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Breast Cancer Before Age 40 Years

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Abstract

Approximately 7% of women with breast cancer are diagnosed before the age of 40 years, and this disease accounts for more than 40% of all cancer in women in this age group. Survival rates are worse when compared to those in older women, and multivariate analysis has shown younger age to be an independent predictor of adverse outcome. Inherited syndromes, specifically *BRCA1* and *BRCA2*, must be considered when developing treatment algorithms for younger women. Chemotherapy, endocrine, and local therapies have the potential to significantly impact both the physiologic health —including future fertility, premature menopause, and bone health—and the psychological health of young women as they face a diagnosis of breast cancer.

Although a diagnosis of breast cancer is distressing at any age, this occurrence in young women is fraught with several unique challenges. This article reviews the distinct epidemiology, etiology, clinicopathologic characteristics, biology, treatment strategies, outcomes, and psychosocial challenges of breast cancer before 40 years of age. Also included in this review are issues of familial breast cancer, fertility, premature menopause, breast cancer during pregnancy, and bone health. The US Surveillance, Epidemiology and End Results (SEER) database was the source of data for the tables and graphs presented here.[1]

Epidemiology

The American Cancer Society (ACS) estimates that 182,460 women in the United States were diagnosed with breast cancer in 2008 and that 40,480 women died of the disease during the year.[2] The incidence of breast cancer appears to have a sigmoid function in women less than 55 years of age (Figure 1, lower panel), with 6.6% of all cases diagnosed before age 40, 2.4% diagnosed before age 35, and 1% diagnosed before age 30 (Figure 2, inset). The individual average risk of a woman developing breast cancer was 1 in 173 by the age of 40 and approximately 1 in 1,500 by the age of 30 (Table 1). Of all cancers diagnosed among women, more than 40% is breast cancer by the age of 40, 20% by the age of 30, and slightly more than 2% by 20 years of age (Figure 1, upper panel).

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The overall incidence of breast cancer in males is approximately 1/100th that of the rate in females. The age-dependence differs also, in that breast cancer occurs at older ages in males, with only 2.6% of all cases in men occurring before age 40 years. Hence, breast cancer in males is not reviewed further in this article.

Although the incidence of breast cancer in females younger than 40 years of age has remained stable for the past 30 years (Figures 3 and 4), the incidence in older women had increased steadily (Figure 3) until it peaked in 2000 then declined steadily thereafter (Figure 4). This decrease has been attributed to the reduction in the use of hormone replacement therapy.[3]

The incidence of breast cancer in young women in the United States also varies according to race and ethnicity. In women over 45, breast cancer is more common in whites than blacks. However, black women under age 35 have more than twice the incidence of invasive breast cancer and three times the breast cancer mortality of young white women.[4-6] In contrast, native American women aged 20-44 have a lower incidence of breast cancer (relative risk [RR] = 0.7) compared to the general population.[7] Women of all ages with low socioeconomic status, as well as young black and Hispanic women, and native American women have an increased likelihood of presenting with advanced disease.[8-10]

Personal risk factors for the early onset of breast cancer differ in interesting ways from those for postmenopausal breast cancer. A positive family history of cancer is a very strong risk factor for women under 35 years of age (RR = 3.22)[4] and suggests the presence of a familial cancer syndrome.

Breast cancer at an early age is more likely to be associated with an increased familial risk, especially in women harboring a germline *BRCA1* mutation.[11] In a study of women with breast cancer diagnosed before age 30, *BRCA1*, *BRCA2*, and *TP53* mutations were found in about half who had strong family histories of breast cancer and in less than 10% of women with non-familial breast cancer.[12] Patients with familial *PTEN* mutations (Cowden syndrome) also have an increased risk for early breast cancer.[13]

There is evidence that breast cancer risk is positively associated with body mass index in postmenopausal women. A large population-based study evaluating approximately 50,000 women indicated that the combination of obesity, high energy (caloric) intake, and sedentary lifestyle is a risk factor in premenopausal women.[14]

Hormonal risk factors are somewhat different for women aged less than 35 years in comparison to older women. Recent oral contraceptive use is a risk factor for early-onset breast cancer (RR = 2.26), particularly for estrogen receptor (ER)-negative tumors. For women aged less than 35 years, early childbearing and multiparity are risk factors, due to a short-term elevation in breast cancer risk for several months immediately following a birth.[15]

Other risk factors for breast cancer in premenopausal women include a history of prior mantle irradiation for Hodgkin lymphoma, early age at menarche, heavy alcohol consumption, and a high intake of red meat.[4,13,16] Intense physical activity and a high intake of certain fruits and vegetables (eg, tomatoes) have been associated with a decreased breast cancer risk in premenopausal women.[17,18]

Increased mammographic density is a risk factor for breast cancer at all ages.[19] In premenopausal women, one study suggests that regular ingestion of multivitamin-multimineral supplements may be associated with higher mean breast density.[20] A recent study examined the effect of raloxifene therapy on mammographic breast density in premenopausal women at high risk for breast cancer. Raloxifene treatment was not associated with decreased breast

density, but it did correlate with decreased breast magnetic resonance imaging volume, a proposed surrogate biomarker for breast cancer risk.[21]

No relationship has been found between calcium/vitamin D intake and the risk of postmenopausal breast cancer,[22] but several studies suggest that high vitamin D intake, with or without calcium, may protect against premenopausal breast cancer. Low calcium or vitamin D intake has been associated with larger and higher grade breast tumors.[23-25] Premenopausal women who consumed at least 400 IU vitamin D and 1,000 mg calcium daily were noted to have an 8.5% (95% confidence interval [CI], 1.8-15.1) lower mean breast density than those who consumed less.[26]

