data from two large trials on early breast cancers and demonstrated a ninefold increased local recurrence risk after BCT in patients younger than 35 years compared to those older than 65.[26] This increased recurrence risk is likely multifactorial and may be the result of tumor biology, inability to obtain negative margins, or the presence of a large intraductal component within the tumor. This conflicting data should be considered carefully, especially when making surgical recommendations for TNBC.[29]

In contrast to BCT, mastectomy encompasses a number of similar procedures, all of which involve removal of the mammary gland and vary by the removal of the overlying skin and nipple–areolar complex. The operations range from simple or total mastectomy (removal of the gland and excess skin with the nipple), skin-sparing mastectomies (leaving 90% of the overlying skin intact), to nipple and areolar-sparing mastectomies (entire skin envelope and nipple–areolar complexes preserved). The modified radical mastectomy involves removal of the entire nipple, breast, skin envelope, and the level I/II axillary lymph nodes. Skin sparing mastectomies have been shown to have similar overall survival rates to simple mastectomies in early-stage breast cancer; most skin-sparing procedures are performed with a plan for immediate or delayed-immediate breast reconstruction.[31,32] Of note, local recurrence rates are similar between young and old patients undergoing mastectomy.[26,29] The type of mastectomy chosen may be influenced by other factors, such as radiation and reconstruction, and should be discussed early in breast cancer care.

Independent of the surgical choice, axillary staging is still required in these patients. These options do not differ from those of the older population and include axillary ultrasound with or without percutaneous biopsy of abnormal findings, sentinel lymph node biopsy, or axillary lymph node dissection. If axillary ultrasound with percutaneous biopsy identifies nodal metastasis, the patient may forego sentinel lymph node biopsy, saving both time and money.[33–36] Of note, lymphedema rates have been reported to be higher in younger patients, the cause of which, whether from increased baseline activity level or more aggressive radiation to nodal basins, remains unclear.[37]

In this young population, the role of contralateral prophylactic mastectomy is a frequent discussion. The overall rates of contralateral prophylactic mastectomies (CPM) are on the rise, especially in those who are of European descent, have a family history of breast/ovarian cancer, or plan to undergo immediate reconstruction.[38–40] Symmetry is often cited as a reason for CPM. CPM has been shown to decrease the risk of a CBC, but multiple studies have failed to demonstrate a survival benefit.[41–44] A recent Cochrane review by Lostumbo et al concluded that there is currently insufficient evidence to support a survival advantage for CPM.[45] Only two publications have indicated a survival benefit for CPM, and only for very select populations. The first by Herrinton et al studied 1,072 patients who underwent CPM, and found a lower breast cancer-specific mortality risk.[44] The second study is a univariate analysis of the SEER database of 8,902 patients undergoing CPM, which found a disease-free and overall survival advantage in the subset of early stage, estrogen-receptor (ER) negative patients (under 50 years of age).[46] However, these results have not been replicated elsewhere. The majority of this information was obtained in a retrospective fashion and extrapolated to calculate cancer risk, making interpretation of benefit difficult to ascertain (Table 1). Given the lack of demonstrated oncologic benefit, patients should be aware of the multiple alternatives to mastectomy to achieve symmetry, including mastopexy, reduction, or augmentation procedures as part of the informed decision-making process.

The benefits to CPM are difficult to quantify, but several associated risks have been identified. An analysis of the American College of Surgeons National Surgery Quality Improvement Program (NSQUIP) revealed patients who had bilateral mastectomies had more postsurgical problems, including wound and infectious complications, compared to those undergoing unilateral mastectomy.[47] In a retrospective study of 600 patients, Miller et al supported that patients electing to have CPM not only had more overall complications, but also more major complications requiring reoperation and rehospitalization.[48] With mixed results regarding CBC and the demonstrated increased risks of complications, the decision for CPM is very subjective, and resides with the patient and the surgical team on a case-by-case basis.

Along with the deliberation of CPM is the discussion of breast reconstruction. Reconstructive procedures can be limited by body habitus, postmastectomy radiation recommendations, and fertility decisions. Those patients interested in future childbearing may not be candidates for autologous

Table 1 Overview of contralateral prophylactic mastectomy trials and reviews: rates, risk reduction and overall survival

Study	Study type and number of subjects (n)	Results
Peralta et al[43]	Retrospective Cohort n=64	1. CPM decreased risk of CBC 2. CPM improved disease free survival at 15 years (55% versus 28%) 3. CPM did not significantly improve overall survival at 15 years (64% versus 48%)
McDonnell et al[41]	Retrospective questionnaire n=745	1. CPM in women <50 with person and family history of breast cancer had risk reduction of CBC 94% 2. CPM in women >50 with person and family history of breast cancer had risk reduction of CBC 96%
Hartman et al[42]	Retrospective Cohort n=26	1. CPM in BRCA1/2 patients reduces risk of CBC by 89-100%
Herrinton et al[44]	Retrospective Cohort n=1,072	1. CPM offers a survival benefit (HR 0.57) 2. CPM decreases risk of CBC
King et al[38]	Retrospective Cohort n=407	1. CPM rates increasing 2. Independent risk factors for CPM: age <50, family history of breast cancer, prior attempt at BCT, immediate reconstruction
Yi et al[39]	Retrospective Cohort n=284	1. CPM rates increasing 2. Independent risk factors: white, age less than 50, invasive lobular carcinoma, clinical stage, reconstruction, BRCA1/2
Stucky et al[40]	Retrospective Cohort n=1,391	1. CPM rates increasing 2. Risk factors for CPM: younger age, family history, genetic testing, triple negative breast cancer, axillary nodal metastasis
Lostumbo et al[45]	Retrospective Review n=7,384	1. CPM showed an improved disease-free survival 2. CPM does not show a survival benefit
Bedrosian et al[46]	Retrospective Cohort n=8902	1. CPM showed an improved disease free survival (HR 0.63): Risk stratification shows results are from early stage ER negative patients with lower disease specific mortality 2. CPM showed improved breast cancer survival at 5 year interval (88.5% vs 83.7%)

