The Influence of Endocrine Effects of Adjuvant Therapy on Quality of Life Outcomes in Younger Breast Cancer Survivors

M. Tish Knobf

Yale School of Nursing, New Haven, Connecticut, USA

Key Words. Breast cancer • Fertility • Gonadal toxicity • Menopause • Quality of life

Learning Objectives
After completing this course, the reader will be able to:

1. Identify risk factors for amenorrhea by age for young women treated with adjuvant chemotherapy.
2. Describe the associated quality of life outcomes with premature menopause as a sequelae of cancer therapy.
3. Discuss the safety and efficacy of fertility preservation options for women with breast cancer.

Abstract
Significance. There are 2.2 million breast cancer survivors, and approximately 25%–30% of newly diagnosed women each year are <50 years of age. Adjuvant therapy has prolonged survival, but the quality of that survival is influenced by persistent and late effects of therapy. Knowledge of treatment outcomes will assist in the design of interventions to prevent or manage persistent and late effects in survivors.

Purpose. The purpose of this paper is to review the incidence of gonadal toxicity associated with adjuvant chemotherapy, side effects of endocrine therapy, quality of life outcomes, fertility concerns, and options to preserve fertility in young (<35 years) and young midlife (35–50 years) breast cancer survivors.

Results. Alkylating agent–based chemotherapy causes destruction of primordial follicles and impairment of follicular maturation resulting in temporary preservation of menses, reversible amenorrhea, irregular menses (perimenopause), or irreversible amenorrhea (ovarian failure—menopause). Younger women have a lower risk for amenorrhea with chemotherapy because of sufficient follicular stores, although the gonadal toxicity will result in an earlier than expected menopause. Premature menopause is associated with poorer quality of life, decreased sexual functioning, menopausal symptom distress, psychosocial distress related to fertility concerns, infertility, and uncertainty about late effects of premature menopause. Routine discussion about the menopausal experience, risks for infertility, and fertility preservation options is recommended.

Implications for Practice. This review identified adverse treatment outcomes for young and young midlife breast cancer survivors that can be minimized or prevented with targeted interventions. The Oncologist 2006;11:96–110

Introduction
There are 2.2 million breast cancer survivors, and approximately 25%–30% of newly diagnosed women each year are <50 years of age. With the lower mortality and longer
survival time resulting from adjuvant therapy [1], chemotherapy or endocrine therapy may be recommended to women <50 years of age, depending on the stage, prognostic factors, and hormone sensitivity of the tumor. Late effects of adjuvant therapy were identified more than a decade ago [2], and the impact of persistent and late effects of cancer treatment on survivors has gained national and international attention [3, 4]. Younger women with breast cancer are more vulnerable to physical and psychological distress [5], and this greater vulnerability may account for the poorer quality of life outcomes that have been reported [6, 7]. There is variability in defining “young” in the breast cancer literature. In women’s health, young is a generally accepted description for women <35 years of age, with midlife beginning at age 35 [8]. This definition of young (<35 years of age) is consistent with published work in breast cancer that has addressed outcomes in younger versus older women [9, 10]. In this paper, young refers to women <35 years of age and young midlife women refers to those 35–50 years of age.

This paper reviews the incidence of gonadal toxicity associated with adjuvant chemotherapy, side effects of endocrine therapy, quality of life outcomes in young and young midlife breast cancer survivors, fertility concerns, and options to preserve fertility.

**Ovarian Function and Chemotherapy Toxicity**

Ovarian toxicity is a predictable side effect of alkylating agent–based chemotherapy and is influenced by the cumulative dose and duration of therapy [11]. Chemotherapy causes destruction of primordial follicles and impairment of follicular maturation [12]. The exact mechanism of ovarian damage is not fully understood, but in vitro studies suggest apoptotic changes in the pregranulosa cells that result in follicular damage [13]. The outcomes of ovarian damage from chemotherapy are dependent on the follicular reserve of the individual woman, which is age-related. Potential outcomes include follicular damage with preservation of menses, temporary amenorrhea, irregular menses (perimenopause), and ovarian failure (menopause).

Younger women who preserve their menses or who develop reversible amenorrhea will experience premature menopause but as a delayed effect rather than the immediate effect observed in older midlife women [13, 14]. For the average woman, the perimenopausal transition begins ≥35 years of age, and over the following 10–15 years, there is a gradual decline in mature functional follicles and decreasing sensitivity to gonadotropin stimulation. These changes are characterized by alterations in bleeding patterns and cycle length, anovulatory cycles, and wide variations in hormonal levels [8, 15]. These transition changes explain the age pattern of amenorrhea and ovarian failure reported in women treated with chemotherapy for breast cancer. The risk for ovarian failure is substantially higher in women who are closer to the average age of natural menopause (51 years in white nonsmoking women) because of diminished follicular reserve.

The outcomes of women with chemotherapy-induced ovarian damage include menstrual changes, menopausal symptoms, changes in fertility potential, and infertility.

A considerable body of research has been published identifying the incidence, and variables of age, dose, and drug(s) associated with ovarian toxicity of adjuvant chemotherapy for breast cancer (Table 1) [14, 16–28]. Age is a strong discriminating factor for ovarian failure [25]. In women <40 years of age who receive a three-drug combination of cyclophosphamide and fluorouracil with either methotrexate (CMF) or an anthracycline (CAF, FAC) for six to nine cycles, the incidence of amenorrhea ranges from 31%–38%, and for women >40 years of age, the incidence of amenorrhea is dramatically higher. The time to develop amenorrhea also corresponds with age. Younger women (<40 years of age) develop amenorrhea in 4–8 months, compared with women who are older (>40 years of age) who can develop amenorrhea in 2–4 months on adjuvant chemotherapy. Based on the fact that higher cumulative doses and longer durations of therapy are associated with a greater risk for amenorrhea, the two-drug combination of doxorubicin and cyclophosphamide (AC) for four cycles was expected to result in less damage to the ovary. There are three studies (Table 1) [26–28] that have explored the incidence of amenorrhea with four cycles of AC regimens with or without a taxane. The incidence of amenorrhea at 12 months was 14% in women <30 years of age and 33% in women aged 30–40 years [27]. In another study, for women <40 years of age, the incidence of amenorrhea at 1 year was 15% [28]. Despite the fact that only one study collected prospective data [27], the findings of these studies suggest that four cycles of AC adjuvant chemotherapy with or without a taxane result in a slightly lower incidence of amenorrhea in younger women than six cycles of CMF. However, women >45 years of age who receive AC with or without a taxane have a >70% risk of becoming menopausal [26, 27, 29].