Clinicopathologic Features, Biology, and Prognosis

The comparison of clinicopathologic and prognostic features of breast cancer arising in younger women with those in their older counterparts has been the subject of published studies for decades.[27-29] Traditionally, breast cancer arising in a younger host is characterized by a more aggressive phenotype. Among 185 premenopausal women carrying a diagnosis of invasive breast cancer, referred for surgery at the European Institute of Oncology from April 1997 to August 2000, those aged less than 35 years had a higher percentage of ER-negative (P <.001), progesterone receptor (PR)-negative (P <.001), vascular or lymphatic invasion (48.6% *υ* 37.3%, P = .006) and pathologic grade 3 tumors (P <.0001) compared with women aged 35-50 years.[30] Differences in tumor size, lymph node involvement, and *Her2/neu* status between younger and older women diagnosed with breast cancer have been less clear.[30-33]

Despite discrepancies in adverse prognostic features, younger age has been shown in several studies to be an independent predictor of adverse outcome.[31,32,34,35] A retrospective evaluation of more than 1,200 women diagnosed with early-stage breast cancer evaluated the relationship between age, typical prognostic factors, treatment, and patient outcome. Interestingly, age younger than 35 proved to be a powerful independent prognostic factor in multivariate analyses, including all potential patient, treatment, and pathology variables, and this was true for time to recurrence (RR = 1.70, P <.001), time to distant failure (RR = 1.60, P <.009), and overall mortality (RR = 1.50, P <.04).[35] This thought-provoking analysis illustrates that young age, after adjustment for all known prognostic factors, proves to be a powerful predictor of recurrence risk and survival.

A second retrospective study evaluating more than 200,000 women in the SEER database, who were diagnosed with breast cancer between the years of 1988-2003, revealed that those under the age of 40 were 39% more likely to die when compared to those age 40 or older (hazard ratio [HR] = 1.39; 95% CI, 1.34-1.45). Moreover, the highest mortality disparity between younger (<40 years) and older women (≥40 years) was present in early stage, rather than later stage disease. Specifically, women aged less than 40 were 44% and 9% more likely to die of stage I (HR = 1.44; 95% CI, 1.27-1.64) and stage II breast cancer (HR = 1.09; 95% CI, 1.03-1.15), respectively.[36,37] Although disparities in outcome between younger and older women diagnosed with breast cancer have been attributed traditionally to adverse prognostic features and later stage at diagnosis, this report implicates a unique biology unifying breast cancer arising in the younger host. In addition, the “triple-negative” phenotype (ER^-, PR^-, $HER2^-$) of breast cancer, which is regarded as the most lethal type of the disease, is most prevalent in young women, particularly in African Americans. In one study, triple-negative breast cancer was found in 56% of black and 42% of white women aged 20-34 years.[38]

A comprehensive, large-scale genomic analysis was conducted to examine further the biology of breast cancer arising in young women, with the goal of providing insight into this historically aggressive disease process. Clinically annotated genomic expression data from more than 700 early-stage breast cancers were identified and placed within two age-defined cohorts (≤45 years

and ≥65 years of age). Clinicopathologic results were consistent with previous reports indicating that the younger women's breast tumors were larger (P = .012), of higher grade (P = .0001), with more lymph node positivity (P = .008), lower ER positivity (P = .027), higher rates of *Her2/neu* over-expression (P = .075), and a trend toward inferior disease-free survival (HR = 1.32, P = .094).[31] Moreover, genomic expression profiling demonstrated significantly lower total mRNA levels of ERα, ERβ, and PR; with higher mRNA levels of both *Her2/neu* and epithelial growth factor receptor (*EGFR/Her1*).[31] Most importantly, application of the statistical tool Gene Set Enrichment Analysis (GSEA) revealed 367 significant gene sets enriched among young women's tumors, specifically distinguishing them from tumors arising in older women.[31] Representative gene sets included those involved with immune function, hypoxia, *BRCA1*, stem cells, apoptosis, histone deacetylase, and multiple, targetable oncogenic signaling pathways, including Myc, E2F, Ras, and mammalian target of rapamycin (mTOR).[31] This work provides one of the first substantiations that breast cancer arising in a younger host is a unique entity characterized not only by adverse prognostic features, but also by a diverse underlying biology against which novel therapeutics should be targeted.

Treatment and Management

Although the principles of managing invasive breast cancer in adolescent girls and young women are the same as in older women, there are a number of management and therapeutic issues requiring special consideration. Adolescents and young women are at particular risk of emotional and psychosocial problems, and require appropriate support from age- and disease-specific psychosocial and medical multidisciplinary teams.[39]

For many reasons, including development, function, body image, and quality of life, breast-conserving surgery, whenever possible, is obviously desirable for most young women. However, the two principle considerations when deciding between breast-conserving surgery and mastectomy are the risk of local recurrence, as well as the overall cosmetic result. One of the most important risk factors for local recurrence after breast-conserving surgery is age <35 years at presentation,[40] as these patients were found to have a nine times higher risk of local recurrence after conservative surgery than patients over 60 years of age.[41] However, no studies have demonstrated conservative surgery in young women to have a negative impact on survival.

All young women should be considered at high risk due to age alone, so adjuvant therapies should be considered during management discussions.[42] However, the use of adjuvant therapies in young women raises issues of long term side effects, including the induction of an early menopause, fertility impairment, and adverse effects on bone mineral density with chemotherapy and endocrine therapies, and of the development of a second malignancy with radiotherapy.

