Chapter 92
Breast Cancer in Younger Women

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OVERVIEW

Breast cancer rarely occurs in young women. Of the hundreds of thousands of breast cancers diagnosed worldwide, fewer than 0.1% occur in women under age 20 years; 1.9% between 20 and 34; and 10.6% between 35 and 44 (1,2). Although fewer than 7% of women diagnosed with breast cancer are younger than 40 years, more than 14,000 young women are diagnosed annually with invasive or noninvasive breast cancer in the United States alone, with thousands more diagnosed worldwide (3–5). Incidence rates appear to be stable over the past several decades in young women in the Western world, despite increases in mammography and reproductive and lifestyle trends (2,6) (Fig. 92.1) (3). A suggestion is that rates are increasing among young women, particularly in less-developed countries, but this may be owing to improvements in awareness, diagnosis, and reporting (7,8).

Despite the relative rarity of breast cancer in young women, it is the leading cause of cancer-related deaths in women under 40, and survival rates for young women with breast cancer are lower than for their older counterparts (4,9). The 5-year relative survival rate for women with breast cancer diagnosed before age 40 years is 82% compared with 89% for women diagnosed at age 40 or older (4). Although controversial, accumulating evidence suggests that young age is an independent risk factor for disease recurrence and death, despite that young women have conventionally received more intensive treatment than older women (10–12). Delays in diagnosis and the lack of effective screening in younger women may contribute to the poorer prognosis because they are more likely to present with larger tumors and more involved lymph nodes (13). However, survival differences more likely reflect biological differences in the type of breast cancer developed in young women. Young women are more likely to develop more aggressive subtypes of breast cancer with unfavorable prognostic features, and are less responsive to conventional therapy compared with disease arising in older premenopausal or postmenopausal women (14–16). Specifically, tumors in young women are more likely to be high-grade, hormone receptor(HR)-negative, and have high proliferation fraction and more lymphovascular invasion. Evidence is mixed about the proportion of ERBB2 (formerly HER-2/*neu*) overexpressing tumors, with more modern studies suggesting similar rates across age cohorts (14–19) A population-based registry study in Korea of young women diagnosed with breast cancer, consisting of 1,444 women age less than 35 years, and 8,441 women age 35 to 50 years, revealed significant differences in clinicopathologic characteristics by age at diagnosis. Women younger than 35 were more likely to have greater T stage ($p < .001$) and N stage ($p < .001$) tumors. Furthermore, in the younger age group, 32.4% were estrogen receptor (ER)-positive, 30.6% ER-negative, and 37.0% unknown compared with 36.6% ER-positive, 27.8% ER-negative, and 35.5% ER-unknown in the older group ($p = .002$). In addition the younger age group was 29.9% PR-positive, 31.9 PR-negative, and 38.2 unknown, compared with 36.6% PR-positive, 27.6 PR-negative, and 35.8 unknown in the older group ($p < .001$). ERBB2 status, as determined by immunohistochemistry score, did not differ between the 263 women in those younger than 35 years compared with the 1,947 women in the older age group for whom ERBB2 status was available ($p = .238$) (15). A recent preliminary investigation suggests that breast cancer arising in young women may represent a distinct biologic entity with unique patterns of deregulated signaling pathways, such as through the Src and E2F oncogenic pathways, which may affect prognosis (20).

Also, increasing evidence suggests that biologic subtypes of breast cancer vary by race as a function of age. In a large, population-based study of breast cancer subtypes within age and racial subsets, the basal-like breast cancer subtype (ER-, PR-, ERBB2-, cytokeratin 5/6 positive, and/or ERBB1+), was more prevalent among premenopausal black women (39%) compared with postmenopausal black women (14%) and non-black women (16%) of any age ($p < .001$), whereas the better prognosis luminal A subtype (ER+ and/or PR+, ERBB2-) was less prevalent (36% vs. 59% and 54%, respectively). This higher prevalence of basal-like breast tumors and lower prevalence of luminal A tumors likely contributes to the poorer prognoses of young black women with breast cancer (21) (see Chapter 32, Prognostic and Predictive Factors: Molecular).

In addition to being at higher risk of dying from breast cancer, despite conventionally receiving more aggressive therapy, young women face a variety of problems unique to, or accentuated by, their young age. They are more likely to be diagnosed at a life stage when role functioning in the home and work can be threatened or disrupted by the diagnosis and treatment of breast cancer. Issues such as attractiveness and fertility may be of substantial importance. Young women are more likely to have young children for whom they are responsible, or desire to have biologic children following treatment. They also have an increased risk of harboring a genetic risk factor for breast cancer, and often suffer from a relative lack of information regarding treatment and survivorship issues compared with older patients. These concerns may contribute to the greater psychosocial distress seen in younger women at both diagnosis and in follow-up (22–25).

Research to date on breast cancer in young women is limited by generally small sample sizes and heterogeneous cut-offs used to differentiate between young and old. Although, age is a continuum and any cut-off is somewhat arbitrary. Many investigators have chosen up to age 35 or 40 to define breast cancer in younger women, recognizing that previous work focusing on premenopausal women is composed primarily of women in their 40s owing to the higher incidence of the disease in older premenopausal women.