Abbreviations: BCT, breast conserving therapy; CBC, contralateral breast cancer; CPM, contralateral prophylactic mastectomies; ER, estrogen receptor; HR, hazard ratio.

abdominal reconstruction, particularly transverse rectus myocutaneous flap. However, other autologous flap reconstructions, such as the deep inferior epigastric perforator flap, may be considered. Several deep inferior epigastric perforator flap patients have been reported to have uncomplicated pregnancies.[49] Other options include latissimus dorsi flaps or tissue expander/implant reconstruction alone.

Breast reconstruction can be performed in an immediate (at the same time as the mastectomy) or delayed fashion (several weeks or more after the initial cancer operation) and the decision is often dependent on postmastectomy radiation recommendations. A meta-analysis of breast reconstruction and radiotherapy by Barry and Kell suggested that previously radiated tissues have more complications, poorer cosmetic outcomes, and decreased patient satisfaction.[50] For patients recommended to undergo postmastectomy radiation, reconstruction is generally deferred until well after the completion of both chemotherapy and radiation therapy.[50]

Adjuvant therapy

Young age is considered an independent risk factor for recurrence and the use of multiple adjuvant therapies is frequently recommended, varying from chemotherapy, antiestrogen therapy, ovarian suppression, or a combination of them. However, these modalities are not without significant long-term medical risks.

Chemotherapeutic regimens are not adjusted for the premenopausal population, but the absence of severe comorbidities and long-term risk of recurrence in the young is heavily weighted in the decision to recommend systemic therapy. Tumor markers, disease stage, and predictive tumor tests, such as Oncotype DX or MammaPrint, are routinely incorporated into the systemic therapy discussion.[51,52] Chemotherapy has been shown to decrease recurrence risk by 35% and mortality risk by 27% in patients under 50 years of age.[53] Furthermore, young patients who did not receive chemotherapy had a higher mortality rate compared to an older population, whereas survival rates were similar in both the young and old who received chemotherapy.[14] One meta-analysis of eight German studies demonstrated that patients younger than 35 years old had a higher rate of complete pathologic responses; however, this finding appears to be closely related to hormone receptor status.[54]

While primarily comparing the efficacy of three chemotherapy regimens, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-30 trial had a secondary aim to evaluate chemotherapy-induced amenorrhea (CIA) and survival in premenopausal patients and found improved survival in patients who achieved CIA.[11] CIA for 6 months or longer confers better prognosis, improving both disease-free survival and overall survival, despite hormone receptor status.[55,56] CIA is proportional to age, meaning younger patients are less likely to be amenorrheic as a result of their treatment.[57] As a result, recently updated American Society of Clinical Oncology guidelines recommend that young patients be evaluated for fertility preservation referral prior to starting therapy.[58]

The ovarian suppression caused by systemic therapy likely has an impact on disease-free breast cancer survival in the premenopausal population. In addition to the ovarian suppression induced by chemotherapy, selective estrogen receptor modulators, such as Tamoxifen, are the current standard for adjuvant hormonal therapy in the premenopausal population, with significant effects on disease-free survival. Patients with hormone receptor positivity are treated with Tamoxifen for 5 years due to the 54% reduction in recurrence risk.[59] Aromatase inhibitors are not recommended in premenopausal women even after CIA since the negative estrogen feedback to the hypothalamus may cause ovarian stimulation and subsequent ovarian recovery. Ovarian function monitoring via serum estradiol and gonadotropin levels may be unreliable in this patient population.[58]

Another hormonal option is ovarian suppression/ablation. Medical therapy is generally the initial approach, but consideration is given to bilateral oophorectomy. The Early Breast Cancer Trialists' Collaborative Group demonstrated that ovarian ablation decreased both breast cancer recurrence and mortality risk.[60] One study by Klijn et al demonstrated a survival benefit of a luteinizing hormone releasing hormone (LHRH) agonist in combination with Tamoxifen over Tamoxifen alone.[61] Several studies demonstrate LHRH-agonist therapy is as effective as chemotherapy in hormone receptor positive-patients.[57,62–65] The Austrian Breast Cancer Study Group (ABCSG) 5 showed ovarian suppression with goserelin in combination with tamoxifen had similar 7-year overall and disease-free survival to chemotherapy; it was also better tolerated.[66] The subsequent ABCSG 12 suggests that an aromatase inhibitor with an LHRH agonist (goserelin) is not inferior to the combination of tamoxifen and LHRH agonist.[67] A large meta-analysis of 16 studies suggested LHRH agonist in combination with tamoxifen and with or without chemotherapy increases disease-free and overall survival in premenopausal patients with early breast cancer.[67] The current Suppression of Ovarian Function Trial is a prospective randomized control trial investigating Tamoxifen versus ovarian suppression plus Tamoxifen in patients who remain premenopausal after chemotherapy, but these results were recently presented nationally (Table 2).[68] With some studies suggesting improved survival with ovarian suppression combined with selective estrogen receptor modulators, as well as a benefit when combined with chemotherapy, ovarian suppression may become a routine adjuvant therapy for breast cancer in the young.