In addition to the appropriate use of radiotherapy, the current choices of adjuvant therapies for premenopausal patients include cytotoxic chemotherapy, ovarian ablation (by surgery, irradiation, or chemical ovarian suppression), anti-estrogen therapy, or any combination of these modalities. However, the optimal combination of chemotherapy for young women has become more controversial with the advent of recent studies examining the role of taxanes and dose-intensive adjuvant therapies.[43] Certainly it is clear that women under 30 years of age with early-stage disease, who do not receive adjuvant chemotherapy, have particularly poor relapse-free survival rates.[44,45] At the current time, anthracycline-containing combinations remain the standard of care. Such regimens have been shown to be more effective than a standard cyclophosphamide, methotrexate, 5-fluorouracil (CMF) combination at 5 years of follow-up. For example, cyclophosphamide, epirubicin, and 5-fluorouracil (CEF) compared with CMF showed 5 year relapse-free and overall survival rates of 63% versus 53% (P = .009) and 77% versus 70% (P = .03), respectively.[46]

It is known that adjuvant chemotherapy for early breast cancer in patients under 50 years of age reduces the relative risk of recurrence by 35% and of death by 27%, and adjuvant chemotherapy alone has been shown to be appropriate for patients with ER-negative tumors.[47] However, 5 years of adjuvant tamoxifen has been shown to reduce the relative risk of recurrence by 54% in women with ER-positive disease[48] and, in the absence of contraindications, all patients with ER-positive tumors diagnosed prior to age 40 require either chemotherapy and endocrine therapy or endocrine therapy alone.

Other clinical trials have shown that patients with node-positive early breast cancer given four cycles of doxorubicin and cyclophosphamide (AC) followed by four cycles of paclitaxel demonstrated a 17% reduction in the risk of recurrence and an 18% reduction in the risk of death compared with four cycles of AC alone,[49,50] while the addition of docetaxel resulted in a significant improvement in disease-free and overall survival for patients with one to three positive lymph nodes.[51] There is also a clear survival advantage for a dose-intense regimen of AC followed by paclitaxel given every 2 weeks with growth factor support as, with a median follow-up of 36 months, there is a 26% reduction in the risk of relapse ($P = .010$) and a 31% reduction in the risk of death ($P = .013$) associated with the dose-intensive arms.[52]

Prior to the advent of targeted therapy for Her2-positive tumors with trastuzamab (Herceptin, Genentech, San Francisco, CA), the ER^{-}/PR-/$HER2^{+}$ phenotype was associated with the highest risk of breast cancer death. In the trastuzamab era, “triple-negative” tumors now have the worst prognosis and, as mentioned earlier, young women have the highest proportion of these tumors. The development of novel therapies for triple-negative tumors is a much needed and fertile area for research.

Further compounding appropriate therapeutic management decisions is the evidence that premenopausal women who achieve chemotherapy-induced amenorrhea demonstrate a better prognosis than those retaining their menstrual cycle. It follows that amenorrhea may be important in the action of chemotherapeutic agents. Both relapse-free and overall survival are improved significantly by the induction of amenorrhea, although the optimal duration of amenorrhea remains unknown.[53-56] However, the likelihood of becoming amenorrheic following adjuvant chemotherapy is inversely dependent on age. Therefore younger women are less likely to gain maximum benefit from the endocrine effect of adjuvant chemotherapy.[57] Unfortunately, in trials evaluating ovarian suppression and amenorrhea to date, chemotherapies used now would be viewed as suboptimal and the proportion of very young women (<35 years) in the trials was small.[55,58-60] It is difficult, therefore, to draw clear conclusions regarding the potential benefit of chemotherapy-induced amenorrhea or ovarian suppression. Conversely, suppression of ovarian function certainly has the potential to create significant health and quality-of-life problems for very young women, including menopausal symptoms, psychological distress, and the need to adjust personal and family plans. Further trials are required to better evaluate the potential benefit of the addition of optimal endocrine therapy to adjuvant chemotherapy in very young women.

Outcomes

Across all histologic subtypes and stages, breast cancer survival rates are comparatively lower for women <40 years of age than for older women.[13] The lowest overall rate of cancer survival for females diagnosed during 2000-2005 was in those aged 25-29 years (72% 5-year relative survival), followed by 20- to 24-year-olds and 30- to 34-year-olds (75% and 76%, respectively) and 35- to 39-year-olds (80%) (Figure 5). In contrast, relative survival for women between age 45 and 80 years was 84%-86% (Figure 5). Fifteen to 19 year olds diagnosed with breast cancer have an 80% survival rate at 5 years (Figure 5), but there is some suggestion that this group may have increased mortality at older ages.[13]

Not only has the survival of women with breast cancer been lower in those less than 40 years at diagnosis, the improvement in survival since 1975 has been less in the younger women. Hence, the discrepancy in survival between younger and older women became progressively worse over the last quarter century (Figure 6). The relative improvement in older women and lack of progress in younger women may be due to the age-dependent biological differences, in that most of the therapeutic efforts have been conducted in middle-age and older women with gratifying success, and not in young women whose cancers require a different treatment approach.

Bleyer et al summarized the significantly worse survival in younger women for all stages of breast cancer in comparison to older women.[61] For 20- to 35-year-old women, compared with women 45-75 years of age, 5-year relative survival for stage I-II breast cancer was 84% versus 92%, respectively; survival for stage III disease was 47% versus 55%; and for stage IV disease was 15% versus 20% (Figure 7). The 5-year relative survival for women under 35 years of age was also inferior for each histologic subtype of breast cancer, including infiltrating ductal, medullary, lobular, and inflammatory breast cancer, as well as Paget's disease of the breast.