RISK FACTORS FOR EARLY ONSET BREAST CANCER AND GENETICS ISSUES

Aside from female gender, increasing age is the strongest risk factor for developing breast cancer. Consequently, younger women are at much lower risk even when compared with older premenopausal women. An average woman has a 1 in approximately 1,800 risk of developing breast cancer in her 20s, 1 in 230 in her 30s, and 1 in 70 in her 40s (4). Family history is the primary risk factor for developing breast cancer at young age, particularly when breast cancer has occurred in a first-degree relative at a young age. Although 5% to 10% of breast cancers are attributable to germ-line mutations such as *BRCA1* and *BRCA2* on chromosomes 17 and 13, respectively, another 15% to 20% of breast cancers are associated with the presence of

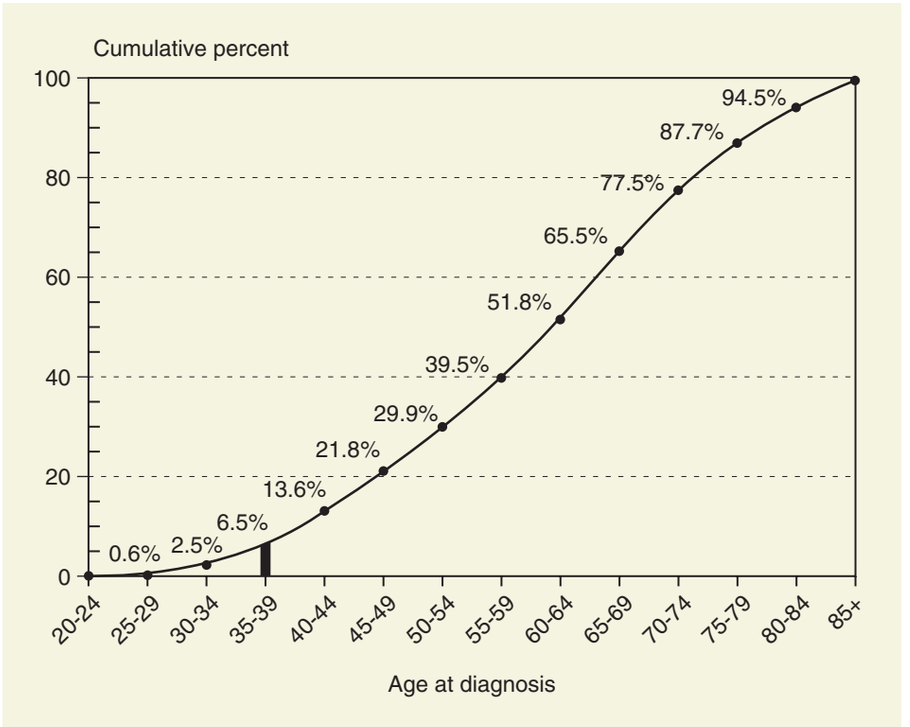

FIGURE 92.1. Cumulative distribution of breast cancer diagnoses by age. (From Hankey BF, Miller B, Curtis R, et al. Trends in breast cancer in younger women in contrast to older women. *J Natl Cancer Inst Monogr* 1994;16:7–14, with permission.)

gene polymorphisms and environmental factors (e.g., radiation; see later). By virtue of her age alone, a young woman diagnosed with breast cancer has a greater probability of carrying a *BRCA* mutation. In an unselected group of women under 40 having surgery for early breast cancer, 9% harbored a deleterious *BRCA1* or *BRCA2* mutation (26). Other factors, including a personal or family history of ovarian cancer, bilateral breast cancer, or Ashkenazi Jewish ancestry, may increase that risk. The meaning of an unknown variant of the *BRCA1* or *BRCA2* genes may also vary by race (27). Young women with breast cancer should consider genetic counseling and testing for *BRCA1* and *BRCA2*, particularly if they have a family history of breast or ovarian cancer. Please see Chapters 18 and 19 for more details.

Some rare genetic disorders may predispose younger women to develop breast cancer. These include Cowden disease (*PTEN* gene mutation on chromosome 10 and associated with hamartomas, as well as with breast or thyroid cancer at a young age), and Li-Fraumeni syndrome (mutation of *TP53* gene on chromosome 17, with increased incidence of soft tissue and bone sarcomas, brain tumors, adrenocortical tumors, and breast cancers) (28) (see Chapter 18 for more detail). Young women exposed to ionizing radiation during childhood and teenage years, such as survivors of pediatric Hodgkin disease treated with mantle field irradiation, are also at high risk of developing breast cancer (29). Despite preconceptions, most cases of breast cancer occurring in young women appear to be spontaneous and not clearly related to either carcinogens in the environment or family cancer syndromes (30). However, environmental and hormonal risk factors for breast cancer are not well characterized for younger women, but appear to be somewhat different than for older women. Although breastfeeding appears to be protective against breast cancer at any age, pregnancy appears to have a dual effect on the risk of breast cancer. Large epidemiologic studies indicate that earlier age at first live birth has a long-term protective effect on the lifetime risk of breast cancer, yet it transiently increases the risk immediately following childbirth for 3 to 15 years postpartum, but reduces the risk in later years (24,31–34). The excess transient early risk of breast cancer is most pronounced among women who are older at the time of their first delivery. Thus, pregnancy has a protective effect for postmenopausal breast cancer and is a risk factor for premenopausal breast cancer, particularly for older premenopausal women. The biologic mechanism for this is not well elucidated. Also contrary to what has been demonstrated in older women, weight gain and higher body mass index appear to be protective against the development of breast cancer at younger age (35–37).

BREAST DIAGNOSTIC ISSUES FOR YOUNG WOMEN

Most lesions arising in the breasts of young premenopausal women will be benign (see Chapter 10 on Benign Breast Disease). Mammography is often of limited value in this population because of high breast tissue density, and targeted ultrasound or magnetic resonance imaging can provide additional discriminatory information in the workup of a breast abnormality (38–40). Breast cancers may be more extensive in younger patients, although it is not clear whether they are at higher risk of multicentricity or bilateral disease, in the absence of a hereditary predisposition, and no evidence indicates that multifocality affects survival in this population (41–46).

