Gabriel and Domchek *Breast Cancer Research* 2010, **12**:212
http://breast-cancer-research.com/content/12/5/212

Breast Cancer RESEARCH

REVIEW

Breast cancer in young women

Courtney A Gabriel[1] and Susan M Domchek[2]*

Abstract

Although uncommon, breast cancer in young women is worthy of special attention due to the unique and complex issues that are raised. This article reviews specific challenges associated with the care of younger breast cancer patients, which include fertility preservation, management of inherited breast cancer syndromes, maintenance of bone health, secondary prevention, and attention to psychosocial issues.

Introduction

Breast cancer incidence increases with age, with the vast majority of women diagnosed after the age of 40 years [1]. Nevertheless, approximately 7% of women diagnosed with breast cancer between 2000 and 2005 were below the age of 40 [2]. Interestingly, breast cancer risk factors, clinical outcomes, and tumor biology are somewhat different in the subgroup of women below 40, suggesting that breast cancer in young women represents a distinct entity [3-7]. The definition of a 'young woman' in the field of breast oncology varies, with most articles referring to women under either age 35 or 40 years as 'young'.

Epidemiology

The incidence of breast cancer in younger women differs according to race. Overall, breast cancer is more common in Caucasian women than in African Americans; however, in women under the age of 35, breast cancer is more than twice as common in African American women. Premenopausal African American women are more likely to have hormone receptor negative tumors (and even more specifically tumors of the basal phenotype) compared to Caucasian women [3,8]. Young African American women are more likely to be diagnosed at a more advanced stage than young Caucasians; however, after adjusting for stage, survival appears equivalent between races [4].

*Correspondence: Susan.domchek@uphs.upenn.edu
[2]Abramson Cancer Center, University of Pennsylvania, 3 West Perelman Center, 3400 Civic Center Boulevard, Philadelphia, PA 19104, USA
Full list of author information is available at the end of the article

Delayed childbirth (first child after age 30 years) is known to be a risk factor for breast cancer in women older than 35. Conversely, early childbearing seems to be a risk factor for developing breast cancer before the age of 35. This discrepancy could possibly be explained by the transient increase in breast cancer risk that occurs around 2 to 7 years following a pregnancy, but more information is needed about this association [3].

The characteristics of tumors that arise in women under the age of 35 differ from those that arise in premenopausal women who are older than 35. Women younger than 35 have a lower rate of ductal carcinoma *in situ*, likely due to detection bias (women in this age range do not typically have screening mammograms) [4]. Tumors in women younger than 35 are more likely to be of a higher histological grade [4] and to be classified as estrogen receptor (ER) and progesterone receptor negative [5,6]. In addition, young women are more likely to have local recurrences, to be diagnosed at a more advanced stage, and to have an inferior 5 year survival compared to their older premenopausal counterparts [4,6,7].

These differences in breast cancer risk factors, tumor characteristics, and clinical outcomes suggest that breast cancer arising in young women may be a distinct clinical entity. A study by Anders and colleagues [5] looked at tumor gene expression between two age specific cohorts (young, ≤45 years; and older, ≥65 years), and identified 367 gene sets that could differentiate tumors in young women from tumors in older women. This suggests that breast cancer in young women may be distinct with a unique underlying biology.

Radiographic diagnosis

Women under the age of 35 do not typically undergo breast cancer screening unless they are at high risk for the development of breast cancer. For this reason, breast cancer cases usually present with breast complaints [9]. The sensitivity of a mammogram is low in this population due to the increased density of a young woman's breasts, which obscures findings on mammograms. Mammograms have not been shown to be clinically beneficial or cost effective in the evaluation of breast symptoms in women under the age of 35 [10-12]. An ultrasound is a more sensitive imaging tool in young women and has the

added benefit of distinguishing solid masses from simple and complex cysts [9,13].

Currently, the American Cancer Society recommends a screening breast MRI for women with a 20 to 25% lifetime risk of breast cancer, which includes women with familial breast cancer syndromes (discussed below) and those who have received chest radiation for Hodgkin's lymphoma [14]. Breast MRI has high sensitivity for malignant lesions; however, specificity is low, which can lead to unnecessary biopsies. In women in high risk groups, the benefits of MRI are considered to outweigh the risks of unnecessary biopsies. MRIs have also been shown to be more sensitive than mammograms, particularly in women with dense breasts [15]; however, according to American Cancer Society guidelines, breast density alone is not justification for MRI screening at the current time.