Young African American women have a disproportionately high breast cancer mortality rate in comparison to other racial groups. One study found that black women <40 had larger tumor size, higher rates of local and distant metastasis, a higher proportion of ER-negativity, and a higher rate of medullary tumors. Relative risk for death was 1.94 for localized disease, 1.58 for regional disease, and 2.32 for metastatic disease compared to white women.[62] Another study showed comparable survival rates in premenopausal black women with early-stage disease, compared to the general population. However, young black women with stages III and IV disease had a worse prognosis despite standard therapy.[63] Because 10% of black women (υ 5% of white women) with breast cancer are diagnosed prior to age 40, and because young black women have worse outcomes, some authors have suggested considering 30- to 39-year-old black women as a high-risk group, and offering them routine mammographic screening.[22]

After black women, the highest mortality in young women is seen in Latinas, followed closely by white, non-Hispanic; native American; and Asian women.[13,64] Interestingly, and in contrast to women in the United States, women <40 years of age in Asia did not have worse outcomes compared to older women, despite more advanced disease at diagnosis and higher grade tumors, suggesting an environmental role for outcome discrepancies.[65]

Decreases in mortality between 1975 and 2000 were three times greater for whites than for blacks under age 40 years.[13] Despite this overall improvement, survival for local breast cancer in women aged 15-29 years, as well as for regional breast cancer in women aged 15-44 years, actually decreased slightly between 1975 and 2000.[13]

Young women treated for breast cancer have disproportionately high rates of second malignancies. Compared to older patients, women under age 50 treated for breast cancer have a significantly increased incidence of tumors of bone, ovary, thyroid, kidney, lung, as well as non-melanoma skin cancer, leukemia, and lymphoma.[66] In addition, women under age 36 treated for early-stage breast cancer have been observed to have a 13% 10-year cumulative incidence of contralateral breast cancer.[66] Both post-lumpectomy radiation therapy (compared with post-mastectomy radiation therapy and/or chemotherapy) and positive family history appear to increase the risk of contralateral breast cancer in young women. In one study, breast cancer patients under the age of 35 treated with radiotherapy had an increased risk for contralateral breast cancer compared to patients treated at older ages (HR = 1.78; 95% CI, 0.85-3.72). The use of post-lumpectomy, compared to post-mastectomy, radiation conferred an additional 50% increased risk of contralateral breast cancer in women under 45 years of age. Interestingly, patients with a strong family history of breast cancer had even higher than

expected rates of contralateral breast cancer following post-lumpectomy radiation. For all ages, adjuvant chemotherapy decreased the rate of contralateral breast cancer for 5 years after therapy, but not thereafter.[67]

Fertility and Pregnancy

Young women undergoing chemotherapy for breast cancer may struggle with fertility and pregnancy issues. To that end, the American Society of Clinical Oncology has published guidelines to address infertility.[68] Unfortunately, there is no way to measure fertility other than to follow patients for subsequent pregnancies and the use of amenorrhea as a surrogate marker for infertility, which is imperfect. Also, many women may continue or resume menses months after the administration of chemotherapy. Data suggest that young women who undergo chemotherapy also may experience premature ovarian failure (POF).[69]

Risks of Infertility

Many of the chemotherapeutic agents used for breast cancer are associated with POF. Both the agent and age of the patient impact on this risk. Goodwin et al[57] evaluated 131 women who received chemotherapy, either CMF or CEF, for breast cancer. The risk of menopause after 1 year approximated 50% by age 40 years. Recently, Reh et al[70] evaluated the impact of doxorubicin and cyclophosphamide (AC) and taxanes on rates of amenorrhea. The use of taxanes did not impact the rate of amenorrhea or levels of estradiol or follicle-stimulating hormone (FSH).

Fertility Preservation

Gonadotropin-releasing hormone analogues have been examined to preserve fertility. However, these studies have been plagued with multiple design limitations and have used resumption of menses as equivalent to fertility. Ismail-Khan et al[71] presented a randomized trial treating 49 women with chemotherapy ± triptorelin and found no benefit to preserving menstrual status. A larger, prospective, randomized study from the Southwest Oncology Group is currently accruing participants to address this question further, but only in patients with ER-negative tumors. Other interventions, such as embryo cryopreservation, have shown the best efficacy. Techniques such as oocyte cryopreservation and ovarian tissue cryopreservation and transplantation, often orthotopically, are under investigation.[68] Additionally, the use of letrozole has been described in ovarian stimulation to avoid large estradiol surges, which may be of concern for breast cancer patients.[72]

Pregnancy and Breast Cancer

Current estimates of breast cancer during pregnancy are 1.3 cases per 10,000 births[73] and, when cancer is diagnosed in women 30 years old or younger, an estimated 10%-20% of cancers are detected either during pregnancy or within the first year postpartum.[74,75]

Breast Cancer Diagnosed During or After Pregnancy

Being pregnant at the time of diagnosis of breast cancer has been associated with a worse outcome. In one study of 797 such cases, compared with 4,177 non-pregnancy-associated breast cancer controls, women diagnosed while pregnant had larger, more advanced tumors, a greater incidence of receptor-negative tumors, and a higher death rate (39.2% *υ* 33.4%, $P = .002$).[15] A smaller study found no association between pregnancy and increased mortality.[76] In contrast, pregnancy and childbirth following a diagnosis of breast cancer do not increase mortality, and actually may improve survival. One study found that 438 women age <45 years at diagnosis, who delivered a child 10 or more months following a diagnosis of breast cancer, had a decreased relative risk of death (RR = 0.54; 95% CI, 0.41-0.71), compared to women

who did not bear children following diagnosis. Women who were pregnant at the time they were diagnosed had a mortality rate similar to the latter group. This suggests that childbirth following breast cancer diagnosis does not increase mortality.[76]

Physiologic changes in the breast may make self-palpation difficult. However, masses that do not resolve within 1-2 weeks should be investigated.[77] Imaging should include mammography with proper shielding, as well as breast ultrasonography.[78,79] A core biopsy of the mass should be obtained. Staging to rule out metastatic disease can include magnetic resonance imaging (MRI) of the thoracic and lumbar spines, a chest x-ray with fetal shielding and an ultrasound of the liver. Computed tomography scans are not recommended during pregnancy due to fetal radiation exposure. Once diagnosed, the woman should be seen in a multidisciplinary setting with surgical oncology, radiation oncology, and maternal-fetal medicine.[80]