TREATMENT ISSUES

Many clinical trials have divided patient populations based on menopausal status, or age greater or less than 50. Virtually no published clinical trials have focused on treatment issues for the youngest women. Trials reporting results of treatments for premenopausal women largely reflect outcomes for patients in

their 40s. Thus, findings from studies that consider average results for premenopausal women may not be directly applicable to very young patients.

Local Therapy Issues

Partly owing to inadequate screening options for young women, breast cancer tends to be larger and more often locally advanced. Consequently, young women may more likely need or benefit from preoperative systemic therapy than older women, although available data in this area are limited. Despite the large benefit that young women obtain from an irradiation boost to the tumor bed, most studies continue to indicate that young age is a risk factor for local recurrence, for both invasive and noninvasive disease (47–53) (Fig. 92.2). No evidence suggests, however, that mastectomy in young women improves survival compared with breast conservation, likely because these women are also at increased risk of systemic recurrence. In a population-based Danish cohort of 9,285 premenopausal women with breast cancer, the incidence of local recurrence was 15.4% after breast-conserving therapy among the 719 women under age 35 compared with 3.0% in women ages 45 to 49, although no difference was found in the risk of death between the two age groups (54). Thus, young age alone is not a contraindication to breast conservation. Nonetheless, an increasing number of young women are opting not only for mastectomy, but for contralateral prophylactic mastectomy (55). Reasons for this trend are not completely clear, nor is there evidence that such aggressive surgical measures will improve outcomes. For some young women, local therapy decisions may be influenced by the presence or absence of a known genetic risk for new primary breast cancer (i.e., a *BRCA1* or *BRCA2* mutation). Thus, prompt genetic counseling and testing for young women at risk for harboring a deleterious genetic mutation should be considered, especially for women for whom the results would have an impact on local therapy decisions. Bilateral prophylactic mastectomy and oophorectomy are increasingly considered for young women with known *BRCA1* or *BRCA2* mutations, despite the current lack of clear benefits of such risk-reducing strategies in breast cancer survivors (56,57).

At present, no relevant data are available on the late effects of radiation therapy plus modern systemic therapy (including anthracyclines, taxanes, and trastuzumab) on cardiac functioning in young women. Moreover, other effects of radiation therapy in patients with very long life expectancy must be taken into account (58).

Attention to margin status may be particularly important for young women undergoing breast conservation treatment. In one evaluation including 37 women younger than 35 with lymph node-negative breast cancer having breast-conserving therapy, local recurrence rates were 50.0% for women with positive margins compared with 20.8% for those with negative margins (51). In a more recent publication, women age 40 or younger with invasive disease had 10-year local recurrence-free survival of 84.4% with negative margins versus 34.6% with positive margins, whereas women over 40 years had local recurrence-free survival of 94.7% if margins were negative compared with 92.6% if margins were positive (52). These findings translated to a 10-year distant disease-free survival (DFS) of 72.0% for younger women with negative margins