Adjuvant whole breast irradiation after breast conservation surgery is the standard for all patients; however, the use of postmastectomy radiation is a growing area of controversy, particularly in the young breast cancer population. Multiple studies demonstrate the benefit of postmastectomy radiation in patients with tumors over 5 cm in diameter, pathologic N2/N3 disease, extracapsular extension of lymph nodes, and skin or chest wall involvement.[70] The Danish Breast Cancer Cooperative Group studied 1,708 stage II or III premenopausal patients comparing local-regional recurrence, distant metastasis, disease-free survival, and overall survival. They found postmastectomy radiation decreased local-regional recurrence and improved survival.[71] The recent National Comprehensive Cancer Network (NCCN) guidelines published in 2013 recommend strongly considering postmastectomy radiation in patients with N1 disease (1–3 positive lymph nodes), but treatment for this population ultimately is at the discretion of the radiation oncologist.[72] Two randomized controlled studies showed improved local-regional control and overall survival in early-stage premenopausal breast cancer patients who received postmastectomy radiation.[70,71]

With this recent data, women younger than 40 are more likely to receive postmastectomy radiation regardless of clinical indication than their older counterparts.[73] A recent retrospective study of 588 patients under 35 years of age treated with postmastectomy radiation demonstrated a significant reduction in local-regional recurrence without any effect on contralateral occurrence, distant recurrence rates, or overall survival after mean follow up of 8.6 years.[74] This information may lead radiation oncologists to provide postmastectomy radiation to younger patients, which will affect reconstruction as well as CPM decisions; thus, this should be discussed early and in conjunction with reconstructive and surgical oncology providers to optimize treatment delivery while minimizing risk.

Table 2 Overview of ovarian suppression and premature ovarian failure trials

	Trial	Number of subjects	Treatment	Results
Ovarian suppression trials	Early Breast Cancer Trialists' Collaborative Group[53]	n=37,000	Ovarian ablation/suppression (OA/S) versus control	1. Disease free survival OA/S 45% vs 39% 2. Overall Survival OA/S 52% vs 46%
	Klijn et al[61]	n=507	1. LHRH agonist 2. LHRH agonist with Tamoxifen	Overall survival improved with combination (HR 0.78)
	Austrian Breast Cancer Study Group 5[66]	n=1,034	1. LHRH agonist and Tamoxifen 2. Chemotherapy (Fluorouracil, Epirubicin, Cyclophosphamide	1. Disease free survival: no difference between the groups (76% vs 72%) 2. Overall Survival: no difference between the groups (91% vs 88%)
	Cuzick et al[68]	n=11,906	1. LHRH agonist 2. LHRH agonist and Tamoxifen 3. Tamoxifen 4. LHRH agonist with chemotherapy (+Tamoxifen)	1. Disease free survival improved with LHRH agonist with chemotherapy with or without Tamoxifen (HR 0.88) 2. Overall Survival after recurrence improved with LHRH agonist with chemotherapy with or without Tamoxifen (HR 0.85)
	Austrian Breast Cancer Study Group 12[67]	n=1803	1. Goserelin and Tamoxifen 2. Goserelin and Anastrozole 4. Goserelin and Tamoxifen with zoledronic acid 5. Goserelin and Anastrozole with zoledronic acid	3. Disease free survival: no difference between the groups (92.8% vs 92%) 4. Overall Survival was worse with anastrazole (HR 1.75)
	Suppression of Ovarian Function with Triptorlein (SOFT) Trial[69]	In progress	1. Tamoxifen 2. Tamoxifen and ovarian function suppresion (OFS) 3. Exemestane and OFS (OFS by GrRH agonist-triptorelin, oophrectomy or irridaiation)	Pending
	Tamoxifen and Exemestrane Trial (TEXT)[69]	In progress	1. OFS and Tamoxifen 2. OFS and Exemestrane	Pending
Premature ovarian failure trials	Del Mastro[91]	n=133	1. Triptorelin 2. No triptorelin	Triptorelin decrases rate of early menopause (8.9% vs 25.9%)
	Zoladex Rescue of Ovarian Function[92]	n=60	1. Goserelin 2. No goserelin	No difference in return of menses (70% vs 56.7%)
	Prevention of Early Menopause (POEM)[90]	n = 218	1. Goserelin 2. No goserelin	1. Decreased premature ovarian failure with goserelin (22% vs 8%) 2. Increased pregnancies (22 vs 13) 3. Disease free survival in ER negative premenopausal patients improved 4. Overall survival ER negative premenopausal patients improved

Abbreviations: ER, estrogen receptor; GrRH, gonadotropin releasing hormone; HR, hazard ratio; LHRH, luteinizing hormone releasing hormone; OA/S, ovarian ablation/suppression; OFS, ovarian function suppression.

Special considerations

Multidisciplinary breast cancer treatment in the young woman may incorporate a different variety of disciplines than the typical breast cancer patient. Consideration should be given to genetic susceptibility, fertility and family planning, and body image/psychosocial issues. These add the specialties of genetics, obstetrics/gynecology, psychology, psychiatry, and social work to the multidisciplinary team.