In addition to considerations of MRI for primary screening, at the current time there is insufficient evidence to recommend for or against a breast MRI for women with personal histories of breast cancer [14] who do not have a *BRCA1* or *BRCA2* mutation.

Genetics

Breast cancer in a woman under age 35 years should prompt one to consider familial breast cancer syndromes and genetic testing for *BRCA1/2* mutations and, less commonly, *TP53* mutations. In a population-based case control study, the likelihood that a woman with breast cancer under the age of 35 had a detectable *BRCA1/2* mutation was 9.4% (compared to a population prevalence of 0.2%) [16]; these findings have been demonstrated by other studies as well. A family history of breast and/or ovarian cancer or Ashkenazi Jewish ancestry makes the probability of having a mutation even higher.

Tumor characteristics can help identify women who are likely to carry a *BRCA1* mutation. High grade triple negative breast cancers (ER negative, progesterone receptor negative, and Her2 negative) are more common in women with *BRCA1* mutations, whereas pathologic and immunohistochemical features of tumors associated with *BRCA2* mutations are similar to those of sporadic cases [17]. A French study found the prevalence of *BRCA1* mutations in women under age 35 years with triple negative and poorly differentiated tumors to be 28.6% (4 out of 14) regardless of family history [18]. Similarly, Lakhani and colleagues [17] derived *BRCA1* mutation carrier probabilities on the basis of ER status and tumor grade, and determined that a woman between the ages of 30 and 34 with an ER-negative, grade 3 tumor has a 26.5% chance of harboring a *BRCA1* mutation compared with a 5% chance in women of the same age range with any tumor type (Table 1).

Table 1. Predicted probabilities of a *BRCA1* mutation based on age and tumor characteristics [17]

Age (years)	All histologies (%)	ER-negative and high grade tumors (%)
<30	8	35
31-34	5	26.5
35-39	2	6.6
40-44	1.5	3.7
45-49	1	2.5
50-59	0.3	0.9

ER, estrogen receptor.

Women who test positive for a *BRCA1/2* mutation have a 40 to 50% chance of developing a second primary breast cancer [19-21]. *BRCA 1/2* carriers are also at increased risk for ovarian cancer, with a lifetime risk of 40 to 50% in *BRCA1* carriers and 10 to 20% in *BRCA2* carriers [22-24]. Studies have shown that a prophylactic bilateral salpingo-oophorectomy (BSO) can reduce the risk of ovarian cancer by as much as 80 to 96% [25,26], decrease the risk of developing a second primary breast cancer [21], and also reduce short-term mortality [27]. For these reasons, a prophylactic BSO is recommended when childbearing is complete. Yearly breast MRIs, in addition to yearly mammograms, are recommended for screening in *BRCA1/2* mutation carriers [14]. Due to the high risk of a second primary, many *BRCA1/2* mutation carriers choose to undergo a prophylactic bilateral mastectomy (PBM) in the setting of unilateral disease. The risks, benefits, and controversies surrounding PBM are discussed below in the section 'Secondary prevention.'

Although very rare, Li-Fraumeni syndrome (LFS) should also be considered when a very young woman is diagnosed with breast cancer. LFS is a highly penetrant, autosomal dominant condition characterized by early onset breast cancer and a variety of other rare tumors, including sarcoma, brain tumors, and adrenocortical carcinoma [28-30]. Many families meeting strict criteria for LFS have identifiable germline mutations in the *TP53* gene [31,32]. Nearly one-third of breast cancers in *TP53* mutation positive families occur prior to age 30 years [33]. Knowledge of the presence of a *TP53* mutation may help make decisions about breast cancer therapy, especially since radiation may substantially increase an LFS patient's risk for a second primary malignancy [34].