The return of menses following 12 months of amenorrhea after treatment in young women is not well documented [22, 23]. A recent prospective study suggests that there can be a return of menses after prolonged amenorrhea (>12 months), which raises issues about the appropriateness of a gynecologic workup to assess uterine pathology for unexplained vaginal bleeding [30].
Table 1. Selected studies establishing chemotherapy-induced ovarian toxicity in young women with breast cancer

<table>
<thead>
<tr>
<th>Study</th>
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<tr>
<td>Koyama et al. [16]</td>
<td>To explore the incidence of amenorrhea associated with cyclophosphamide therapy for breast cancer</td>
<td>Descriptive</td>
<td>Menstrual history</td>
<td>( n = 18 ) premenopausal women who received daily cyclophosphamide as adjuvant therapy</td>
<td>15/18 women (83%) developed permanent amenorrhea, at an average dose of cyclophosphamide of 5.2 g in women in their 40s and 9.3 g in women in their 30s.</td>
<td>There is a dose relationship between age and onset of ovarian toxicity.</td>
</tr>
<tr>
<td>Rose and Davis [17]</td>
<td>To assess ovarian function in women who received adjuvant therapy with L-PAM or CMF chemotherapy</td>
<td>Descriptive</td>
<td>Menstrual history, LH, FSH, estrone, estradiol, and androstenedione levels</td>
<td>( n = 33 ) (16 premenopausal; 17 postmenopausal). Age range: 32–51 yrs, premenopausal; 50–72 yrs, postmenopausal</td>
<td>69% of premenopausal women developed amenorrhea and 12.5% developed irregular menses within 6 mos of chemotherapy.</td>
<td>Women in the study who continued to menstruate were &lt;35 yrs of age.</td>
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<tr>
<td>Samaan et al. [18]</td>
<td>To determine the incidence and mechanism of chemotherapy-induced amenorrhea in women with breast cancer</td>
<td>Descriptive</td>
<td>Menstrual history, LH, FSH, estradiol, and serum prolactin levels</td>
<td>( n = 131 ); 55/131 were premenopausal; CAF chemotherapy regimen</td>
<td>71% of premenopausal women developed amenorrhea; those with amenorrhea had high LH and FSH and low estradiol levels.</td>
<td>Authors concluded that amenorrhea associated with chemotherapy is a result of primary ovarian failure.</td>
</tr>
<tr>
<td>Padmanabhan et al. [19]</td>
<td>To assess ovarian function in premenopausal women receiving CMF chemotherapy</td>
<td>Descriptive</td>
<td>Menstrual history, LH, FSH, estradiol, and prolactin levels</td>
<td>( n = 74 ) (39 controls, 35 chemotherapy); median age: 45 yrs, controls; 35 yrs, chemotherapy</td>
<td>13% of women in the control group and 77% of women in the chemotherapy group became amenorrheic within 12 mos.</td>
<td>Median age of women who maintained menses was lower (35 yrs) than that of women who developed amenorrhea (46 yrs).</td>
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<tr>
<td>Goldhirsch et al. [20]</td>
<td>To examine the incidence of amenorrhea in women with breast cancer who received no adjuvant therapy, one perioperative course or 6 courses of CMFP chemotherapy</td>
<td>Descriptive</td>
<td>Menstrual history within the first 9 mos after surgery</td>
<td>( n = 1,127; n = 199 ), no treatment; ( n = 353 ), one cycle; ( n = 188,6–7 ) cycles of chemotherapy</td>
<td>Amenorrhea was observed in 21% of women who did not receive chemotherapy, 31% who received one perioperative cycle, and 68% who received a standard 6–7 cycles with CMF regimens.</td>
<td>Younger women (&lt;40 yrs) who had 6 cycles of CMFP had a lower incidence of amenorrhea (33%) than older women (81%).</td>
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<tr>
<td>Mehta et al. [21]</td>
<td>To assess the endocrine profile in women with breast cancer who received CMF chemotherapy for 12 cycles</td>
<td>Descriptive, prospective</td>
<td>Menstrual history, serum estrone, estradiol, androstenedione, LH, and prolactin levels</td>
<td>( n = 70; n = 21, &lt;35 yrs; n = 32,35–45 yrs; n = 17, &gt;45 yrs )</td>
<td>77% became amenorrheic, which varied by age: 52%, &lt;35 yrs; 84%, 35–45 yrs; 94%, &gt;45 yrs.</td>
<td>Plasma hormone levels fluctuated across the first 3 cycles. Gradual declines in estradiol and increases in LH were observed after cycle 4 in women who developed amenorrhea.</td>
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<tr>
<td>Bonadonna et al. [22]</td>
<td>To describe the outcomes of CMF adjuvant therapy in women with breast cancer</td>
<td>Descriptive, longitudinal</td>
<td>Menstrual history, sample (( n = 103 )) of chemotherapy group (( n = 207 ))</td>
<td>( n = 103; n = 32, &lt;40 yrs; n = 71, &gt;40 yrs )</td>
<td>Younger women (&lt;40 yrs) had a lower incidence of amenorrhea (22%) than older women (61%). Also, only 3% of younger women became perimenopausal in contrast to 33% of older women.</td>
<td>In women over the age of 40 years, the moderate incidence of irregular menses suggests a high risk for earlier than expected menopause.</td>
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<tr>
<td>Luporsi and Weber [23]</td>
<td>To assess the incidence of amenorrhea in premenopausal women</td>
<td>Descriptive</td>
<td>Menstrual history</td>
<td>( n = 249 ); median age, 43 yrs; age range, 23–55 yrs; CAF ( \times ) 6 cycles</td>
<td>Incidence of amenorrhea varied by age: 0%, &lt;32 yrs; 15%, 32–37 yrs; 55%, 38–39 yrs; 79%, 40–41 yrs; 88%, 42–47 yrs; 92%, &gt;48 yrs; amenorrhea was reversible in many of the women &lt;42 yrs of age.</td>
<td>Resumption of menses after a period of amenorrhea indicates some level of follicular reserve, but these women may experience an earlier than expected menopause.</td>
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<tr>
<td>Lower et al. [24]</td>
<td>To determine the prevalence of menstrual abnormalities in women with breast cancer who receive adjuvant chemotherapy</td>
<td>Retrospective, case series</td>
<td>Menstrual history data collected before, during, and after chemotherapy</td>
<td>( n = 109 ) premenopausal women; 63% received methotrexate-based therapy, 30% received anthracyclines, and 7% received both</td>
<td>Amenorrhea was reported in 36% of women during therapy and in 46% by 1 year later. No difference among chemotherapy regimens was noted. No woman &lt;30 yrs of age developed menstrual irregularities. The risk for amenorrhea increased with age (24%, &lt;40 yrs; 44%, 41–45 yrs; 89%, &gt;50 yrs).</td>
<td>In addition to amenorrhea, menstrual irregularities were reported in 12% of women aged 36–50 yrs, suggesting a perimenopausal pattern and/or onset of earlier than expected menopause.</td>
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<tr>
<td>Goodwin et al. [25]</td>
<td>To determine predictors of menopause in young women who receive adjuvant therapy</td>
<td>Descriptive, predictive</td>
<td>n = 183; mean age, 44 yrs; chemotherapy, CMF, CEF with or without tamoxifen</td>
<td>44% of women developed amenorrhea. The mean age of those who developed menopause was 45.5 yrs, compared with 42.5 yrs for women who maintained ovarian function.</td>
<td>Data suggest that the risk for menopause with adjuvant chemotherapy increases in women &gt;35 yrs old and that by age 45, most women will become menopausal.</td>
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<tr>
<td>Stone et al. [26]</td>
<td>To assess chemotherapy-related amenorrhea in women ≤50 yrs of age with breast cancer receiving chemotherapy with or without a taxane</td>
<td>Descriptive, retrospective</td>
<td>Menstrual history questionnaire</td>
<td>( n = 81 ); 74% received AC; 26% received AC+T; mean age at treatment, 41 yrs (range, 24–50 yrs)</td>
<td>With AC, the incidence of amenorrhea was 43% and differed by age: 0%, &lt;35 yrs; 14%, 35–40 yrs; 39%, 40–45 yrs; 100%, &gt;45 yrs.</td>
<td>The data suggest that younger women treated with AC may have a higher rate of preserved ovarian function when compared with previous studies. The incidence of amenorrhea with AC+T did not differ significantly from that with AC.</td>
</tr>
<tr>
<td>Partridge et al. [14]</td>
<td>To evaluate the age of menopause in women who remained premenopausal at the end of adjuvant therapy</td>
<td>Descriptive</td>
<td>International Breast Cancer Study Group Trial V; no chemotherapy, 1 cycle of preoperative chemotherapy, 6 cycles CMF, or combination preoperative and CMF</td>
<td>( n = 672 ); ( n = 96 ), &lt;35 yrs; ( n = 156 ), 35–39 yrs; ( n = 422 ), 40–44 yrs</td>
<td>Women who received CMF ( \times ) 6–7 cycles who maintained their menses at the end of therapy went into an earlier menopause than women who received no treatment or one treatment of chemotherapy.</td>
<td>Women &gt;35 yrs of age had a higher incidence of early menopause.</td>
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Side Effects of Adjuvant Endocrine Therapy