Hereditary breast cancer accounts for less than 10% of all breast cancers, however, current NCCN guidelines state any patient younger than 50 years old and any patient with TNBC should be referred for genetic counseling.[3,75] A breast cancer patient younger than 35 years of age has a 9.4% chance of

having a gene mutation, more than ten times the probability found in the general population.[76] Identification of a deleterious genetic mutation can impact screening, treatment, and lifestyle choices of the patient as well as other family members. Ashkenazi Jewish ancestry or a family history of breast or ovarian cancer increases the chances of having a genetic mutation.[76]

BRCA1 and BRCA2 gene mutations comprise 66%–75% of all inherited breast cancer cases.[7] These mutations increase the relative risk of breast cancer tenfold. BRCA1-associated breast cancer is more likely to involve higher-grade tumors, basal-like subtypes, and TNBC.[76] Patients between the ages of 30 and 34 with ER-negative high-grade tumors had a 26%–28% chance of having a deleterious BRCA1 mutation.[78,79] BRCA2-associated breast cancers have similar phenotypes to sporadic breast cancers and are more likely to be hormone positive and luminal subtypes.[80–82] BRCA1/2 patients have a 50% probability of developing CBC and a lifetime risk of 20%–50% of ovarian cancer.[80–82] Ovarian cancer screening requires ultrasound and CA-125 serum blood levels, but these have poor sensitivity.[83] Bilateral salpingo-oophorectomy decreases the risk of ovarian cancer by 80%–96% as well as decreases the risk for a second breast cancer; however, this risk-reducing approach is recommended after child bearing has been completed.[82] Bilateral risk-reducing mastectomy is offered as an alternative to screening regimens.

In addition to BRCA, other genes have been associated with an increased risk for breast cancer including p53, PTEN, and Lynch syndromes. Less than 1% of hereditary breast cancers are caused by Li–Fraumeni syndrome (LFS) and Cowden's disease. LFS is an autosomal dominant condition, resulting from a mutation in the p53 gene, causing breast cancer (most frequently), leukemia, sarcomas, and adrenal tumors. LFS-associated breast cancer is identified before the age of 30 in one-third of the cases, and is frequently HER2/Neu positive.[84] LFS may affect breast cancer treatment, as radiation may significantly increase the risk of a second malignancy, and thereby eliminate BCT as an option. Cowden's disease, caused by a PTEN mutation, is rare condition associated with tumors of the skin, thyroid, and endometrium in addition to breast cancer.[85]

Another special consideration in the young breast cancer population is family planning. Infertility after chemotherapy is related to the patient's age, the drug regimen, and the duration of treatment.[86,87] Currently, the American Society of Clinical Oncology guidelines recommend early discussion of possible infertility as a result of breast cancer treatment with referral to reproductive specialists for those patients interested in fertility preservation.[88] A retrospective study showed that most breast cancer patients less than 40 years old were concerned about infertility.[89] Therefore, fertility preservation options should be discussed prior to starting any systemic therapy.

Fertility preservation options include embryo cryopreservation, oocyte cryopreservation, and ovarian preservation with luteinizing hormone releasing hormone (LHRH) agonists. Embryo cryopreservation is the most effective, with live birth rates around 33% in patients less than 35 years old, 30% in patients 35–37 years old, and 25% in patients 38–40 years old.[7] Ovarian preservation with LHRH agonists is the only option that does not require in vitro fertilization. It suppresses gonadotropins and halts follicular development. Studies currently have mixed results (Table 2), but a study by Del Mastro et al showed decreased rates of early menopause after chemotherapy and LHRH agonist combined compared to chemotherapy alone.[90–92] No overall increase of recurrence has been shown following fertility treatments.[58] Breast cancer should not prevent child bearing for those who wish to have a family, but early discussion regarding fertility options should be performed.

Fertility assessment is only the first of the fertility concerns; the second is pregnancy after breast cancer. Pregnancy is advised to be delayed until 9 months after any radiation treatment.[1] In addition, Tamoxifen is teratogenic; patients are advised to have definitive contraception plans while on treatment. Most women are counseled to wait 2 years prior to becoming pregnant, but there is a paucity of data on this subject.[93] Multiple studies indicate that pregnancy after breast cancer does not increase recurrence or mortality risk.[94–98] Although some small retrospective studies suggest pregnancy after breast cancer is associated with improved survival, this likely reflects a selection bias, as healthier patients are more likely to pursue childbearing and become pregnant.[14,58] Rarely, patients are diagnosed with pregnancy-associated breast cancer, affecting 1.3 per 10,000 births.[1] Studies suggest that breast cancer diagnosed during pregnancy has a worse prognosis, as pregnant breast cancer patients present with larger tumors, more advanced disease, and higher receptor negativity; however, when matched for stage, pregnancy does not adversely affect survival.[99] These patients are best served by a closely integrated care team encompassing surgeons, medical oncologists, obstetrics, maternal fetal medicine, and social work.[1]

A new breast cancer diagnosis can cause distress in any new patient, but younger patients experience more physiological and emotional distress and decreased energy levels after their treatment compared to the general breast cancer population.[100]

Concerns about fertility, employment, child care, body image, and sexuality contribute to emotional distress in this population. African Americans, married patients, or those who have a stable partner were found to have less emotional distress. Sexual dysfunction, particularly vaginal dryness, is also a concern.[101] A retrospective study of 500 breast cancer patients demonstrated that social and emotional function after 6 years was inversely proportional to age at diagnosis.[102] An Australian study of 700 patients under 60 years old indicated more anxiety about recurrence was associated with younger age, although no significant association was found between recurrence and psychosocial factors.[103]