Breast surgery can be done safely in all trimesters of pregnancy, although many surgeons will wait until the end of the first trimester when the rate of spontaneous abortion is lower.[81] Radiation therapy is not done routinely for breast cancer until after delivery in order to avoid radiation to the fetus. Chemotherapy has been administered safely during pregnancy in the second and third trimesters.[80] The largest prospective cohort of women treated prospectively on a standardized protocol is from the University of Texas M.D. Anderson Cancer Center, with 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) chemotherapy. At the last published update, 57 women had been treated, with 40 women alive and disease-free, three women with recurrent breast cancer, 12 dying from breast cancer, one woman dying from another cause, and one lost to follow-up. All women delivered live births with a median gestational age of 37 weeks.[81] Long-term follow-up on the children is needed and currently underway. Other chemotherapies, such as taxanes, have been reported.[82] The use of trastuzumab should be avoided during pregnancy due to the concern of oligohydramnios and, if warranted, started after delivery.[83]

Pregnancy Diagnosed During or After Breast Cancer

Studies of pregnancy after a diagnosis and treatment of breast cancer are retrospective and most are case-controlled investigations. Although one study[84] showed an increased risk for relapse, most other studies show either no difference in recurrence or a decrease in risk of recurrence.[76] Breast cancer survivors and their medical caregivers are advised to fully discuss the risk of recurrence when discussing post-cancer reproductive choices.

Bone Health

As a majority of young women diagnosed with early-stage breast cancer will survive many years following diagnosis and treatment, bone loss associated with both adjuvant endocrine and cytotoxic chemotherapeutics must be taken into consideration to prevent long-term complications including osteopenia, osteoporosis, and potentially disabling fractures. Traditionally, the postmenopausal breast cancer population had been the focus of bone health research, given the success of aromatase inhibitors, agents well-known to cause bone loss across both class and schedule.[85] More recently, the adverse effects of premature menopause, a common consequence of systemic therapies as described above, on future bone health are receiving appropriate attention as accelerated bone loss has the potential to affect survivorship significantly.

A recent analysis of more than 400 premenopausal women with early-stage breast cancer who developed ovarian failure (defined as >3 months of amenorrhea and follicle-stimulating hormone >30 U/L) following adjuvant chemotherapy, and then were treated with or without zoledronic acid 4mg intravenously every 3 months (Zometa, Novartis Oncology, East Hanover, NJ), reports a mean 6.4% decline in lumbar spine (LS) bone mineral density (BMD) among

those who did not receive bisphosphonate therapy. Accelerated bone loss was prevented (2.8% increase in LS BMD) among those who received zoledronic acid concurrent with adjuvant chemotherapy, with a minimal side effect profile.[86] A second randomized, double-blind, multi-center phase III study evaluated the addition of zoledronic acid (4 mg intravenously every 3 months) versus placebo for 1 year among 101 women receiving chemotherapy for early-stage breast cancer. Consistent with the previous report, placebo was associated with a significant decline in LS BMD at both 6 (2.4%) and 12 (4.1%) months. In contrast, BMD remained stable among patients receiving zoledronic acid (P <.0001).[87] Therapy was well-tolerated and there were no reports of either renal insufficiency or osteonecrosis of the jaw.

Finally, zoledronic acid has demonstrated anti-tumor and anti-metastatic activity in preclinical and early clinical studies, providing a rationale for the recently reported Austrian Breast Cancer Study Group (ABCSG) 12 trial. Over 1,800 premenopausal women with endocrine-responsive early-stage breast cancer were randomized to ovarian suppression with the gonadotrophin-releasing hormone (GnRH) agonist goserelin and tamoxifen or anastrozole (Arimidex, AstraZeneca, Wilmington, Delaware) with or without zoledronic acid for 3 years. At a median follow-up of 60 months, there was no significant difference in disease-free survival between patients who received tamoxifen versus anastrozole alone (HR = 1.10; P = .59). However, the addition of zoledronic acid to endocrine therapy significantly reduced the risk of events during disease-free survival by 36% compared with endocrine therapy alone (HR = 0.64; P = .01), and there was a nonsignificant trend in overall survival favoring therapy with zoledronic acid (HR = 0.60; P = .10). Treatment was well-tolerated in all four study arms.[88] The 5-year follow-up of the ABCSG-12 BMD substudy also indicated stable BMD among those receiving concomitant zoledronic acid, with bone loss observed among those receiving endocrine therapy and ovarian suppression alone.[89] Although formal guidelines do not yet exist, awareness of the issue of BMD among young, premenopausal women facing systemic therapy for breast cancer is paramount, and early incorporation of bisphosphonate therapy may improve not only bone health but also breast cancer prognosis.

Inherited Breast Cancer and Risk Reduction

Family history is a known risk factor for breast cancer, with elevated risk due to both increasing number and decreasing age of first-degree relatives affected. For example, in a large, population-based study, risk of breast cancer was increased 2.9-fold among women whose relative was diagnosed prior to age 30, but the increase was only 1.5-fold if the affected relative was diagnosed after age 60 years.[90] While twin studies indicate familial aggregation among women diagnosed with breast cancer, identification of true germline mutations, including *BRCA1*, *BRCA2*, *p53* (Li Fraumeni), *PTEN* (Cowden's syndrome), and *STK11* (Peutz-Jeghers), are quite rare, on the order of 5%-6%.[91-93] However, the management of young women at an increased risk of developing breast cancer via a germline mutation requires careful consideration, as screening, risk reduction, and implications for relatives are of upmost importance.