Young and young midlife women with hormonally sensitive breast cancer may receive endocrine therapy alone or following chemotherapy [31]. In addition to symptoms associated with the hormonal changes of induced menopause, endocrine therapy is also associated with a variety of other symptoms. Adjuvant therapy with tamoxifen (Nolvadex®, AstraZeneca Pharmaceuticals, Wilmington, DE) has a symptom profile that includes vasomotor symptoms, vaginal complaints (dryness, itching, discharge), amenorrhea, insomnia, and mood disturbances [6, 27, 28, 32–35]. Endocrine therapy with aromatase inhibitors is not recommended for women who become amenorrheic following chemotherapy because the amenorrhea may not be permanent and not reflect a true menopause [36]. However, there are clinical trials with aromatase inhibitors combined with ovarian suppression in premenopausal women [31]. Symptoms associated with aromatase inhibitors include hot flashes, vaginal dryness, bleeding and discharge, sleeping difficulties, fatigue, musculoskeletal complaints, headache, decreased libido, and breast tenderness [37, 38], all of which may negatively impact a woman’s quality of life [37, 39].

Quality of Life in Young Midlife Breast Cancer Survivors

Young and young midlife women with breast cancer are more vulnerable to psychosocial distress because of their developmental stage in life [5, 40, 41]. They may be single, married without children, parenting young to adolescent children, and establishing careers. The multiple demands of the cancer illness are layered on top of the multiple demands of a young woman’s life cycle, and women become more vulnerable to psychological morbidity as they attempt to manage multiple stressors [5, 42, 43]. Younger spouses experience emotional distress, have difficulty communicating about the illness and providing psychological support and often have difficulty carrying out household and childcare responsibilities [5]. Families with school-aged children who have a mother diagnosed with breast cancer are particularly vulnerable to poorer psychological outcomes [44, 45]. Experiencing premature menopause can further increase a young woman’s vulnerability, resulting in a greater risk for emotional distress and a poorer quality of life [6, 7]. Vulnerability was identified as the basic problem for young women diagnosed and treated for breast cancer who experienced premature drug-induced menopause [46]. This vulnerability was found to be related to physical and