In particular, surgical choices impact emotional status and quality of life. Mastectomy appeared to have a greater effect on quality of life.[104] Mastectomy patients reported poorer body image and overall well-being than those electing BCT.[105] One study prospectively studied the psychological effects of 142 patients undergoing mastectomy or BCT and found patients undergoing mastectomy to feel less in control of their lives and sexual relations, and two studies suggested that patients who underwent mastectomy as well as those who had CPM reported more sexual dysfunction, particularly after immediate CPM.[103,104] Patients with CPM also were found to have poorer body image related to feeling self-conscious and having dissatisfaction from scars.[104] In the overall breast cancer population, patients with BCT reported better body image, more physical functioning, and higher sexual activity after 5 years.[106] Preoperatively, patients tend to underestimate quality of life after mastectomy with or without reconstruction and BCT, while overestimating the stigma of the same operations.[107] As a result, attempts to predict postoperative quality of life are being made to help patients better understand surgical options and the impact on their lifestyle.[108]

Conclusion

Breast cancer is the most common cancer in women in the United States. As the most commonly diagnosed cancer in women between the ages of 25 and 39, breast cancer treatment in this age population requires special consideration and is not uncommon. Although surgical and medical options available to young patients are very similar to those for the general breast cancer population, other factors play a role in the overall care of these patients, and treatment plans may differ significantly due to age-related concerns. Hereditary breast cancer and other risk factors may predispose these women to other cancers and markedly affect treatment options. In addition, concerns about family members and family planning require the integration of additional subspecialties to breast cancer management, such as genetic counselors and reproductive specialists. The young adult population is a unique and complex breast cancer population, mandating a multidisciplinary approach with a variety of providers in order to optimize the comprehensive care available to this young population. Given the complexity and integrated nature of the treatment planning, an early multidisciplinary approach significantly improves the delivery of all modalities of care to optimize surgical, oncologic, and survivorship outcomes.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Anders CK, Johnson R, Litton J, Phillips M, Bleyer A. Breast cancer before age 40 years. *Semin Oncol*. 2009;36:237–249.
2. Assi HA, Khoury KE, Dbouk H, Khalil LE, Mouhieddine TH, El Saghir NS. Epidemiology and prognosis of breast cancer in young women. *J Thorac Dis*. 2013;5:S2–S8.
3. Gabriel CA, Domchek SM. Breast cancer in young women. *Breast Cancer Res*. 2010;12:212.
4. DeSantis C, Howlader N, Cronin KA, Jemal A. Breast cancer incidence rates in U.S. women are no longer declining. *Cancer Epidemiol Biomarkers Prev*. 2011;20:733–749.
5. DeSantis C, Ma J, Bryan L, Jemal A. Breast cancer statistics, 2013. *CA Cancer J Clin*. 2014;64:52–62.
6. Anders CK, Fan C, Parker JS, et al. Breast carcinomas arising at a young age: unique biology or a surrogate for aggressive intrinsic subtypes? *J Clin Oncol*. 2008;29:e18–e20.
7. Tichy JR, Lim E, Anders CK. Breast cancer in adolescents and young adults: a review with a focus on biology. *J Natl Compr Canc Netw* 11:1060–1079.
8. Gnerlich JL, Deshpande AD, Jeffe DB, Sweet A, White N, Margenthaler JA. Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease. *J Am Coll Surg* 2009;208:341–347.
9. Anders CK, Hsu DS, Broadwater G, et al. Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression. *J Clin Oncol* 2008;26:3324–3330.
10. de Bock GH, van der Hage JA, Putter H, Bonnema J, Bartelink H, van de Velde CJ. 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.
11. Wapnir IL, Anderson SJ, Mamounas EP, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. *J Clin Oncol* 2006;24:2028–2037.
12. Bharat A, Aft RL, Gao F, Margenthaler JA. Patient and tumor characteristics associated with increased mortality in young women (< or =40 years) with breast cancer. *J Surg Oncol* 2009;100:248–251.
13. Albain KS, Allred DC, Clark GM. Breast cancer outcome and predictors of outcome: are there age differentials? J Natl Cancer Inst Monogr 1994:35–42.
14. Kroman N, Jensen MB, Wohlfahrt J, Mouridsen HT, Andersen PK, Melbye M. Factors influencing the effect of age on prognosis in breast cancer: population based study. BMJ 2000;320:474–478.
15. Kollias J, Ellis IO, Elston CW, Blamey RW. Clinical and histological predictors of contralateral breast cancer. *Eur J Surg Oncol* 1999;25:584–589.