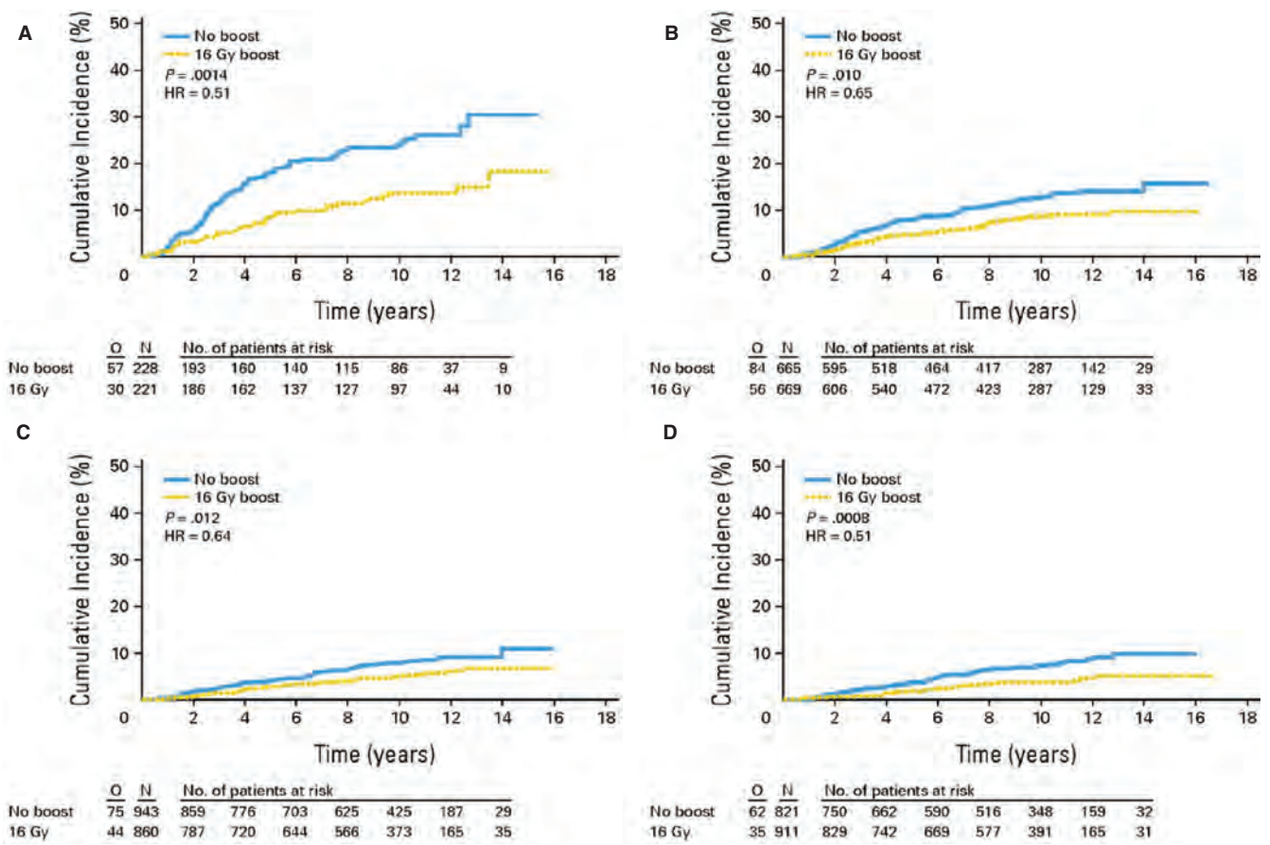

FIGURE 92.2. Cumulative incidence of ipsilateral breast cancer recurrence according to age. Age **(A)** ≤40, **(B)** 41 to 50, **(C)** 51 to 60, and **(D)** > 60 years. (From Bartelink, H. et al. *J Clin Oncol* 2007;25:3259–3265, with permission.)

compared with 39.7% (relative risk [RR] = 3.4) for the younger age group with positive margins, whereas for older women, no significant difference was seen in DFS among those with negative compared to positive margins.

Systemic Therapy Issues

Adjuvant treatment recommendations are based on tumor and patient characteristics predicting the risk of systemic recurrence and potential responsiveness to therapy, as well as the patient's preferences and values. Increasingly, treatments are tailored, regardless of age, to the phenotypic subtype of the tumor as assessed by conventional factors, such as grade, proliferation rate, estrogen and progesterone receptors, and ERBB2 expression. More recent application of genetic signature technology has provided additional predictive information regarding the degree of risk and responsiveness to therapy (see Chapter 32). However, most of the data on adjuvant treatment response was obtained during an era when details related to endocrine responsiveness were either incomplete or imprecise. Even today, endocrine responsiveness evaluation requires improved reporting of steroid hormone receptors and a better understanding of the role of ERBB2 overexpression and amplification (59,60). Currently it is recommended that the estimation of endocrine responsiveness should be the first consideration in tailoring adjuvant therapies for patients with breast cancer, regardless of age (61). Adjuvant chemotherapy has historically been used extensively in premenopausal patients because of its overwhelming beneficial effects on outcome (62,63). The incremental benefits of newer cytotoxic drugs and regimens, including the addition of the taxanes, dose density, and trastuzumab, appear to be present across age groups, although data for very young women are limited (64–68).

Adjuvant Systemic Therapy in Patients with Hormone Receptor-Negative Disease

For premenopausal women with hormone receptor (HR)-negative disease, adjuvant chemotherapy is a very important component of successful treatment. Only one trial, however, has prospectively tested the use of chemotherapy in women with HR-negative, node-negative disease (National Surgical Adjuvant Breast and Bowel Project [NSABP] B13) (69,70). Table 92.1 displays the relative risk of relapse for the chemotherapy-treated group compared with the surgery alone group. No difference was found between the risk for very young compared with the older premenopausal patients, with a 38% reduction in the risk of recurrence from the use of chemotherapy. Novel biologic and chemotherapeutic regimens (e.g., platinum agents) that have shown early promise in women with early (e.g., trastuzumab) and advanced disease (e.g., bevacizumab, platinum agents) may also be particularly relevant in the treatment of young women with breast cancer, because this population is more likely to develop HR-negative disease (71).

Adjuvant Systemic Therapy in Patients with Hormone Receptor-Positive Disease: Chemotherapy and Endocrine Therapy

Controversy exists about the optimal management of young women with HR-positive breast cancer (72). Since the 1990s, adjuvant tamoxifen has been the mainstay of endocrine therapy for premenopausal women when the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview, a large meta-analysis consisting of dozens of randomized trials, revealed a beneficial effect in women under 50 similar to the benefit seen for older women (62,73). The first adjuvant systemic therapy for premenopausal women with breast cancer was ovarian ablation, but its use was almost abandoned in the mid-1970s when the benefits of adjuvant cytotoxic chemotherapy became clear. When the results of all trials of ovarian ablation were summarized by the EBCTCG meta-analysis, the beneficial effect of ovarian ablation appeared to be large in the absence of chemotherapy, whereas no apparent advantage was seen when ovarian ablation was added to cytotoxic chemotherapy (74). More than 80% of the women in this chemotherapy alone group experienced ovarian function suppression with the cytotoxic treatment, however, and the cohort was also a mixture of women with ER-positive and ER-negative disease (75). The International Breast Cancer Study Group (IBCSG) evaluated treatment outcome for very young women compared with older premenopausal women who received adjuvant chemotherapy alone. Very young premenopausal women (<35 years of age) with HR-positive tumors had a worse outcome compared with older premenopausal women, and compared with both older and younger women with HR-negative disease (76). This led to the hypothesis that the effects of cytotoxic chemotherapy on ovarian function, and the timing and duration of treatment related-amenorrhea differ between older and younger premenopausal women. Very young women are much less likely to experience ovarian dysfunction with chemotherapy resulting in a poorer prognosis in the absence of additional endocrine therapy (77–79) (see Chapter 96: Reproductive Issues in Breast Cancer Survivors). To confirm the interaction between age and ER status in premenopausal women treated with chemotherapy alone, the IBCSG, NSABP, Eastern Cooperative Oncology Group (ECOG), and Southwestern Oncology Group (SWOG) conducted a pooled analysis of 9,864 patients. Table 92.2 summarizes the results from all four cooperative groups. In each analysis, the relative risk of an event, estimated from a Cox proportional hazards regression model stratified by study and treatment group, was substantially higher for young patients with ER-positive tumors compared with the reference population of older patients with ER-positive tumors. This phenomenon was not observed for