In a recent study, Gonzalez and colleagues [35] examined the characteristics of 525 patients whose samples were submitted for clinical *TP53* genetic testing, of whom 91 (17%) had detectable mutations. Several working definitions for LFS exist for identifying families with *TP53* mutations; these consider age of onset of cancer diagnosis, type of cancer, and cancer in first and second degree relatives. In this study, two of these definitions, the classic LFS criteria and the Chompret's criteria, identified 95% of patients with *TP53* mutations [35]

Table 2. Classification schemes for Li-Fraumeni syndrome

Scheme	
Classic LFS [29]	Proband diagnosed with sarcoma before 45 years of age, AND
	A first-degree relative with cancer before 45 years of age, AND
	Another first- or second-degree relative with any cancer diagnosed under 45 years of age or with sarcoma at any age
Chompret's [112,113]	I. Proband with sarcoma, brain tumor, breast cancer, or adrenocortical carcinoma before age 36 years, AND at least one first or second degree relative with cancer (other than breast cancer if the proband has breast cancer) under the age of 46 years or a relative with multiple primaries at any age
	II. Proband with multiple primary tumors, two of which are sarcoma, brain tumor, breast cancer, and/or adrenocortical carcinoma, with the initial cancer occurring before the age of 36 years, regardless of the family history
	III. Proband with adrenocortical carcinoma at any age of onset, regardless of the family history

LFS, Li-Fraumeni syndrome.

(Table 2). Of women with breast cancer under 30 and no family history in first or second degree relatives, 1 of 14 (7%) had a detectable mutation. A second study found no detectable mutations in 95 unselected *BRCA1/2* negative women diagnosed with breast cancer under the age of 30 [36].

Although *de novo TP53* mutations have been reported in individuals without a family history [37,38] such *de novo* mutations are uncommon and, therefore, there is currently insufficient evidence to routinely recommend *TP53* mutation testing in breast cancer patients under the age of 30 in the absence of a personal or family history suggestive of LFS. Since the use of the classic LFS and Chompret's criteria in combination have a high sensitivity in identifying individuals with *TP53* mutations, individuals meeting their criteria should be referred for testing [35] (Table 2).

Treatment

Young women are generally treated similarly to their older counterparts. Options for local therapy include a mastectomy or breast conserving surgery followed by radiation. As in older women, factors guiding surgical decisions include tumor size, location, ability to achieve a good cosmetic outcome, prior radiation or any contraindication to radiation, and patient preference. However, younger women have higher local recurrence rates than older women when treated with breast conservation [39-41]. In an analysis of two large randomized trials comparing mastectomy versus breast conservation plus radiation, Voogd and colleagues [39] found that women under age 35 years treated with breast conservation had a nine times greater risk of recurrence than women over the age of 60 (hazard ratio, 9.24; 95% confidence interval (CI), 3.74 to 22.81); however, younger patients treated with a mastectomy did not have an increased recurrence rate compared to older patients. Freedman and colleagues [41] retrospectively analyzed risk factors for local recurrence after breast conservation plus radiation and found that in women under the age of 35 whose excised tumors had both negative margins and a non-extensive intraductal component, the rate of local recurrence was similar to that of older women. This finding suggests that the increased risk of local recurrence in this age group may be due to the extensive intraductal components of the tumors and difficulty in achieving negative margins in young patients.

In addition to appropriate radiotherapy, adjuvant therapy with chemotherapy and/or hormonal therapy should be strongly considered in young women. A Danish study showed that young women with early stage disease who were not treated with cytotoxic therapy had an increased risk of dying compared to older age groups. This risk increased with decreasing age of diagnosis, with those under the age of 35 having the poorest prognosis. In contrast, young women who did receive cytotoxic therapy had a comparable prognosis to their older counterparts [42]. In another study, women under the age of 30 with stage I disease had a particularly poor relapse-free survival compared to older controls, presumably because very few of these women received adjuvant chemotherapy [43].

Women who achieve chemotherapy-induced amenorrhea have a better prognosis than women who retain their menses [44,45]. The NASBP B-30 trial (National Surgical Adjuvant Breast and Bowel Project Protocol B-30) looked at the efficacy of three different adjuvant chemotherapy regimens containing doxorubicin, cyclophosphamide, and docetaxel (one regimen did not contain cyclophosphamide). The study's secondary aim was to correlate chemotherapy-induced amenorrhea with survival in premenopausal women. Overall survival was significantly improved in women who achieved at least 6 months of chemotherapy-induced amenorrhea, regardless of chemotherapy, and, surprisingly, regardless of hormone receptor status [44]. These data suggest that the therapeutic effects of chemotherapy are, at least in part, due to ovarian suppression. The effect of chemotherapy

on the menstrual cycle is dependent upon the age of the patient, with young premenopausal women (<35 years) less likely to achieve amenorrhea with chemotherapy compared with older premenopausal women [46,47]. It is unknown whether chemotherapy can be replaced by ovarian suppression alone (such as with a luteinizing releasing hormone (LHRH) agonist). In patients with hormone responsive tumors, four studies suggest that the use of a LHRH agonist in the adjuvant setting is as efficacious as chemotherapy with fewer side effects [48-53]. However, these studies all used older chemotherapy regimens (that is, cyclophosphamide, methotrexate, fluorouracil (CMF)) without subsequent hormonal therapy; thus, it is currently unclear how LHRH agonists would compare against third generation regimens plus tamoxifen [54].