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<tr>
<td>Swain et al. [27]</td>
<td>To describe the menstrual history and its relationship to symptoms, QOL, and survival in women in each arm of the trial</td>
<td>Descriptive</td>
<td>Prospective trial data; 24-month follow-up; AC+T chemotherapy</td>
<td>n = 394 participants in the menstrual history/QOL component of the trial out of a total of 528 women</td>
<td>Amenorrhea increased with age at 6-mo follow-up: 11%, 30–40 yrs; 36%, 40–50 yrs; 39%, 50–60 yrs and further increased at the 12-mo follow-up: 29%, &lt;30 yrs; 42%, 30–40 yrs; 66%, 40–50 yrs; 77%, 50–60 yrs.</td>
<td>Amenorrhea occurred in a substantial number of women who received AC+T. Relationship to symptoms and QOL are forthcoming from this study.</td>
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<tr>
<td>Fornier et al. [28]</td>
<td>To determine the incidence of long-term (≥12 months) amenorrhea in women &lt;40 yrs of age with adjuvant anthracycline- and taxane-based chemotherapy</td>
<td>Descriptive, correlational</td>
<td>Retrospective chart review</td>
<td>n = 166; mean age, 35.6 yrs; age range, 27–40 yrs</td>
<td>15% incidence of amenorrhea ≥12 months with chemotherapy. Median age of women with amenorrhea was 38 yrs, compared with 36 yrs for women who maintained menses.</td>
<td>Anthracycline and taxane combination adjuvant therapy is associated with a relatively low incidence of long-term amenorrhea in young women.</td>
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Abbreviations: AC, doxorubicin, cyclophosphamide; AC+T, doxorubicin, cyclophosphamide, plus a taxane; CAF, cyclophosphamide, doxorubicin, 5-fluorouracil; CEF, cyclophosphamide, epirubicin, fluorouracil; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; CMFP, cyclophosphamide, methotrexate, 5-fluorouracil, prednisone; CMFT, cyclophosphamide, methotrexate, 5-fluorouracil, tamoxifen; FSH, follicle-stimulating hormone; LH, luteinizing hormone; L-PAM, l-phenylalanine mustard; QOL, quality of life.
psychosocial distress associated with diagnosis and treatment, existential concerns, lack of adequate preparation for the menopausal experience, uncertainty, severity of menopausal symptoms, and changes in self-concept. "Becoming menopausal" was a realization by women that menopause was more than the cessation of monthly menses. Women reported distress at the age inappropriateness of the abrupt menopause, uncertainty related to menopausal symptoms, uncertainty related to the temporary or permanent nature of amenorrhea, feeling older, having no peers to talk with about the experience, and loss of fertility. Young women report feeling different than other women their age, have concerns about early menopause, and describe multiple losses, including loss of menstruation and loss of fertility [46, 47].

There is an integral relationship among quality of life, chemotherapy-induced menopause, the menopausal symptom experience (from induced menopause and/or endocrine therapy), and sexuality for breast cancer survivors [6, 46, 48–51]. Young women report worse emotional well-being, more psychological distress, higher anxiety, more unmet needs, and greater concerns about finances, work, and self-image than older women (Table 2) [7, 40–42, 49, 52–59]. Chemotherapy is associated with induced menopause and menopausal symptoms, which contribute to lower levels of physical functioning and poorer quality of life for young midlife women after breast cancer treatment [6, 40, 54, 56, 58, 60–62]. Psychological distress is associated with the loss of menstrual function and loss of choice to have more children, even for those women who have completed their family planning, but is most significantly related to infertility for young women who have not yet started their families [46, 48, 56, 63].

Menopausal symptoms reported by breast cancer survivors include vasomotor symptoms (hot flashes, night sweats), fatigue, sleep disturbances, joint pains, dyspareunia, mood swings, cognitive changes, and vaginal dryness [34, 35, 51, 64, 65]. Although vasomotor symptoms and vaginal dryness are reported as the only true physiologic effects of estrogen withdrawal [66], there are data suggesting a neuroendocrine link to other symptoms, such as cognitive changes, mood swings, and related symptomatology, such as insomnia due to hot flashes. More severe vasomotor symptoms have been reported by breast cancer survivors [35, 64], and the suspected etiology is the abrupt change in the hormonal environment of women and rapid decrease in estrogen. Women's emotional, physical, and functional well-being are negatively impacted by the persistence and severity of menopausal symptoms after treatment [6, 32]. Women with more severe menopausal symptoms who did not feel that they were adequately prepared for the chemotherapy-induced menopause experience reported greater uncertainty and psychological distress [67].

Young women who receive adjuvant chemotherapy and experience drug-induced menopause are at a greater risk for negative changes in sexuality and poorer sexual functioning outcomes [6, 48, 51, 68–71]. As women gradually recover from therapy, sexuality and sexual function regain priority as a valued quality of life component [43, 63, 72]. Breast cancer survivors who received systemic adjuvant therapy report less sexual satisfaction than healthy women [73], lower levels of sexual function [68, 74], decreased libido [75], difficulty reaching orgasm, dyspareunia associated with vaginal dryness [71], and less sexual satisfaction [68, 71], and they don't perceive themselves as feminine or sexually attractive as they did before treatment. Sexual function-