Table 92.1 RELATIVE RISK OF RELAPSE COMPARING PATIENTS IN THE CHEMOTHERAPY GROUP (METHOTREXATE → FLUOROURICIL) VERSUS THE NO ADJUVANT THERAPY GROUP: RESULTS FROM THE NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT TRIAL B-13 FOR ESTROGEN RECEPTOR–NEGATIVE, NODE-NEGATIVE CASES

Age-Group	Patients (N)	Events (N)	Relative Risk	95% Confidence Interval	*p*-Value
<35	69	28	0.62	(0.29, 1.30)	.21
35–49	371	107	0.62	(0.42, 0.91)	.01

From Goldhirsch A, Gelber RD, Yothers G, et al. Adjuvant therapy for very young women with breast cancer: need for tailored treatments. *J Natl Cancer Inst Monogr* 2001;30:44–51, with permission.

Table 92.2 RELATIVE RISK OF RELAPSE[a] AND CORRESPONDING 5-YEAR DISEASE-FREE SURVIVAL[b] FOR PREMENOPAUSAL WOMEN IN CHEMOTHERAPY ALONE GROUPS IN TRIALS CONDUCTED BY THE INTERNATIONAL BREAST CANCER STUDY GROUP (IBCSG), THE NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT (NSABP), THE EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG), AND THE SOUTHWEST ONCOLOGY GROUP (SWOG)[c]

		ER-positive		ER-negative		
Group	Total Patients (N)	<35	≥35[b]	<35	≥35[b]	Interaction *p*-Value
		Relative Risk of Relapse (Number of Events/Number of Patients)				
IBCSG	2,233	1.84 (72/96)	1.00 (737/1353)	1.13 (50/88)	1.02 (370/696)	.009
NSABP	5,849	1.72 (254/402)	1.00 (1210/2716)	1.27 (214/441)	1.12 (1045/2290)	.0001
ECOG	1,112	1.54 (42/71)	1.00 (274/602)	1.40 (40/73)	1.26 (195/366)	.17
SWOG	670	2.67 (11/29)	1.00 (48/293)	0.81 (7/55)	1.13 (52/293)	.012

ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; IBCSG, International Breast Cancer Study Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; SWOG, Southwest Oncology Group.

[a]Includes breast cancer relapses, second primary breast tumors, and deaths without relapse for IBCSG (also includes nonbreast second primaries), ECOG, and SWOG; includes only breast cancer relapses (other events are censored) for NSABP.

[b]Premenopausal ≥35 years of age for IBCSG, ECOG, and SWOG; 35 to 49 years for NSABP. Chemotherapy regimens of the various trials included in the collaboration: IBCSG: classic CMF (cyclophosphamide, methotrexate, fluorouracil) for 12, 9, 6, or 3 courses; NSABP: melphalan + fluorouracil ± methotrexate × 12; melphalan + fluorouracil + doxorubicin × 12; AC (doxorubicin + cyclophosphamide) × 4 ± CMF (given intravenously on day 1, 8 q 28 days) × 6; classic CMF × 6; AC "intensified dose" × 4; AC "intensified dose" with growth factors × 4; ECOG: classic CMF × 12 or 6 courses; CAF × 6 courses; intensive "16-week regimen"; SWOG: classic CMF × 6 courses; CAF × 6 courses.

[c]Cohorts defined by age and estrogen receptor status are compared with the reference population of older women with estrogen receptor-positive tumors (number of events/number of patients are shown in parentheses).

From Goldhirsch A, Gelber RD, Yothers G, et al. Adjuvant therapy for very young women with breast cancer: need for tailored treatments. *J Natl Cancer Inst Monogr* 2001;30:44–51, with permission.

patients with ER-negative tumors. In recent years, it has become clear that in patients with HR-positive disease, the beneficial effects of cytotoxic agents are probably a result of a complex mixture of cytotoxic and endocrine effects of chemotherapy. IBCSG Trial VIII compared sequential chemotherapy followed by the gonadotropin-releasing hormone agonist goserelin with each modality alone in 1,063 pre- and perimenopausal women with lymph node-negative breast cancer (80). Women were randomized to goserelin for 24 months (n = 346), six courses of "classic" CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy (n = 360), or six courses of classic CMF followed by 18 months of goserelin. (CMF → goserelin; n = 357). (A fourth no adjuvant treatment arm with 46 patients was discontinued early). Of patients, 20% were aged 39 years or younger and median follow-up was 7 years. Patients with ER-negative tumors had better DFS if they received CMF (5-year DFS for CMF = 84%, 95% confidence interval [CI], 77%–91%; 5-year DFS for CMF → goserelin = 88%, 95% CI, 82%–94%) than if they received goserelin alone (5-year DFS = 73%, 95% CI, 64%–81%). By contrast, for patients with ER-positive disease, chemotherapy alone and goserelin alone provided similar outcomes (5-year DFS for both treatment groups = 81%, 95% CI, 76%–87%), whereas sequential therapy (5-year DFS = 86%, 95% CI, 82%–91%) provided a statistically nonsignificant improvement compared with either modality alone, primarily because of the results among younger women (Fig. 92.3). The DFS results shown in Figure 92.3 according to treatment group illustrate that outcomes for older premenopausal women with ER-positive disease cannot be used to define appropriate treatment choices for younger women (in this example, ≤39 years). For some young patients, endocrine therapy alone may suffice, or a combined endocrine therapy approach may be optimal (61,80–83).