Although the therapeutic effects of chemotherapy appear to be at least partially due to effects on the endocrine system, chemotherapy alone is insufficient for the treatment of hormone receptor positive tumors in young women [55]. Endocrine therapy should be offered to young women with hormone responsive tumors. The usual treatment is tamoxifen, but ovarian suppression/ablation (with LHRH analogs, oophorectomy, or ovarian radiation) can be used as alternative therapy or added in combination with tamoxifen [51,56-60]. In women who remain premenopausal after chemotherapy, it is currently unclear whether adding ovarian suppression to tamoxifen is superior to tamoxifen alone. This is the subject of several randomized clinical trials, including the Suppression of Ovarian Function Trial (SOFT; NCT00917969).

Aromatase inhibitors are avoided in women who are premenopausal at diagnosis even if they develop chemotherapy-associated amenorrhea as there are concerns that reduced estrogen feedback to the hypothalamus and pituitary will stimulate gonadotropin release and thus ovarian stimulation. Chemotherapy-induced amenorrhea may not be permanent (and is less likely to be permanent the younger the woman is), and aromatase inhibitors can promote the recovery of ovarian function in these women. Thus, aromatase inhibitors should be used with caution in women with chemotherapy-induced amenorrhea, and serum estradiol and gonadotropin levels should be serially monitored to ensure that ovarian function is not recovering [61]. There is some evidence that treatment with an aromatase inhibitor plus ovarian suppression with an LHRH analog is efficacious in premenopausal women, and is at least as efficacious as tamoxifen plus an LHRH agonist, as shown in the ABCSG 12 trial (by the Austrian Breast and Colorectal Cancer Study Group) [62]. How this combination compares to tamoxifen alone is currently being investigated by the SOFT trial (NCT00917969).

Breast cancer diagnosed during pregnancy is rare, with an incidence of 1 in 3,000 pregnancies [63]. Diagnosis and treatment of breast cancer during pregnancy requires special consideration and is beyond the scope of this review. A recent article published by Litton and colleagues [64] reviews the challenges in diagnosis and treatment of breast cancer during pregnancy.

Fertility

Preserving fertility is a concern that affects treatment decisions for many young women faced with a new diagnosis of breast cancer [65]. Chemotherapy can cause amenorrhea and, in some cases, permanent menopause. A recent prospective study examined differences in chemotherapy-induced amenorrhea among chemotherapy regimens (CMF; doxorubicin and cyclophosphamide (AC); doxorubicin, cyclophosphamide, and paclitaxel (ACT)). The rate of chemotherapy-induced amenorrhea among the three regimens was similar; however, patients treated with CMF were less likely to resume their menses [46]. The risk of chemotherapy-induced menopause is also dependent on the patient's age at diagnosis. Women under the age of 35 who undergo chemotherapy have a lower risk of menopause (approximately 15%) compared to, for example, a 40-year-old woman who has a greater than 40% risk of menopause. Tamoxifen may marginally increase a woman's risk of early menopause [47]. More importantly, because of teratogenicity, women must wait until they complete treatment with tamoxifen before getting pregnant. The optimal treatment duration is 5 years, and fertility declines with age.

Fortunately, pregnancy after a diagnosis of early stage breast cancer does not appear to increase the risk of relapse [66]. In fact, a recent meta-analysis presented at the 2010 European Breast Cancer Conference suggested that pregnancy after a diagnosis of breast cancer is associated with improved survival when compared to breast cancer patients that do not have a pregnancy after their diagnosis [67]. One possible explanation for this supposed survival advantage is the 'healthy mother effect,' as women who feel healthy may be more likely to conceive, leading to selection bias [68]. However, there are also biologic theories as to why pregnancy may protect against relapse, such as alloimmunization against breast cancer cells [69], or the cytotoxic effects of high dose estrogen during pregnancy [70,71]. Nonetheless, pregnancy after a diagnosis of early stage breast cancer does not appear to decrease survival.