### Table 2. Psychosocial outcomes and quality of life in younger women treated for breast cancer

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<tr>
<td>Vinokur et al. [52]</td>
<td>To assess adjustment of women with breast cancer over the first yr after diagnosis</td>
<td>Descriptive cohort (time 1, 3.9 mos after diagnosis; time 2, 4–6 mos after time 1)</td>
<td>Mailed questionnaires, interview</td>
<td>n = 274; mean age, 58.8 yrs; 41%; 40–54 yrs; 27%; 55–64 yrs; 24%; 65–74 yrs; 8%; 75–84 yrs</td>
<td>Improvement in physical functioning over time; no change in mental health and well-being.</td>
<td>Younger women reported worse mental health and well-being and perceived breast cancer to be a greater threat to their lives that did older women.</td>
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<tr>
<td>Mor et al. (53)</td>
<td>To examine the effect of age on women’s perceptions of the psychosocial impact of their illness</td>
<td>Descriptive, combination of two data sets</td>
<td>Survey</td>
<td>n = 262; younger was defined as &lt;54 yrs of age, which was 55% of the sample</td>
<td>Younger women reported more unmet needs, greater difficulty maintaining daily lives, lower levels of emotional well-being, and more financial difficulties.</td>
<td>Age-related differences persist even after controlling for potential confounding variables such as stage of disease, education, marital status, and social support.</td>
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<tr>
<td>Bloom and Kessler [42]</td>
<td>To determine if a breast cancer diagnosis and treatment caused psychosocial morbidity</td>
<td>Cross-sectional</td>
<td>Demographic/medical; general health perception; social readjustment, social support, self-Esteem</td>
<td><em>n</em> = 948; younger was defined as &lt;50 yrs of age, which was 35% of the sample</td>
<td>Factors that increase psychosocial risk include being younger, divorced, or widowed, and having children &lt;21 yrs of age, more symptoms, poorer physical functioning, and poorer health perceptions.</td>
<td>Self-esteem and perceived social support can mediate effects of diagnosis and treatment. Women &gt;60 yrs of age were found to do much better in this area than women &lt;40 yrs of age.</td>
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<td>Ferrell et al. [54]</td>
<td>To explore concerns and validate a QOL model across three age groups of women with breast cancer (&lt;40 yrs, 40–60 yrs, &gt;60 yrs)</td>
<td>Cross-sectional, descriptive</td>
<td>Interview, QOL-BC questionnaire</td>
<td><em>n</em> = 21; mean age, 50 yrs (range, 22–79 yrs); mean time since diagnosis, 34 mos; 81% received adjuvant chemotherapy</td>
<td>Survivorship issues included physical, psychological, social, and spiritual issues, but psychological issues were reported as most distressful.</td>
<td>In the physical domain, menstrual changes, fertility issues, fatigue, and pain were most distressful.</td>
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<td>Wang et al. [55]</td>
<td>To identify concerns and needs of women with breast cancer</td>
<td>Descriptive, cross-sectional</td>
<td>Interview</td>
<td><em>n</em> = 102; mean age, 49 yrs (range, 27–78 yrs); younger was defined as &lt;50 yrs of age</td>
<td>Women reported concerns about family (93%), health (90%), the future (63%), and finances (40%) and the need for counseling and support (73%).</td>
<td>Younger women were more concerned about finances, work, and self-esteem.</td>
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<tr>
<td>Spencer et al. [56]</td>
<td>To describe the strongest concerns of women within the first year post-treatment</td>
<td>Descriptive, cross-sectional</td>
<td>PCBC, POMS, CES-D, PAIS, SIP</td>
<td><em>n</em> = 223; mean age, 54 yrs (range, 27–87); 38% received adjuvant chemotherapy; 37% received tamoxifen</td>
<td>Strongest concerns were fear of recurrence, pain, death, side effects of chemotherapy, and finances. Chemotherapy was associated with a large number of concerns.</td>
<td>Younger women who received chemotherapy reported concerns about menopause, fertility, body image, sexuality, and partner relationship.</td>
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<td>Wenzel et al. [57]</td>
<td>To compare QOL in younger (&lt;50 yrs) and older (≥50 yrs) women with breast cancer</td>
<td>Descriptive</td>
<td>Mailed questionnaire: FACT-B, CES-D, Impact Events Scale</td>
<td><em>n</em> = 304; younger was defined as &lt;50 yrs of age, which was 53% of the sample</td>
<td>Symptoms of depression, disease-specific intrusive thoughts, global QOL disturbance, and emotional well-being were worse in younger women.</td>
<td>Younger women are at higher risk for disruption in QOL, and targeted interventions are recommended.</td>
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<tr>
<td>Arora et al. [58]</td>
<td>To assess quality of life 1 month and 6 months after primary surgery</td>
<td>Descriptive, secondary analysis</td>
<td>QOL-FACT-B</td>
<td><em>n</em> = 103; mean age, 45.8 yrs; 43% received chemotherapy</td>
<td>Improvement over time in physical, emotional, and functional well-being and body image; social and sexual functioning declined over time. Women who received chemotherapy reported lower levels of physical and sexual functioning.</td>
<td>The findings of a decline in physical, social, and sexual functioning over time in young women with breast cancer who receive chemotherapy suggests the need for assessment and intervention.</td>
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<tr>
<td>Cimprich et al. [40]</td>
<td>To determine life-stage variables (age at diagnosis, years of survival) and QOL</td>
<td>Cross-sectional, descriptive</td>
<td>Mailed survey: QOL-Cancer Survivors Scale</td>
<td><em>n</em> = 105; stratified age groups: younger, 27–44 yrs; middle, 45–65 yrs; older, 66–79 yrs; mean time since diagnosis, 11.5 yrs</td>
<td>Older age long-term survivors reported worse QOL in the physical domain and younger women reported poorer QOL in the social domain, with a greater impact on sexuality and more family distress than either middle or older women.</td>
<td>Age at diagnosis can predict QOL, with worse outcomes for younger women related to reproductive issues (fertility and menstrual changes), emotional well-being, family distress, and sexuality.</td>
</tr>
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ing outcomes for women who receive adjuvant endocrine therapy are mixed, with some suggesting no effect [6, 33, 71] and others suggesting an adverse effect related to symptoms during therapy and the specific endocrine therapy taken [76, 77]. The negative impact of breast cancer treatment on the quality of life domain of sexuality for breast cancer survivors (Table 3) represents an important area for education, communication, support, and intervention, especially in younger women [43, 60, 65, 70, 74, 75].

### FERTILITY

#### Uncertainty and Need for Contraceptive Counseling

Follicular damage resulting from chemotherapy is not an all-or-nothing phenomenon [13]. There is considerable uncertainty about the degree of damage because there is no way to measure follicular stores. If amenorrhea occurs, it may reverse, with a return to normal cycles, and those

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**Table 2.** (continued)

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<tr>
<th>Study</th>
<th>Aim</th>
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<th>Sample</th>
<th>Results</th>
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<tbody>
<tr>
<td>Ganz et al. [7]</td>
<td>To evaluate QOL and health outcomes of younger female survivors of breast cancer</td>
<td>Descriptive, correlational; mailed questionnaire</td>
<td>Breast Cancer Prevention Trial Checklist, QOL (Rand Short Form), CES-D, PANAS, Sexual Activity Questionnaire</td>
<td>n = 577; mean age, 49.5 yrs (range, 30–62 yrs); average time from diagnosis, 6 yrs. Menopausal status at diagnosis: 68% premenopausal, 15% perimenopausal, 9% postmenopausal. 62% received adjuvant chemotherapy; 37% received tamoxifen</td>
<td>Problems reported included partner relationship, sexuality, and body image. All women who reported problems had a lower QOL. Coping strategies included using social support, wishful thinking, and positive cognitive restructuring.</td>
<td>Psychologic distress most evident for the younger women in the cohort, those diagnosed at 25–34 yrs of age. Experiencing menopause after treatment may contribute to poorer health perceptions and QOL.</td>
</tr>
<tr>
<td>Avis et al. [49]</td>
<td>To assess the influence of nonmedical factors on QOL in younger women with breast cancer</td>
<td>Descriptive, cross-sectional</td>
<td>Mailed questionnaires: FACT-B, CARES, WOC-CA</td>
<td>n = 204 ± 50 yrs of age, diagnosed within the past 3.5 yrs</td>
<td>Problems reported included partner relationship, sexuality, and body image. All women who reported problems had a lower QOL. Coping strategies included using social support, wishful thinking, and positive cognitive restructuring.</td>
<td>Potential modifiable factors related to QOL outcomes were identified in younger women with breast cancer.</td>
</tr>
<tr>
<td>Kroenke et al. [59]</td>
<td>To explore changes in physical and psychosocial functioning before and after breast cancer by age at diagnosis</td>
<td>Cohort (Nurse’s Health Study)</td>
<td>HRQOL: Medical Outcomes Short Form (SF-36), CARES-SF</td>
<td>n = 1,082; 11%, &lt;40 yrs; 68%, 41–64 yrs; 21%, &gt;65 yrs</td>
<td>Younger women (&lt;40 yrs) reported greater declines in HRQOL, specifically in physical and social functioning and mental health, than middle aged (40–64 yrs) and older (&gt;65 yrs) women.</td>
<td>Assessment of the needs of women with breast cancer may need to be addressed in the context of life stage.</td>
</tr>
<tr>
<td>Goodwin et al. [41]</td>
<td>To investigate psychological distress and HRQOL after a breast cancer diagnosis</td>
<td>Prospective data collected shortly after diagnosis (average 9.7 weeks) and at 1 year postdiagnosis</td>
<td>Profile of Mood States, Impact Events Scale, Psychosocial Adjustment to Illness Scale, Mental Adjustment to Cancer Scale, EORTC QLQ-C30</td>
<td>n = 397; mean age, 52 yrs; 52% of sample premenopausal; 39% received adjuvant chemotherapy; 44% received tamoxifen</td>
<td>At baseline, younger age was associated with more psychosocial distress, which persisted at one year (p &lt; .05).</td>
<td>Adjusting for age, adjuvant chemotherapy was associated with a greater adverse impact on adjustment, role, and social and vocational functioning.</td>
</tr>
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</table>