Tamoxifen

Tamoxifen, the most thoroughly studied selective ER modulator (SERM), has not been specifically investigated in very young patients. This drug typically increases the estradiol secretion from premenopausal ovaries. The updated EBCTCG meta-analysis of all randomized trials of adjuvant tamoxifen has revealed that 2 to 5 years of treatment has similar efficacy in all age groups, including patients less than 40 years of age (62). However, several analyses have suggested that the youngest women in various treatment groups seem to get less benefit from tamoxifen alone (15,16,70). These findings suggest an opportunity to improve on treatment results for this patient population. It is also important to note that, although risks associated with tamoxifen (e.g., blood clot, stroke, and uterine cancer) tend to be much lower in younger patients than older patients, younger women are more likely to develop ovarian cysts because of high estradiol levels resulting in ovarian hyperstimulation while on tamoxifen (84,85).

Adjuvant Ovarian Ablation (Suppression) with or without Tamoxifen

The combination of ovarian suppression or ablation and tamoxifen has been tested in advanced disease and proved superior to either treatment alone (86). In a trial conducted in Asia, the combination of oophorectomy and tamoxifen compared with no adjuvant therapy resulted in an 11% absolute benefit in DFS and an 18% benefit in overall survival (OS) at 10 years (87). In the subset of patients with ER-positive tumors, 10-year DFS probabilities were 66% in the treated group compared with 47% in the control group, corresponding to 10-year OS rates of 82% and 49%, respectively. In a subset analysis from this same study, ERBB2 overexpression appeared to have a favorable influence on response to adjuvant oophorectomy and tamoxifen in women with ER-positive disease (88).

Acceptance of ovarian function suppression, tamoxifen, or the combination may be a significant problem for premenopausal women in general and for younger patients in particular (89). Issues include objective and subjective symptoms of menopause, psychological distress, and adjustment to changes in personal and family plans. Chemotherapy seems

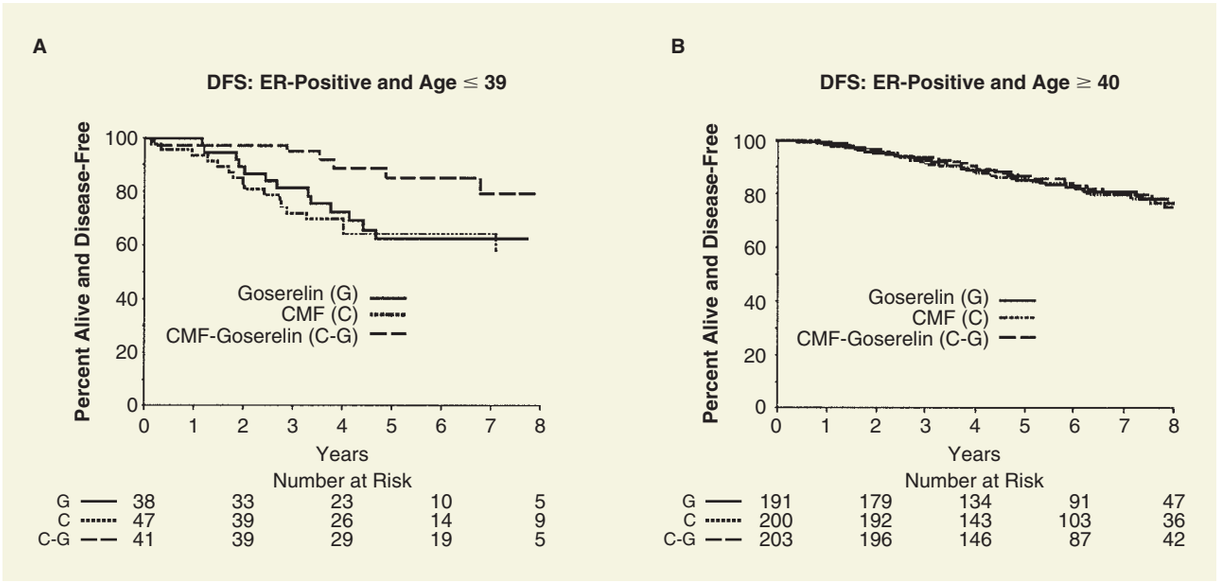

FIGURE 92.3. Kaplan-Meier plots of disease-free survival (DFS) for the ER-positive cohort enrolled in International Breast Cancer Study Group (IBCSG) Trial VIII comparing six courses of cyclophosphamide, methotrexate, and 5-fluorouracil (C), 24 months of goserelin (G), and six courses of C followed by 18 months of goserelin (C-G) at 7 years of median follow-up. Results for subgroups according to age less than 39 years **(A)** and age 40 years or more **(B)** are shown. (From International Breast Cancer Study Group (IBCSG). 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, with permission.)

easier to offer to younger patients because of its shorter duration and lesser degree of long-term effects on endocrine function than ovarian suppression, although recent evidence suggests most premenopausal healthy women would choose ovarian suppression over CMF chemotherapy, hypothetically (90). Long-term symptoms of acute ovarian suppression may be a particular problem for some patients. However, in an evaluation of 874 pre- and perimenopausal women in IBCSG Trial VIII (see previous section in this chapter), patients receiving goserelin alone showed a marked improvement or less deterioration in quality of life (QOL) measures over the first 6 months than those patients treated with CMF, yet no differences were seen at 3 years except for hot flashes (91). As reflected in the hot flashes scores, patients in all three treatment groups experienced induced amenorrhea, but the onset of ovarian function suppression was slightly delayed for patients receiving chemotherapy. Of note, in this study, younger patients (<40 years) who received goserelin alone returned to their premenopausal status at 6 months after the cessation of therapy, whereas those who received CMF showed only marginal changes from their baseline hot flashes scores, likely indicative of minimal ovarian dysfunction.