BRCA1 and *BRCA2*, located on chromosomes 17 and 13, respectively, are thought to account for the majority of inherited breast cancers.[94] The estimated lifetime risks of developing breast cancer among *BRCA1* and *BRCA2* carriers are 47%-66% and 40%-57%, respectively, compared to a 12.5% risk among the general population.[95] In addition, patients harboring *BRCA* mutations are at higher lifetime risk for the development of ovarian cancer, bilateral breast cancer, and male breast cancer; the last with *BRCA2*. Although there is no universal approach, it is recommended that clinicians discuss intensive surveillance of the breasts and ovaries, chemo-prevention, and prophylactic surgery (ie, bilateral mastectomy and bilateral salpingo-oophorectomy) with their patients diagnosed with a *BRCA* mutation, on an individualized basis. Specifically addressing breast surveillance, and according to the National

Cancer Comprehensive Network (http://www.nccn.org/professionals/physician_gls/PDF/breast-screening.pdf), annual mammography and clinical breast examination every 6-12 months is recommended among women diagnosed with a genetic predisposition to breast cancer, beginning at 25 years of age. Periodic self-examinations starting at age 18 years are encouraged. Bilateral breast MRI is recommended as an adjunct to annual mammography and is also in accordance with the ACS recommendations on MRI screening based on both observational and non-randomized screening trials. In addition, the ACS recommends annual screening MRI as an adjunct to mammography among women who have a first-degree relative diagnosed with a *BRCA* mutation but remain untested themselves.[96]

Tamoxifen remains the only drug approved for risk reduction of breast cancer among high-risk premenopausal women. Although the Study of Tamoxifen and Raloxifene (STAR) reports raloxifene (Evista, Lilly, Indianapolis, IN) as being as effective as tamoxifen in reducing the breast cancer risk among high-risk women, raloxifene is reserved for postmenopausal women and should only be considered among premenopausal women in the setting of a clinical trial.[97] Recommendations for tamoxifen are based on the phase III National Surgical Adjuvant Breast and Bowel Project (NSABP) chemo-prevention trial (BCPT-P1), which demonstrated a 49% reduction in the incidence of invasive breast cancer (P <.0001) and a 50% reduction in non-invasive breast cancer (P <.002) among 13,388 high-risk women randomized to tamoxifen compared to placebo. Side effects associated with tamoxifen use were not inconsequential as both endometrial cancer (RR = 2.5) and thrombotic events were more common among tamoxifen-treated women.[98] Subsequently, investigators sought to identify the effect of tamoxifen on breast cancer incidence among women enrolled in the NSABP P-1 trial harboring a *BRCA1* or *BRCA2* mutation. Results indicated a 62% risk reduction (RR = 0.38; 95% CI, 0.06-1.56) among *BRCA2* carriers; however, there was no effect among *BRCA1* carriers. This difference is felt to be attributed to the higher incidence of ER-negative breast cancers diagnosed among *BRCA1* carriers and is consistent with the reduction in incidence of ER-positive but not ER-negative tumors among all women enrolled in the NSABP P-1 trial.[98,99] Identification of the optimal target population thought to benefit most from chemoprevention remains to be determined, as does the effect of chemoprevention on overall survival.

Psychosocial Issues

Although a diagnosis of breast cancer can be distressing to patients across all age groups, diagnosis at a younger age presents a variety of unique psychosocial and emotional challenges, including, but not limited to, interactions with spouse/children, body image, sexuality, and loss of fertility/premature menopause.[69,100] A retrospective study evaluating more than 500 breast cancer survivors aged 25-50 years illustrated that emotional and social functioning, vitality, and depression 6 years (range, 2-10 years) following diagnosis were inversely proportional to age at diagnosis.[101] A clinical trial randomizing patients to mastectomy or breast-conserving therapy evaluated 142 women prospectively for psychological response to their respective local therapies. Six months following diagnosis, patients who underwent mastectomy reported significantly less control over events in their lives (P = .003) and more difficulty with sexual relations (P = .021) than did their conservatively treated counterparts.[102]

A novel web-based survey evaluating the effects of breast cancer diagnosis and treatment among more than 600 young breast cancer survivors (median age, 32.9 years) indicated that 57% were concerned about infertility with treatment and 29% reported that these concerns affected treatment decisions. Approximately 75% discussed these concerns with their physicians and 51% felt that their concerns were addressed adequately.[69] Finally, to address the concern that psychosocial issues might play a role in cancer recurrence, a population-based study of more than 700 Australian women aged less than 60 years was conducted. While this

study did not reveal an association between breast cancer recurrence and measured psychosocial factors, it did indicate that greater anxious preoccupation was associated with younger age ($P = .03$).[102] Currently, a large-scale clinical trial cosponsored by the Eastern Cooperative Oncology Group and the National Cancer Institute is being conducted to evaluate quality of life, including physical, psychological, social, and spiritual functioning, and women aged less than 45 or over 55 years and their partners (http://clinicaltrials.gov/ct2/show/NCT00309933; Principal Investigator: Victoria Champion, DNS). This trial should provide invaluable insight into the needs of both patient populations.

Conclusions

Although thought to be a relatively uncommon condition, potentially one third of all breast cancers are diagnosed among premenopausal women. Breast cancers diagnosed at a younger age harbor aggressive clinicopathologic features and, more recently, have been recognized as a unique biologic entity. Special considerations, including infertility, pregnancy, bone health, genetic syndromes, and psychosocial issues must be addressed when developing treatment algorithms, including local therapies and adjuvant chemotherapeutic/endocrine strategies, among young women diagnosed with breast cancer. Finally, younger age at breast cancer diagnosis confers an inferior prognosis when compared to older women, illustrating the need for biologically driven clinical trials devoted specifically to the former population, with the overall goal of improving outcome.