Abbreviations: CARES, Cancer Rehabilitation Evaluation System; CARES-SF, CARES-Short Form; CES-D, Center for Epidemiologic Studies depression scale; EORTC, European Organization for Research and Treatment of Cancer; FACT-B, functional assessment of cancer therapy-breast; HRQOL, health-related quality of life; PAIS, psychosocial adjustment to illness scale; PANAS, positive and negative affect scale; PCBC, profile of concerns about breast cancer; MS, profile of mood states; QLQ-C30, EORTC quality of life questionnaire; QOL, quality of life; QOL-BC, quality of life-breast cancer; SIP, sickness impact profile; WOC-CA, ways of coping-cancer version.


Table 3. Sexuality outcomes in women treated with adjuvant therapy for breast cancer

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<tr>
<td>Young-McCaughan [71]</td>
<td>To describe sexual functioning in women treated with chemotherapy or endocrine therapy compared with no adjuvant therapy</td>
<td>Descriptive, mailed survey</td>
<td>Symptom questionnaire: Derogotis Sexual Functioning Inventory</td>
<td>n = 67; mean age, 56.2 yrs; 32.3% &lt; 49 yrs; mean time since diagnosis, 7 yrs (39% were 1–5 yrs since diagnosis)</td>
<td>Women treated with chemotherapy were more likely to report vaginal dryness, decreased libido, dyspareunia, and difficulty reaching orgasm. There was an overall negative effect on sexual functioning for women who received chemotherapy versus endocrine or no therapy.</td>
<td>Data suggest that younger women who experience induced menopause have more menopausal symptoms and sexual dysfunction.</td>
</tr>
<tr>
<td>Ganz et al. [51]</td>
<td>To describe psychosocial concerns and QOL in breast cancer survivors 2 and 3 years after initial surgery</td>
<td>Descriptive, cohort survey</td>
<td>Mailed survey: CARES, FLIC, Rand Health Survey, POMS. Interviews on a random sample</td>
<td>n = 139; mean age in the 2-yr sample was 57 yrs (range, 35–79), and in the 3-yr sample it was 59 yrs (range, 36–80)</td>
<td>QOL and functional ability of breast cancer survivors at 2 and 3 yrs is similar to the recovery at 1 year. However, they report persistent sexual problems, rated as moderate to severe.</td>
<td>Interview data suggest that premature menopause and menopausal symptoms may contribute to sexual dysfunction.</td>
</tr>
<tr>
<td>Ganz et al. [6]</td>
<td>To describe HRQOL, partner relationships, sexual functioning, and body image concerns (by age, menopausal status, and treatment)</td>
<td>Descriptive, cross-sectional survey</td>
<td>Rand SF-36, CES-D, Dyadic Adjustment Scale, BCPT Symptom Checklist, WSFQ, CARES (subcales)</td>
<td>n = 864; age distribution: 34%, &lt; 50 yrs; 29%, 50–59 yrs; 37%, ≥60 yrs; mean time since diagnosis, 2.8–3.2 yrs; 38% received adjuvant chemotherapy; 47% receiving current tamoxifen</td>
<td>65.5% of sample were sexually active; sexual satisfaction was similar across age groups; poorer sexual functioning reported by women who received chemotherapy and in young women who became menopausal. No difference in sexual functioning between women who received tamoxifen and those who did not.</td>
<td>There is a greater risk for sexual dysfunction in women &lt;50 yrs of age and who experience chemotherapy-induced menopause.</td>
</tr>
<tr>
<td>Lindley et al. [69]</td>
<td>To evaluate QOL, physical symptoms, and sexual function after adjuvant therapy</td>
<td>Descriptive, cross-sectional</td>
<td>Interview; FLIC, SDS, Rand SF-36</td>
<td>n = 86; mean age, 54 yr (range 29–86); 36% received tamoxifen only, 26% received chemotherapy only, and 38% received chemotherapy and tamoxifen</td>
<td>60% reported decreased sexual interest, and of those, 42.5% related it to the cancer. Dyspareunia, vaginal dryness, and changes in sexual function were reported as significantly higher (&gt;43%), as compared with a recall of these problems 1 year earlier. There was a change in sexual functioning in all women after treatment, but it was greatest for women with drug-induced menopause.</td>
<td>Hormonal changes associated with chemotherapy-induced premature menopause may contribute to sexual dysfunction.</td>
</tr>
<tr>
<td>Dorval et al. [73]</td>
<td>To compare QOL of breast cancer survivors at least 8 yrs after treatment to an aged-matched healthy control group</td>
<td>Descriptive, cross-sectional</td>
<td>Telephone interviews</td>
<td>n = 124 breast cancer survivors; n = 262 matched controls; 54% of breast cancer survivors &lt; 59 yrs of age</td>
<td>QOL outcomes similar between the groups, except breast cancer survivors reported significantly less sexual satisfaction.</td>
<td>Poorer sexual satisfaction among long-term breast cancer survivors suggests a need for health care providers to address sexuality. Menopausal symptoms may be related to sexual functioning and satisfaction.</td>
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<tr>
<td>Spencer et al.</td>
<td>To describe the strongest concerns of women within the first year post-treatment</td>
<td>Descriptive, cross-sectional</td>
<td>Profile concerns: BC, POMS, CES-D, PAIS, SIP</td>
<td>( n = 223; \text{mean age, } 54 \text{ yrs (range 27–87)}; 38% \text{ received adjuvant chemotherapy}; 37% \text{ received tamoxifen.} )</td>
<td>Chemotherapy was significantly associated with feeling less feminine and less sexually desirable. Younger women reported more partner concerns, more sexuality issues, and more concerns about early menopause and fertility.</td>