The ongoing study Suppression of Ovarian Function Trial (SOFT) randomizing premenopausal women with HR-positive disease to tamoxifen, tamoxifen and ovarian suppression, or exemestane and ovarian suppression should further elucidate the role of ovarian suppression, and optimal endocrine therapy in young women with breast cancer. (www.ibscg.org) The lack of acceptability resulting in premature closure of the Premenopausal Endocrine Responsive Chemotherapy Trial (PERCHE), a randomized trial evaluating the role of chemotherapy in the setting of combined endocrine therapy, will hamper the availability of more definitive evidence regarding the benefits and risks of chemotherapy in addition to endocrine therapy in very young patients. The optimal duration and the timing of adjuvant endocrine therapy options in very young patients with HR-positive disease, also remain open questions.

BREAST CANCER DIAGNOSED DURING PREGNANCY

It is more likely that younger rather than older premenopausal women will be faced with concurrent pregnancy and the diagnosis of breast cancer, although the issues are similar, irrespective of age. Cytotoxic treatments have been safely administered, beginning in the second trimester, after the completion of organogenesis, although there are risks (92–94). Tamoxifen is contraindicated during pregnancy, because it has been associated with teratogenicity. Reportedly, however, many babies have been born without obvious abnormality after *in utero* exposure (95). Issues regarding whether to maintain the pregnancy and the timing of breast cancer treatment are complex both from a medical and psychosocial standpoint (for additional details, see Chapter 68).

BREAST DISEASE IN ADOLESCENTS

Breast disease in adolescent females is fortunately uncommon, with most presenting lesions being benign, most commonly fibroadenomas (96,97). For most breast lesions in children and adolescents, open biopsy can be avoided (98). Breast cancer is very rare in this population. Because of this, neither the prognosis nor optimal management of the disease in this age group is clear. Available case series suggest that adolescents with breast tumors comprise a mix of histologic subtypes including cystosarcoma phyllodes, and more commonly, adenocarcinomas including invasive intraductal, invasive lobular, signet ring, and secretory adenocarcinomas (99,100). Treatment recommendations should be tailored to the specific histology, and attention to psychosocial issues, including adherence with therapy, is prudent in the care of teenagers with breast cancer.

BREAST CANCER IN CHILDHOOD CANCER SURVIVORS

Young women with a history of treatment for childhood cancer, in particular those treated with chest ("mantle") irradiation for Hodgkin's Disease, are at dramatically increased risk of early onset breast cancer (101,102) (See Chapter 20 in this text). Treatment considerations in this unique subgroup may be complicated by previous systemic therapy, recommendations against further radiation therapy, and psychosocial issues.

TREATMENT OF YOUNG WOMEN WITH ADVANCED DISEASE

Very young women who present with metastatic disease are generally treated using an algorithm reflecting the general incurability of the disease, and employing ovarian function suppression together with other treatment options if the disease is endocrine responsive (see Chapter 73 and 74 in this text). The sequential use of endocrine therapy followed at the time of disease progression by chemotherapy, similar to the conventional approach in older premenopausal and postmenopausal women, is reasonable, although this has not been specifically tested in younger patients. Young patients with metastatic disease may be particularly vulnerable to psychosocial distress, particularly if they have young dependents (103).

QUALITY OF LIFE AND PSYCHOSOCIAL ISSUES

A growing body of evidence suggests that younger women with breast cancer are at increased risk of psychosocial distress compared with older women, both at diagnosis and follow-up (104–110). In a large prospective cohort study, women age 40 and younger who developed breast cancer experienced significant declines in their QOL compared with age-matched women without breast cancer (111). Adjusting for disease severity and treatment factors, young women who developed breast cancer had the largest relative declines in QOL following diagnosis compared with middle-aged and elderly women who developed breast cancer. In a survey of women who were 50 years or younger at diagnosis and disease-free at 6 years follow-up, women generally reported high levels of physical functioning, but the youngest women (ages 25–34 at diagnosis) exhibited the greatest degree of psychosocial distress, particularly with social and emotional functioning as well as vitality (22). Many young women also feel isolated and lacking information (112). When they attend breast cancer support groups, their issues are often substantially different from those of the older women. Others in their age cohort are planning for the future, whereas young women with breast cancer are facing a life-threatening and physically mutilating disease. Little information is available regarding work and life decisions made by these women. And although access to psychosocial support is associated with a better QOL in breast cancer survivors, these results have not been presented separately for the youngest patients (113–116).