If a woman desires to bear children after her breast cancer treatment, she should be counseled on fertility preservation options. Fertility preservation should be discussed as early as possible, as these fertility procedures must be initiated prior to starting systemic therapy. Options to preserve fertility include ovarian preservation

with LHRH analogs, embryo cryopreservation via *in vitro* fertilization, and oocyte or ovarian tissue cryopreservation [72].

Ovarian preservation with LHRH analogs is the only fertility option that does not involve assisted reproductive techniques. LHRH analogs stop ovarian follicular development by suppressing gonadotropins, which, theoretically, can protect a woman's ovaries from damage from cytotoxic therapy. However, the efficacy of LHRH analogs for fertility preservation has not yet been established. Several small studies have looked at the use of LHRH agonists given concurrently with chemotherapy to preserve ovarian function with mixed results. Randomized controlled trials are currently underway to evaluate this strategy in women with cancer [73].

To date, the most effective approach to preserve fertility in cancer patients is embryo cryopreservation. However, this procedure requires *in vitro* fertilization and, thus, a participating male partner (or sperm donor). Oocyte and ovarian tissue cryopreservation are emerging options for women who do not have a male partner at diagnosis. However, these methods are currently investigational, and have resulted in lower pregnancy rates when compared to embryo cryopreservation [74-78].

Both embryo and oocyte cryopreservation require controlled ovarian stimulation, which is associated with a marked increase in estradiol levels. To avoid the potential risks of rising estradiol levels during ovarian stimulation, Oktay and colleagues [79] have developed an ovarian stimulation protocol using the aromatase inhibitor letrozole, which results in estradiol levels that are similar to unstimulated cycles. Oocyte and embryo yields using this protocol have been comparable to those using standard ovarian stimulation protocols, and after 23.4 months of follow-up, recurrence and survival rates were comparable to unstimulated controls. The lag time between surgery and chemotherapy was greater in the group undergoing stimulation, likely due to the extra time needed for ovarian stimulation. However, time to the start of chemotherapy for the group undergoing stimulation was well within 12 weeks, which has been established as an acceptable time frame between surgery and chemotherapy for breast cancer [80,81].

In summary, fertility preservation is possible in young women undergoing treatment for breast cancer. Oncologists should discuss options to preserve fertility prior to initiating systemic treatment, and refer to fertility specialists when appropriate.

Bone health

Women who experience chemotherapy-induced amenorrhea have been shown to experience a rapid decline in bone density compared to women who retain their menstrual function [82]. In one prospective study, the incidence of vertebral fractures was markedly increased in women followed from diagnosis of breast cancer (mean follow-up 2.1 years) compared to age-matched controls [83]. For this reason, there has been recent interest in preventing bone loss in premenopausal women undergoing treatment for breast cancer.

Two randomized trials have shown that zoledronic acid, an intravenous bisphosphonate, prevents bone loss in premenopausal women undergoing treatment for breast cancer. The zoledronic acid was well tolerated, and there were no reports of renal insufficiency or osteonecrosis of the jaw in either trial [84,85]. Additionally, preclinical and clinical studies suggest that bisphosphonates may have antitumor and antimetastatic properties [86-89]. In the ABCSG 12 trial, 1,803 premenopausal women receiving adjuvant hormonal therapy for early breast cancer were randomly assigned to receive goserelin plus tamoxifen or anastrazole with or without zolendronic acid. There was no difference in disease free survival between the two hormonal therapy groups; however, the addition of zolendronic acid led to a significant improvement in disease-free survival (hazard ratio, 0.64; 95% CI, 0.46 to 0.91; $P = 0.01$), and insignificant trend towards overall survival (hazard ratio, 0.60; 95% CI, 0.32 to 1.11; $P = 0.11$). This study only included women with endocrine responsive tumors who did not receive chemotherapy, so it is unknown if these results are generalizable to all women with breast cancer [62]. Conversely, a meta-analysis evaluating the effect of clodronate, another bisphosphate, on breast cancer outcomes showed no difference in overall survival, bone metastasis free survival, and non-skeletal metastasis free survival in those receiving adjuvant clodronate compared to those who did not receive adjuvant bisphosphonate treatment [90]. Currently, there are no formal guidelines regarding the use of bisphosphonates in the adjuvant treatment of breast cancer. Results from ongoing studies (AZURE, NSABP-B-34, S0307 - all of which are closed to accrual) are expected to clarify the role of bisphosphonates in maintaining bone health and improving breast cancer outcomes.