<td>Chemotherapy-induced early menopause is associated with concerns about sexuality, femininity, sexual functioning, and fertility.</td>
</tr>
<tr>
<td>Ganz et al.</td>
<td>To identify variables that might predict sexual health (interest, satisfaction, dysfunction) in breast cancer survivors</td>
<td>Descriptive, correlational</td>
<td>Rand SF-36, CES-D, Dyadic Adjustment Scale, BCPT Symptom Checklist, WSFQ, CARES (sub-scales)</td>
<td>Two samples: ( n = 472, n = 662; \text{age }&lt;50, 48% \text{ and } 37%, \text{respectively; } 44%–46% \text{ received chemotherapy and } 43%–47% \text{ are receiving current tamoxifen use.} )</td>
<td>Significant predictors of less sexual interest were vaginal dryness and poorer body image, and those that predicted more sexual interest were a partner since diagnosis, better mental health, and better dyadic adjustment. Vaginal dryness, chemotherapy, and premature menopause were predictive of more sexual dysfunction.</td>
<td>The strongest predictors of sexual health (vaginal dryness, quality partner relationship, body image, emotional well-being) are potentially mutable factors, and interventions should be designed to target these factors.</td>
</tr>
<tr>
<td>Mortimer et al.</td>
<td>To define the incidence of sexual dysfunction in women with breast cancer treated with tamoxifen</td>
<td>Descriptive, cross-sectional</td>
<td>CES-D, Sexual History Form, BCPT Symptom Checklist</td>
<td>( n = 57; \text{mean age, } 53 \text{ yrs (range, 36–84); median duration of tamoxifen use, 12 mos; 53% \text{ received prior chemotherapy} )</td>
<td>41% of women were sexually active; sexual function was similar to comparable groups of women, but 54% reported dyspareunia and vaginal dryness.</td>
<td>There was less estrogen effect (high maturation index) in younger than older women. Data suggest an estrogen agonist effect on the vagina in postmenopausal women and an estrogen antagonist effect in younger women, which may be associated with symptoms and sexual function.</td>
</tr>
<tr>
<td>Bergland et al.</td>
<td>To study the sexual effects of adjuvant goserelin, tamoxifen, or the combination versus no adjuvant therapy among premenopausal women with or without chemotherapy</td>
<td>Prospective, longitudinal (for 3 yrs after therapy was initiated); data were collected at baseline and at 6 follow-up time points</td>
<td>Relationship Sexuality Scale</td>
<td>( n = 294; \text{mean age, } 45 \text{ yrs. Across the endocrine groups, } 18%–25% \text{ of women received chemotherapy} )</td>
<td>Goserelin had a negative effect on sexual functioning during treatment. The addition of tamoxifen had a negative effect, but only when used in combination with goserelin. Women who received chemotherapy had a higher level of sexual dysfunction. Sexual dysfunction improved in the endocrine-only treated patients but not in women who received chemotherapy.</td>
<td>The medical castration produced by goserelin versus the weak estrogenic properties of tamoxifen may explain the lack of negative effect on sexual functioning with tamoxifen versus the negative impact from goserelin and goserelin plus tamoxifen with or without chemotherapy in premenopausal women.</td>
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who develop irregular menses may subsequently ovulate in another cycle [78, 79]. Because of this variability and potential return of menstrual function even after a prolonged period of amenorrhea [30], serum hormone levels are not useful as predictors of permanent ovarian failure. Thus, contraceptive counseling is essential for women who experience menstrual changes associated with chemotherapy. Women on adjuvant endocrine therapy can become pregnant and should also be a targeted group for counseling. Pregnancy while on tamoxifen is not recommended because of possible teratogenic effects on the fetus, and women should be counseled to wait at least 12 weeks after discontinuation before attempting conception because of the abruptness of onset. The most distressing menopausal symptoms were vaginal dryness, hot flashes, and changes in sexual function.

### Desire for Pregnancy: Communication and Decision Making

The desire for biologic motherhood and genetically related children is an important issue for many cancer survivors [82, 83]. In breast cancer, many clinicians recommend that women wait to consider pregnancy for 2–3 years, when the highest risk for early recurrence has passed. Decision making about pregnancy in breast cancer survivors is associated with considerable uncertainty. Women have concerns about fear of recurrence and concerns about the potential effect of pregnancy on survival, and those who take endocrine therapy for 5 years have concerns about their fertility potential over time. In addition, there is a level of uncertainty among physicians about pregnancy after breast cancer treatment. A recent review of case control and cohort studies on pregnancy outcomes after breast cancer treatment suggests that there is no adverse effect on survival, but the authors conclude that there is still a lack of definitive evidence [84]. Breast cancer survivors who have successful pregnancies after treatment report that it helped normalize their life and the transition to wellness and that having children improved the quality of their lives [85].