FERTILITY AND PREGNANCY AFTER BREAST CANCER

Young women with breast cancer may face the risk of becoming amenorrheic with treatment, either temporarily or permanently, resulting in potential infertility, onset of menopausal symptoms, problems with sexual functioning, and exposure to long-term risks of early menopause. The risk of amenorrhea is related to increasing patient age and treatment received (117,118) (Fig. 92.4). For some young women, cessation of menses may be welcome and may improve outcomes for women with HR-positive disease. For many young women, however, the threat or experience of infertility may be devastating. Discussion of this important survivorship issue should

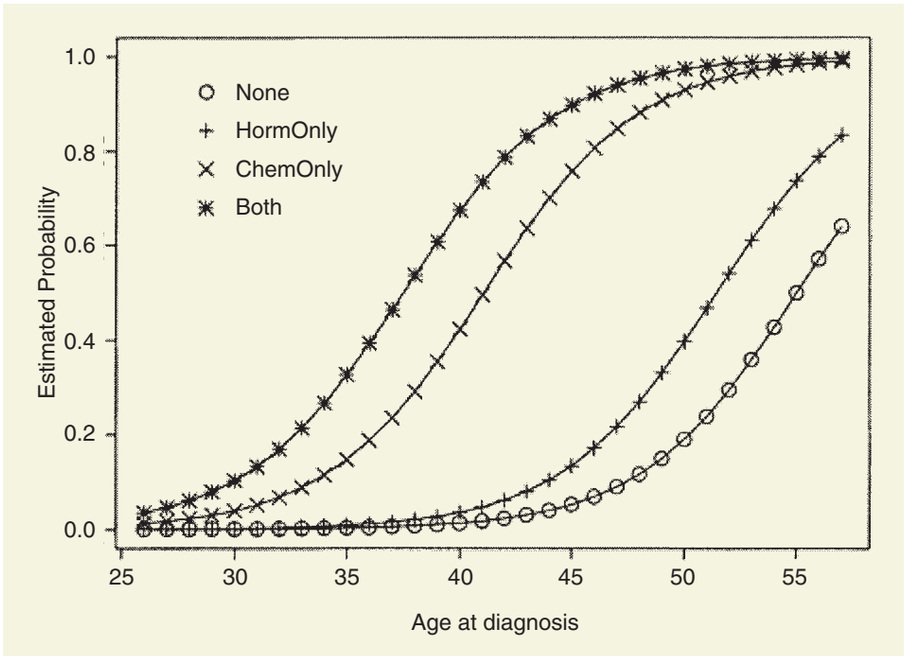

FIGURE 92.4. Probability of menopause during the first year after diagnosis (according to a model). (From Goodwin PJ, Ennis M, Pritchard KI, et al. Risk of menopause during the first year after breast cancer diagnosis. *J Clin Oncol* 1999;17: 2365–2370, with permission.)

commence early in the treatment decision process because some women may elect to try to preserve fertility through intervention or forgo some therapy (119,120). However, available fertility preservation strategies including gonadotropin-releasing hormone (GnRH)-agonist treatment during chemotherapy, as well as cryopreservation of embryos, oocytes, or ovarian tissue are hampered by either limited efficacy, safety concerns, or both (121). Young breast cancer survivors can be reassured that at the present time no clear risk in having a biologic child exists. However, studies are limited by substantial biases, including the *healthy mother* bias, and concerns remain for some (122,123). Pregnancy after breast cancer is a very complex and personal decision for a woman who remains at risk for recurrent disease (for additional details, see Chapter 96 Reproductive Issues in Breast Cancer Survivors).

MENOPAUSAL SYMPTOMS AND SEXUAL FUNCTIONING

Menopausal symptoms and sexual dysfunction are common in breast cancer survivors. To date, most breast cancer survivors included in evaluations of sexual dysfunction have been over age 40, reflecting the demographics of breast cancer. Little information is available focusing on sexual dysfunction in very young breast cancer survivors, and no intervention studies have been conducted. Research has, however, identified risk factors for sexual dysfunction in breast cancer survivors including younger age, premature menopause, and the use of chemotherapy (124). The use of tamoxifen and type of breast surgery may also have an impact on sexual functioning, especially in young breast cancer survivors. In a survey of 371 women diagnosed with breast cancer age 40 and younger (mean age at diagnosis 33 years and mean age at follow-up 36 years) where 77% of these women were premenopausal at follow-up, many reported bothersome sexual functioning or menopausal-type symptoms (125). In particular, 46% of women reported hot flashes and 39% reported dyspareunia. Current ovarian suppression, menopausal status, baseline anxiety before the diagnosis, pregnancy after the diagnosis, prior chemotherapy, and lower perceived financial status were associated with more bothersome symptoms. Evidence indicates that intervention to improve menopausal symptoms and sexual functioning is effective, although limited research to date focuses on very young women (126).

CONCLUSIONS

When a very young woman is diagnosed with breast cancer, she may face several threats to her future health and well-being. Most concerning, a young woman with breast cancer is more likely than an older woman to have an adverse prognosis. The differential in prognosis by age may reflect, in part, biological differences between breast cancer that develops in a younger compared with an older woman. Prognosis may, however, also be affected by suboptimal therapy, particularly endocrine therapy, in the youngest patients who are least likely to lose ovarian functioning as a result of systemic therapy. Because of the relative rarity of breast cancer in young women, large pooled analyses and multinational clinical trials are necessary to address the many controversies and improve therapy for younger patients. Late health and psychosocial effects of breast cancer in young women should also be considered in this vulnerable population.

MANAGEMENT SUMMARY

Local Therapy

- Consider preoperative systemic therapy for women with locally advanced disease or those with large tumors who desire breast preservation.
- Careful attention to margin status and boost irradiation after lumpectomy is warranted to minimize the higher risk of local recurrence associated with young age.

Systemic Therapy

- Consider the endocrine as well as the direct cytotoxic effects of chemotherapy.
- Optimize endocrine therapy given evidence for benefits in young women with hormone receptor-positive disease.

Psychosocial and Survivorship Issues

- Evaluate concerns about future fertility early on and refer for consideration of fertility preservation strategies as needed before systemic therapy.
- Consider genetic testing (e.g., *BRCA1* or *BRCA2* testing), early on if it would have an impact on a woman's treatment decisions.
- Provide psychosocial support and referrals given the increased distress often seen in young women with breast cancer.

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