Secondary prevention

Women treated for breast cancer are at increased risk of developing a contralateral breast cancer (CBC), with young age being an important risk factor [91-95]. In addition, the local recurrence rate is higher in young women treated with breast conservation compared to their older counterparts [39,40]. Guidelines recommend that women with a history of breast cancer have yearly mammograms to screen for CBCs and local recurrences. However, mammograms are less sensitive in younger women due to increased breast density [10-12]. Although MRIs are more sensitive than mammograms in young

women [15], there is no consensus regarding breast MRI for young women with a personal history of breast cancer [14]. To decrease their risk of local recurrence and CBC, some women choose to have PBM for unilateral disease. Multiple studies have shown that a PBM reduces the risk of a CBC by as much as 95% [96-98]. A recent population-based study has shown that the proportion of women who choose to have a PBM is increasing, and has more than doubled between the years 1998 and 2003 [99]. Age has been shown to be an important predictor in the selection of bilateral mastectomy, with women younger than 40 years more likely to have this procedure [100]. Although a PBM can dramatically decrease the risk of a CBC, evidence that the procedure improves disease-specific or overall survival is lacking [101]. One recent study, based on data from the Surveillance, Epidemiology and End Results (SEER) program, has suggested that bilateral mastectomy at the time of a unilateral breast cancer diagnosis may improve survival in women under the age of 50 with triple negative tumors [102], but more data are needed.

BRCA 1/2 mutation carriers have an even higher risk for developing a second primary breast cancer [19-21]. Both prophylactic BSO and tamoxifen use have been shown to decrease the risk of a second primary [21]. A retrospective cohort study that compared *BRCA1/2* mutation carriers with breast cancer who underwent a PBM with those who did not showed that a PBM reduced the risk of developing a CBC by 91%. After adjustment for BSO uptake, there was no difference in overall survival among the two groups [103]. PBMs are not without complications, which occur more frequently in women undergoing immediate reconstruction [104]. For these reasons, in women with *BRCA1/2* mutations and in sporadic cases, PBMs are considered an option rather than a mandate and remain a personal decision. Patients should be aware of the risks, benefits, and uncertainties of this procedure.

Observational studies suggest that some lifestyle and dietary factors are associated with breast cancer prognosis. Physical activity and maintaining a healthy weight are associated with a decreased risk of recurrence [105]. Vitamin D deficiency has been associated with an increase in distant recurrence and death in women treated for early stage breast cancer [106]. Although there are no randomized trials that tell us whether exercise programs, maintaining a healthy weight, or vitamin D supplementation improve prognosis, in otherwise healthy women, there appear to be few downsides to these interventions.

Psychosocial issues

A diagnosis of breast cancer is distressing at any age but younger patients seem to experience a greater degree of psychological distress than their older counterparts [107]. A retrospective study looking at quality of life in 577 breast cancer survivors who were under age 50 years at diagnosis found that women younger than 35 reported more emotional distress and less energy than older survivors even years after initial treatment. Women who experienced treatment-induced menopause reported lower health perceptions than their peers. African American women and women who were either married or had a stable partner were less likely to experience emotional distress [108]. It is not known why younger breast cancer patients suffer more emotionally than older patients. It has been theorized that breast cancer is viewed as a disease of older women and a diagnosis in this age group is an emotional shock. In addition, younger women often have more physical demands - such as taking care of young children and/or working full time - which may make it especially difficult to endure treatment [107,108].

Concern over loss of fertility may also contribute to the emotional distress experienced by younger breast cancer survivors [65]. Sexual dysfunction, most notably vaginal dryness, is also a common complaint among breast cancer survivors [109]. Breast cancer survivors who have had a mastectomy as opposed to breast conservation surgery report poor body image, which may contribute further to sexual dysfunction [110]. In conclusion, younger women are at high risk for emotional distress when faced with a diagnosis of breast cancer. Clinicians should consider early referral to support and counseling services in this high risk group.

The Young Survival Coalition [111] is an international organization dedicated to increasing awareness and providing resources for young women diagnosed with breast cancer under the age of 40. Through this organization, young women can find local support groups and community events geared towards young women with breast cancer, which can hopefully reduce the sense of isolation felt when diagnosed with this disease at such a young age.