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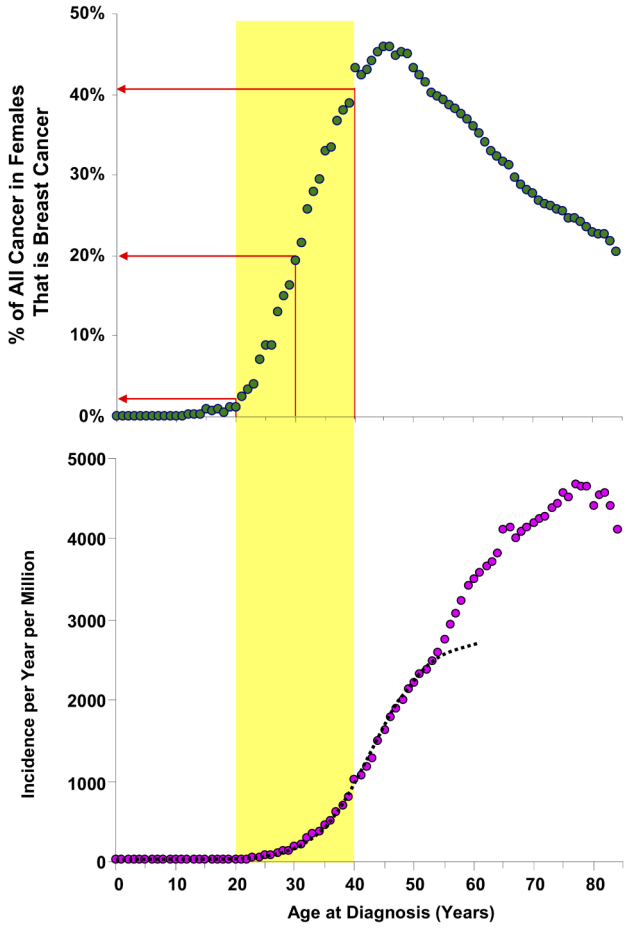

Figure 1.
Breast cancer in females by single year of age at diagnosis, SEER17, 2000-2005. The yellow zone designates the 20- to 39-year age range.

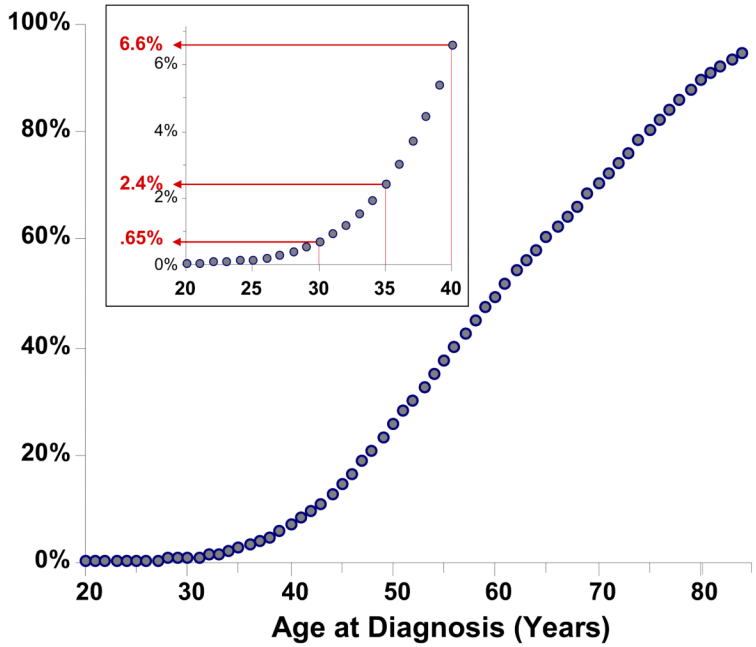

Figure 2.
Cumulative percent of breast cancer in females, SEER17, 2000-2005.

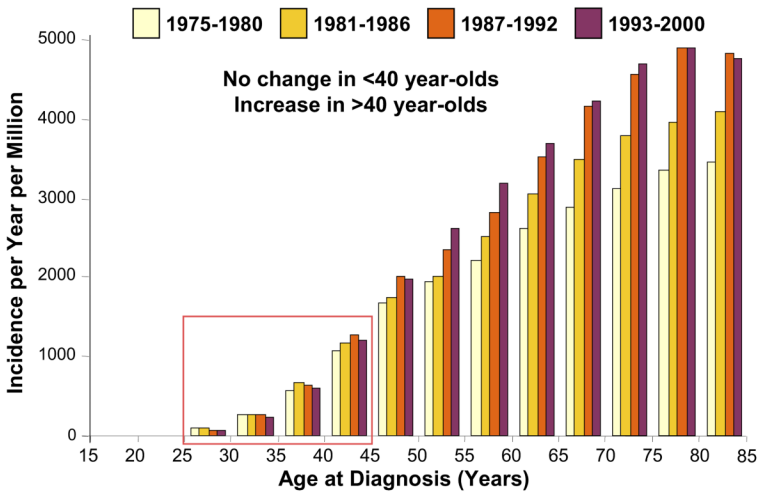

Figure 3.
Incidence of breast cancer in females by 6-year eras, 1975-2000, SEER9.

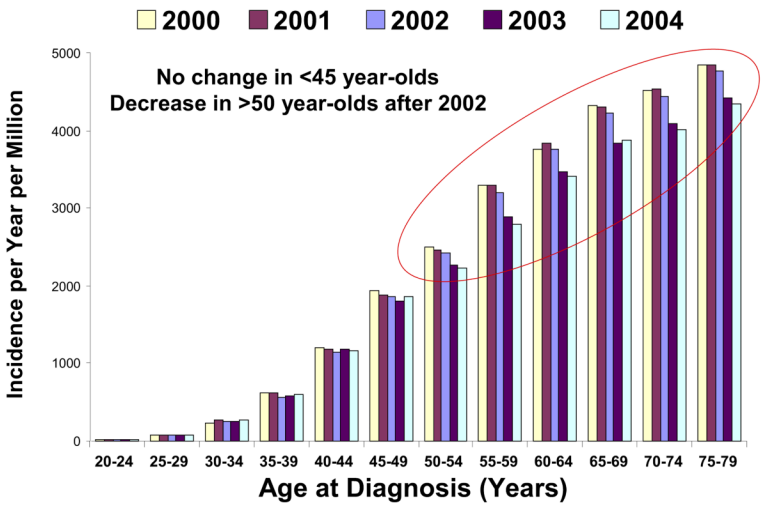

Figure 4.
Incidence of breast cancer in females per calendar year, 2000-2004, SEER17.