16. Hartman M, Czene K, Reilly M, et al. Genetic implications of bilateral breast cancer: a population based cohort study. *Lancet Oncol* 2005;6:377–582.
17. Lee KD, Chen SC, Chan CH, et al. Increased risk for second primary malignancies in women with breast cancer diagnosed at young age: a population-based study in Taiwan. *Cancer Epidemiol Biomarkers Prev* 2008;17:2647–2655.
18. Cuckle H. Breast cancer screening by mammography: an overview. *Clin Radiol* 1991;43:77–80.
19. Foxcroft LM, Evans EB, Porter AJ. The diagnosis of breast cancer in women younger than 40. *Breast* 2004;13:297–306.
20. Hindle WH, Davis L, Wright D. Clinical value of mammography for symptomatic women 35 years of age and younger. *Am J Obstet Gynecol* 1999;180:1484–1490.
21. Kolb TM, Lichy J, Newhouse JH. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. *Radiology* 2002;225:165–175.
22. Mandelson MT, Oestreicher N, Porter PL, et al. Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. *J Natl Cancer Inst* 2000;92:1081–7.
23. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin* 2007;57:75–89.
24. Pediconi F, Catalano C, Roselli A, et al. The challenge of imaging dense breast parenchyma: is magnetic resonance mammography the technique of choice? A comparative study with x-ray mammography and whole-breast ultrasound. *Invest Radiol* 2009;44:412–421.
25. Christian MC, McCabe MS, Korn EL, Abrams JS, Kaplan RS, Friedman MA. The National Cancer Institute audit of the National Surgical Adjuvant Breast and Bowel Project Protocol B-06. *N Engl J Med* 1995;333:1469–1674.
26. Voogd AC, Nielsen M, Peterse JL, et al. Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. *J Clin Oncol* 2001;19:1688–1697.
27. Nguyen PL, Taghian AG, Katz MS, et al. Breast cancer subtype approximated by estrogen receptor, progesterone receptor, and HER-2 is associated with local and distant recurrence after breast-conserving therapy. *J Clin Oncol* 2008;26:2373–2378.
28. Abdulkarim BS, Cuartero J, Hanson J, Deschenes J, Lesniak D, Sabri S. Increased risk of locoregional recurrence for women with T1-2N0 triple-negative breast cancer treated with modified radical mastectomy without adjuvant radiation therapy compared with breast-conserving therapy. *J Clin Oncol* 29:2852–2858.
29. Freedman GM, Hanlon AL, Fowble BL, Anderson PR, Nicolaou N. Recursive partitioning identifies patients at high and low risk for ipsilateral tumor recurrence after breast-conserving surgery and radiation. *J Clin Oncol* 2002;20:4015–4021.
30. Kurtz JM, Jacquemier J, Amalric R, et al. Why are local recurrences after breast-conserving therapy more frequent in younger patients? *J Clin Oncol* 1990;8:591–598.
31. Patani N, Mokbel K. Oncological and aesthetic considerations of skin-sparing mastectomy. Breast Cancer Res Treat 2008; 111:391–403.
32. Kasem A, Mokbel K. Evolving role of skin sparing mastectomy. *World J Clin Oncol* 5:33–35.
33. Lee MC, Joh JE, Chau A. Axillary staging prior to neoadjuvant chemotherapy: the roles of sentinel lymph node biopsy and axillary ultrasonography. *Cancer Control* 19:277–285.
34. Houssami N, Ciatto S, Turner RM, Cody HS, 3rd, Macaskill P. Preoperative ultrasound-guided needle biopsy of axillary nodes in invasive breast cancer: meta-analysis of its accuracy and utility in staging the axilla. *Ann Surg* 254:243–251.
35. Cools-Lartigue J, Meterissian S. Accuracy of axillary ultrasound in the diagnosis of nodal metastasis in invasive breast cancer: a review. *World J Surg* 36:46–54.
36. Oz A, Demirkazik FB, Akpinar MG, et al. Efficiency of ultrasound and ultrasound-guided fine needle aspiration cytology in preoperative assessment of axillary lymph node metastases in breast cancer. *J Breast Cancer*; 15:211–7.
37. Parbhoo S. Lymphoedema in young patients with breast cancer. *Breast* 2006;15 Suppl 2:S61–S64.
38. King TA, Sakr R, Patil S, et al. Clinical management factors contribute to the decision for contralateral prophylactic mastectomy. *J Clin Oncol* 29:2158–21564.
39. Yi M, Hunt KK, Arun BK, et al. Factors affecting the decision of breast cancer patients to undergo contralateral prophylactic mastectomy. *Cancer Prev Res* (Phila); 3:1026–34.
40. Stucky CC, Gray RJ, Wasif N, Dueck AC, Pockaj BA. Increase in contralateral prophylactic mastectomy: echoes of a bygone era? Surgical trends for unilateral breast cancer. *Ann Surg Oncol* 17 Suppl 3:330–337.
41. McDonnell SK, Schaid DJ, Myers JL, et al. Efficacy of contralateral prophylactic mastectomy in women with a personal and family history of breast cancer. *J Clin Oncol* 2001;19:3938–3943.
42. Hartmann LC, Sellers TA, Schaid DJ, et al. Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. *J Natl Cancer Inst* 2001;93:1633–1637.
43. Peralta EA, Ellenhorn JD, Wagman LD, Dagis A, Andersen JS, Chu DZ. Contralateral prophylactic mastectomy improves the outcome of selected patients undergoing mastectomy for breast cancer. *Am J Surg* 2000;180:439–445.
44. Herrinton LJ, Barlow WE, Yu O, et al. Efficacy of prophylactic mastectomy in women with unilateral breast cancer: a cancer research network project. *J Clin Oncol* 2005;23:4275–4286.
45. Lostumbo L, Carbine NE, Wallace J. Prophylactic mastectomy for the prevention of breast cancer. *Cochrane Database Syst Rev*: CD002748.
46. Bedrosian I, Hu CY, Chang GJ. Population-based study of contralateral prophylactic mastectomy and survival outcomes of breast cancer patients. *J Natl Cancer Inst* 102:401–409.
47. Osman F, Saleh F, Jackson TD, Corrigan MA, Cil T. Increased postoperative complications in bilateral mastectomy patients compared to unilateral mastectomy: an analysis of the NSQIP database. *Ann Surg Oncol* 20:3212–3217.
48. Miller ME, Czechura T, Martz B, et al. Operative risks associated with contralateral prophylactic mastectomy: a single institution experience. *Ann Surg Oncol*;20:4113–4120.
49. Patel KM, Basci D, Nahabedian MY. Multiple pregnancies following deep inferior epigastric perforator (DIEP) flap breast reconstruction. *J Plast Reconstr Aesthet Surg*;66:434–436.
50. Barry M, Kell MR. Radiotherapy and breast reconstruction: a meta-analysis. *Breast Cancer Res Treat*;127:15–22.
51. Drukker CA, Bueno-de-Mesquita JM, Retel VP, et al. A prospective evaluation of a breast cancer prognosis signature in the observational RASTER study. *Int J Cancer* 133:929–936.
52. Nguyen MT, Stessin A, Nagar H, et al. Impact of Oncotype DX Recurrence Score in the Management of Breast Cancer Cases. *Clin Breast Cancer* 14:182–190.
53. Polychemotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 1998;352:930–942.
54. von Minckwitz G, Eidtmann H, Rezai M, et al. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. *N Engl J Med* 366:299–309.
55. Walshe JM, Denduluri N, Swain SM. Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. *J Clin Oncol* 2006;24:5769–5779.
56. Swain SM, Jeong JH, Geyer CE, Jr., et al. Longer therapy, iatrogenic amenorrhea, and survival in early breast cancer. *N Engl J Med* 362:2053–2065.
57. Goodwin PJ, Ennis M, Pritchard KI, Trudeau M, Hood N. Risk of menopause during the first year after breast cancer diagnosis. *J Clin Oncol* 1999;17:2365–2370.