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**Table 3. (continued)**

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<tr>
<td>Wilmoth [48]</td>
<td>To describe aspects of sexuality that are important to breast cancer survivors</td>
<td>Qualitative, descriptive</td>
<td>Interview</td>
<td>( n = 18; ) mean age, 50.5 yrs; 50% &lt; 24 mos since diagnosis; 94% received adjuvant therapy</td>
<td>The concept of an altered sexual self included description of multiple losses (missing parts, loss of menses, becoming old, decreased sexual sensations [arousal, vaginal dryness, breast], and loss of womanhood).</td>
<td>Young women were inadequately prepared for chemotherapy-induced menopause and were surprised by the abruptness of onset. The most distressing menopausal symptoms were vaginal dryness, hot flashes, and changes in sexual function.</td>
</tr>
<tr>
<td>Ganz et al. [60]</td>
<td>Descriptive</td>
<td>Mailed survey questionnaire within 1 month after primary therapy</td>
<td>QOL-Rand SF-36, Ladder of Life Scale, CES-D, PANAS, Revised Dyadic Adjustment Scale, BCPT Symptom Checklist</td>
<td>( n = 558; ) mean age, 56.9 yrs; 26% &lt; 50 yrs of age; 50% received adjuvant chemotherapy, 55% receiving current tamoxifen</td>
<td>More sexual problems and a greater lack of sexual interest reported by women who received chemotherapy.</td>
<td>Younger age, difficulty with lubrication, and perceiving a more negative impact on their sex life predicted more sexual dysfunction.</td>
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Fertility Preservation

There is a recognized need to discuss fertility and options to preserve fertility before adjuvant chemotherapy for young women with breast cancer, yet women report that physicians described the side effects of therapy, but only one third to one half report that their concerns related to fertility were adequately discussed [82, 86]. In the U.S., there is a trend to marry later and to delay childbearing. If options to preserve fertility are not explored prior to treatment, the ovarian damage and subsequent premature menopause may prevent the possibility of a pregnancy after therapy. Potential options for fertility preservation include cryopreservation of oocytes, embryo cryopreservation with in-vitro fertilization (IVF), oocyte donation with IVF, ovarian tissue cryopreservation with IVF, and gonadotropin-releasing hormone (GnRH) agonists to protect ovarian function [87, 88].

Cryopreservation of oocytes is not a viable option because of poor outcomes related to cryodamage of the oocyte in the process, and the exceptionally low pregnancy rate does not justify the use of this option for routine clinical practice [89]. In contrast, embryo cryopreservation with IVF is feasible, with established outcomes. For women with breast cancer, concerns and issues related to this option before the initiation of adjuvant therapy include the need for a partner or donor, compressed timing for decision making, potential risks of ovarian stimulation, and delay in initiating treatment because of the time required for ovarian stimulation and the IVF procedure [90]. Alternatives to standard ovarian stimulation have been investigated for women with hormonally dependent cancers. Tamoxifen with or without follicle-stimulating hormone [91, 92] and letrozole (Femara®; Novartis Pharmaceuticals Corporation, East Hanover, NJ) combined with IVF have resulted in a good follicle yield, mature oocytes, and a sufficient number of embryos for cryopreservation [92]. These data should be considered preliminary, and further research is needed to verify the safety and efficacy of the approach. A second alternative, the use of a GnRH antagonist, was published as a case study of six women with cancer, four of whom were diagnosed with breast cancer [93]. The data suggest a potential role for the use of a GnRH antagonist for ovarian stimulation that reduces the duration of the fertility procedure and allows for earlier initiation of cancer therapy.

Ovarian tissue cryopreservation with IVF is an experimental procedure that includes harvesting ovarian tissue and implantation of the ovarian tissue followed by IVF. The feasibility of harvesting ovarian tissue has been established [13, 94], and preliminary data suggest that implantation is feasible [88, 90], but more research is needed on cryopreservation protocols, cryoprotectants, and transplantation techniques [89]. In July 2005, a case report was published of a successful pregnancy and birth in a woman with a history of non-Hodgkin’s lymphoma using transplantation of cryopreserved ovarian tissue and IVF [95]. The authors state that they cannot rule out that the egg comes from the native ovary, but the patient’s 24-month history of amenorrhea following high-dose chemotherapy and laboratory data on the hormonal profile argue that the fertilization was related to the transplanted tissue. This initial case of a pregnancy in a cancer patient with transplanted tissue provides data to support continued investigation on the efficacy and safety of the approach. In addition to establishing the biologic feasibility, many other issues need to be addressed, such as the transfer of malignant cells, cost, insurance coverage, access, decision making, and long-term pregnancy outcomes and sequelae in women with a history of breast cancer.

The administration of a GnRH agonist during chemotherapy has been investigated as a method of protecting the oocytes and ovarian function. GnRH agonists act on the hypothalamic–pituitary axis to suppress ovarian function, creating an artificial prepubertal hypogonadotropic state [12, 83, 96]. Data from nonrandomized studies with lymphoma [96] and breast cancer [97] suggest that administration of a GnRH agonist provides protection against gonadal toxicity, demonstrated by a resumption of menses in a high percentage of women. Two additional studies reported on the use of a luteinizing hormone-releasing hormone (LHRH) analogue (goserelin [Zoladex®; AstraZeneca Pharmaceuticals]) in women with breast cancer who received adjuvant therapy and reported a protective effect, with resumption of menses in 59%–86% of the women treated [98, 99]. These initial findings suggest a potential role for the concept of gonadal quiescence.

In addition to biologic motherhood, parenting options should be included in the discussions of fertility. Surrogate pregnancy and adoption of a child are viable parenting options for breast cancer survivors.

Summary

Ovarian failure in young and young midlife women who receive adjuvant chemotherapy with or without endocrine treatment is associated with poorer quality of life, decreased sexual functioning, menopausal symptom distress, psychosocial distress related to fertility concerns and infertility, and uncertainty about late effects of premature menopause, such as bone loss [2]. Health care providers need to more fully understand the experience of women with chemotherapysize-induced gonadal damage. This review identifies the vulnerability of younger women diagnosed with breast cancer and the influence of premature, induced menopause on quality of life. The end of therapy is an emotionally distressing time for women, characterized by ambivalence,
uncertainty, and anxiety as they attempt to transition from active treatment to survivorship [7, 57, 60, 63, 100, 101]. As treatment ends, women begin to recognize that menopause means more than a loss of monthly menses [46–48]. Persistent menopausal symptoms are common [6, 32, 34, 64, 65], and the impact of menopause on sexuality and sexual function becomes more apparent.

Communication is central to cancer care delivery. Critical times for information preparation and discussion related to the acute, persistent, and late effects of gonadal toxicity include before treatment, at the end of treatment, and over the first year following adjuvant therapy. These times represent periods of high vulnerability for younger women with breast cancer. In addition to communication between the woman and her primary oncology providers, an interdisciplinary group of providers should be identified for appropriate referral to manage physical and psychological symptoms, distress and sexuality and sexual function problems, for fertility consultations, and for targeted interventions for healthy lifestyle behaviors aimed at risk reduction. Cancer treatment has prolonged survival, we now need to address the quality of life of those cancer survivors [3, 4].

Acknowledgments
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Disclosure of Potential Conflicts of Interest
The author indicates no potential conflicts of interest.

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