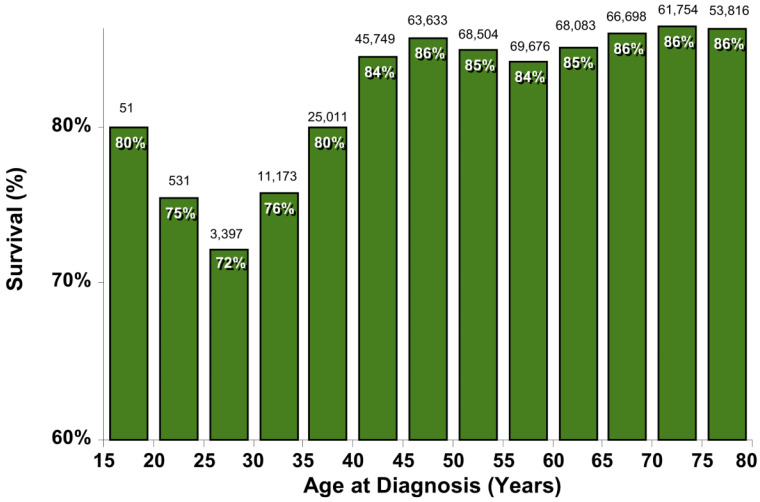

Figure 5.

Five-year relative survival of females diagnosed with breast cancer during 2000-2005, SEER17. The numbers above the bars designate the number of patients with breast cancer in the SEER17 registry for 2000-2005. Data obtained on January 20, 2009 from the SEER Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 17 Regs Limited-Use + Hurricane Katrina Impacted Louisiana Cases, Nov 2007 Sub (1973-2005 varying), linked to county attributes, total US, 1969-2005 counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2008, based on the November 2007 submission.

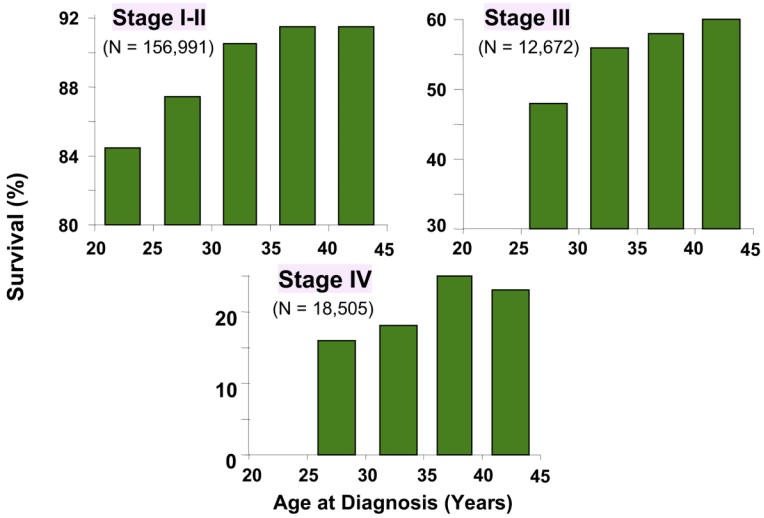

Figure 6.

Five-year relative survival of females diagnosed with breast cancer during 1975-1999 by stage, SEER9. The numbers in parentheses designate the number of patients with breast cancer in the SEER9 registry for 2000-2005. Data obtained on from SEER Program (www.seer.cancer.gov) SEER*Stat Database: Incidence–SEER9.

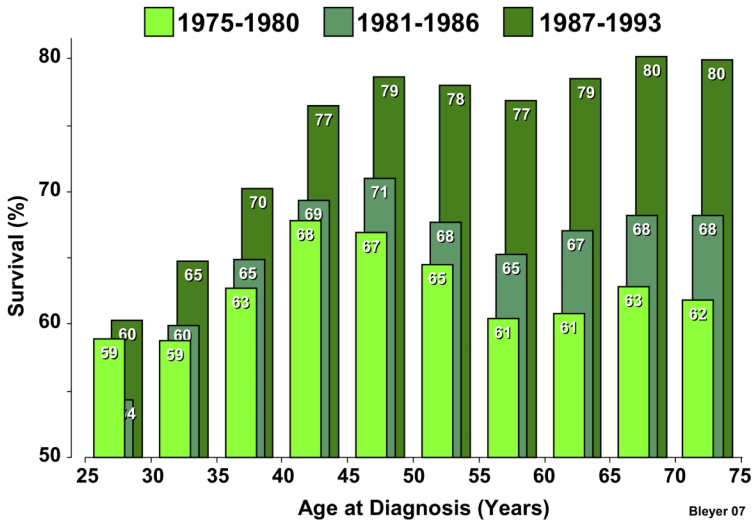

Figure 7.
Ten-year relative survival of females diagnosed with breast cancer during 1975-1980, 1981-1986 and 1987-1993, SEER9.

Table 1

Risk of Breast Cancer as Function of Age Estimated From Women Diagnosed in the US SEER17 Registries, 2004

Age (yr)	Risk: 1 in ×
15	571,429
20	75,188
25	8,684
30	1,523
35	453
40	173
45	82
50	45
55	30
60	21
65	15
70	12
75	9
80	8
85	7