58. Lee MC, Gray J, Han HS, Plosker S. Fertility and reproductive considerations in premenopausal patients with breast cancer. *Cancer Control* 17:162–172.
59. Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 1998;351:1451–1467.
60. Ovarian ablation in early breast cancer: overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 1996;348:1189–1196.
61. Klijn JG, Blamey RW, Boccardo F, Tominaga T, Duchateau L, Sylvester R. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. *J Clin Oncol* 2001;19:343–53.
62. Jonat W, Kaufmann M, Sauerbrei W, et al. Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: The Zoladex Early Breast Cancer Research Association Study. *J Clin Oncol* 2002;20:4628–4635.
63. Bernhard J, Zahrieh D, Castiglione-Gertsch M, et al. Adjuvant chemotherapy followed by goserelin compared with either modality alone: the impact on amenorrhea, hot flashes, and quality of life in premenopausal patients--the International Breast Cancer Study Group Trial VIII. *J Clin Oncol* 2007;25:263–270.
64. Castiglione-Gertsch M, O'Neill A, Price KN, et al. Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative breast cancer: a randomized trial. *J Natl Cancer Inst* 2003;95:1833–1846.
65. von Minckwitz G, Graf E, Geberth M, et al. CMF versus goserelin as adjuvant therapy for node-negative, hormone-receptor-positive breast cancer in premenopausal patients: a randomised trial (GABG trial IV-A-93). *Eur J Cancer* 2006;42:1780–1788.
66. Jakesz R, Hausmaninger H, Kubista E, et al. Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer--Austrian Breast and Colorectal Cancer Study Group Trial 5. *J Clin Oncol* 2002;20:4621–4627.
67. Gnant M, Mlineritsch B, Schippinger W, et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med* 2009;360:679–691.
68. Cuzick J, Ambroisine L, Davidson N, et al. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. *Lancet* 2007;369:1711–1723.
69. Zickl L PF, G Fleming, O Pagani, B Walley, KN Price, RD Gelber, MM Regan, International Breast Cancer Study Group, and North American Breast Cancer Group. SOFT and TEXT: Trials of tamoxifen and exemestane with and without ovarian function suppression for premenopausal women with hormone receptor-positive early breast cancer. *Cancer Research* 2012;72.
70. Recht A, Edge SB, Solin LJ, et al. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001;19:1539–1569.
71. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med* 1997;337:949–955.
72. National Comprehensive Cancer Network Version 2.2013 http://infoonco.es/wp-content/uploads/2011/10/breast_cancer_2.2013.pdf Accessed June 2014.
73. Freedman RA, Virgo KS, Labadie J, He Y, Partridge AH, Keating NL. Receipt of locoregional therapy among young women with breast cancer. *Breast Cancer Res Treat* 135:893–906.
74. Quan ML, Osman F, McCready D, Fernandes K, Sutradhar R, Paszat L. Postmastectomy radiation and recurrence patterns in breast cancer patients younger than age 35 years: a population-based cohort. *Ann Surg Oncol* 21:395–400.
75. Bevers TB, Anderson BO, Bonaccio E, et al. NCCN clinical practice guidelines in oncology: breast cancer screening and diagnosis. *J Natl Compr Canc Netw* 2009;7:1060–1096.
76. 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.
77. Brose MS, Rebbeck TR, Calzone KA, Stopfer JE, Nathanson KL, Weber BL. Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. *J Natl Cancer Inst* 2002;94:1365–1372.
78. Lakhani SR, Van De Vijver MJ, Jacquemier J, et al. The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2. *J Clin Oncol* 2002;20:2310–2318.
79. Lidereau R, Eisinger F, Champeme MH, et al. Major improvement in the efficacy of BRCA1 mutation screening using morphoclinical features of breast cancer. *Cancer Res* 2000;60:1206–1210.
80. Seynaeve C, Verhoog LC, van de Bosch LM, et al. Ipsilateral breast tumour recurrence in hereditary breast cancer following breast-conserving therapy. *Eur J Cancer* 2004;40:1150–1158.
81. Haffty BG, Harrold E, Khan AJ, et al. Outcome of conservatively managed early-onset breast cancer by BRCA1/2 status. *Lancet* 2002;359:1471–1477.
82. Metcalfe K, Lynch HT, Ghadirian P, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. *J Clin Oncol* 2004;22:2328–2335.
83. Smith IE, Dowsett M, Yap YS, et al. Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. *J Clin Oncol* 2006;24:2444–2447.
84. Kleihues P, Schauble B, zur Hausen A, Esteve J, Ohgaki H. Tumors associated with p53 germline mutations: a synopsis of 91 families. *Am J Pathol* 1997;150:1–13.
85. He X, Arrotta N, Radhakrishnan D, Wang Y, Romigh T, Eng C. Cowden syndrome-related mutations in PTEN associate with enhanced proteasome activity. *Cancer Res* 73:3029–3040.
86. Surbone A, Petrek JA. Childbearing issues in breast carcinoma survivors. *Cancer* 1997;79:1271–1278.
87. Petrek JA, Naughton MJ, Case LD, et al. Incidence, time course, and determinants of menstrual bleeding after breast cancer treatment: a prospective study. *J Clin Oncol* 2006;24:1045–1051.
88. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol* 2006;24:2917–2931.
89. Partridge AH, Gelber S, Peppercorn J, et al. Web-based survey of fertility issues in young women with breast cancer. *J Clin Oncol* 2004;22:4174–4183.
90. Halle C. F. Moore JMU, Kelly-Anne Phillips, Frances M. Boyle, Erika Hitre, David James Porter, Prudence A. Francis, Lori M. Minasian, Richard D. Gelber, Lori J. Goldstein, Henry Leonidas Gomez, Carlos Vallejos, Ann H. Partridge, Shaker R. Dakhil, Silvana Martino, William E. Barlow, Carol J. Fabian, Frank L. Meyskens, Gabriel N. Hortobagyi, Kathy S. Albain. Phase III trial (Prevention of Early Menopause Study [POEMS]-SWOG S0230) of LHRH analog during chemotherapy (CT) to reduce ovarian failure in early-stage, hormone receptor-negative breast cancer: An international Intergroup trial of SWOG, IBCSG, ECOG, and CALGB (Alliance). *J Clin Oncol* 32:5s, 2014 (suppl; abstr LBA505) 2014.
91. Del Mastro L, Boni L, Michelotti A, et al. Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer: a randomized trial. *JAMA* 306:269–276.
92. Gerber B, von Minckwitz G, Stehle H, et al. Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: the GBG 37 ZORO study. *J Clin Oncol* 29:2334–2341.
93. Lawrenz B, Banys M, Henes M, Neunhoeffer E, Grischke EM, Fehm T. Pregnancy after breast cancer: case report and review of the literature. *Arch Gynecol Obstet* 283:837–843.

94. Lewis LN, Hickey M, Doherty DA, Skinner SR. How do pregnancy outcomes differ in teenage mothers? A Western Australian study. *Med J Aust* 2009;190:537–541.
95. de Bree E, Makrigiannakis A, Askoxylakis J, Melissas J, Tsiftsis DD. Pregnancy after breast cancer. A comprehensive review. *J Surg Oncol* 101:534–542.
96. Hickey M, Peate M, Saunders CM, Friedlander M. Breast cancer in young women and its impact on reproductive function. *Hum Reprod Update* 2009;15:323–339.
97. Gadducci A, Cosio S, Genazzani AR. Ovarian function and childbearing issues in breast cancer survivors. *Gynecol Endocrinol* 2007;23:625–631.
98. Kranick JA, Schaefer C, Rowell S, et al. Is pregnancy after breast cancer safe? Breast J;16:404–411.
99. Mueller BA, Simon MS, Deapen D, Kamineni A, Malone KE, Daling JR. Childbearing and survival after breast carcinoma in young women. *Cancer* 2003;98:1131–1140.
100. Wenzel LB, Fairclough DL, Brady MJ, et al. Age-related differences in the quality of life of breast carcinoma patients after treatment. *Cancer* 1999;86:1768–1774.
101. Broeckel JA, Thors CL, Jacobsen PB, Small M, Cox CE. Sexual functioning in long-term breast cancer survivors treated with adjuvant chemotherapy. *Breast Cancer Res Treat* 2002;75:241–248.
102. Ganz PA, Greendale GA, Petersen L, Kahn B, Bower JE. Breast cancer in younger women: reproductive and late health effects of treatment. *J Clin Oncol* 2003;21:4184–4193.
103. Phillips KA, Osborne RH, Giles GG, et al. Psychosocial factors and survival of young women with breast cancer: a population-based prospective cohort study. *J Clin Oncol* 2008;26:4666–4671.
104. Lee MC, Bhati RS, von Rottenthaler EE, et al. Therapy choices and quality of life in young breast cancer survivors: a short-term follow-up. *Am J Surg* 206:625–631.
105. Schain WS, d'Angelo TM, Dunn ME, Lichter AS, Pierce LJ. Mastectomy versus conservative surgery and radiation therapy. Psychosocial consequences. *Cancer* 1994;73:1221–1228.
106. Arndt V, Stegmaier C, Ziegler H, Brenner H. Quality of life over 5 years in women with breast cancer after breast-conserving therapy versus mastectomy: a population-based study. *J Cancer Res Clin Oncol* 2008;134:1311–1318.
107. Waljee JF, Ubel PA, Atisha DM, Hu ES, Alderman AK. The choice for breast cancer surgery: can women accurately predict postoperative quality of life and disease-related stigma? *Ann Surg Oncol* 18:2477–2482.
108. Tsai JT, Hou MF, Chen YM, Wan TT, Kao HY, Shi HY. Predicting quality of life after breast cancer surgery using ANN-based models: performance comparison with MR. *Support Care Cancer* 21:1341–1350.