Conclusion

Management of young women with breast cancer differs from that of their older counterparts. Breast cancers in women under ages 35 to 40 years have more aggressive features, tend to be diagnosed at a later stage, and have inferior outcomes. Differences in risk factors and gene expression suggest that breast cancer in young women may be a distinct entity. Radiographic diagnosis in this population is challenging due to increased breast density. Genetic testing for the *BRCA1* and *BRCA2*, and in certain cases, *TP53* mutations, should be considered. Treatment is generally the same as for older women; however, the optimal type of hormonal therapy is currently unknown

(but is actively being investigated). Fertility preservation is often a top concern for many women. They should be referred to a fertility specialist as early as possible - definitely prior to initiating systemic therapy. Treatment related menopause can lead to a rapid decline in bone density, and there may be a future role for the use of bisphosphonates in the adjuvant setting to both maintain bone health and prevent breast cancer recurrence. Prophylactic contralateral mastectomies are increasingly pursued, but it is unclear if they improve survival. Lastly, young women with breast cancer are at greater risk for psychological distress. Clinicians should consider early referral to support services in this high risk group.

Abbreviations

BSO, bilateral salpingo-oophorectomy; CBC, contralateral breast cancer; CI, confidence interval; CMF, cyclophosphamide, methotrexate, fluorouracil; ER, estrogen receptor; LFS, Li-Fraumeni syndrome; LHRH, luteinizing releasing hormone; MRI, magnetic resonance imaging; PBM, prophylactic bilateral mastectomy; SOFT, Suppression of Ovarian Function Trial.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

CG performed the literature search, reviewed relevant articles, and wrote primary drafts of the review article. SD reviewed and revised drafts, and made ongoing recommendations regarding necessary additions or changes to the article.

Author details

[1]Abramson Cancer Center, University of Pennsylvania, 16 Penn Tower, 3400 Spruce Street, Philadelphia, PA 19104, USA. [2]Abramson Cancer Center, University of Pennsylvania, 3 West Perelman Center, 3400 Civic Center Boulevard, Philadelphia, PA 19104, USA

Published: 28 October 2010

References

1. **Breast Cancer Facts & Figures 2009-2010** [http://www.cancer.org/docroot/STT/STT_0.asp]
2. Anders CK, Johnson R, Litton J, Phillips M, Bleyer A: **Breast cancer before age 40 years.** *Semin Oncol* 2009, **36:**237-249.
3. Althuis MD, Brogan DD, Coates RJ, Daling JR, Gammon MD, Malone KE, Schoenberg JB, Brinton LA: **Breast cancers among very young premenopausal women (United States).** *Cancer Causes Control* 2003, **14:**151-160.
4. Winchester DP, Osteen RT, Menck HR: **The National Cancer Data Base report on breast carcinoma characteristics and outcome in relation to age.** *Cancer* 1996, **78:**1838-1843.
5. Anders CK, Hsu DS, Broadwater G, Acharya CR, Foekens JA, Zhang Y, Wang Y, Marcom PK, Marks JR, Febbo PG, Nevins JR, Potti A, Blackwell KL: **Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression.** *J Clin Oncol* 2008, **26:**3324-3330.
6. Nixon AJ, Neuberg D, Hayes DF, Gelman R, Connolly JL, Schnitt S, Abner A, Recht A, Vicini F, Harris JR: **Relationship of patient age to pathologic features of the tumor and prognosis for patients with stage I or II breast cancer.** *J Clin Oncol* 1994, **12:**888-894.
7. Colleoni M, Rotmensz N, Robertson C, Orlando L, Viale G, Renne G, Luini A, Veronesi P, Intra M, Orecchia R, Catalano G, Galimberti V, Nolé F, Martinelli G, Goldhirsch A: **Very young women (<35 years) with operable breast cancer: features of disease at presentation.** *Ann Oncol* 2002, **13:**273-279.
8. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, Karaca G, Troester MA, Tse CK, Edmiston S, Deming SL, Geradts J, Cheang MC, Nielsen TO, Moorman PG, Earp HS, Millikan RC: **Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study.** *JAMA* 2006, **295:**2492-2502.
9. Foxcroft LM, Evans EB, Porter AJ: **The diagnosis of breast cancer in women younger than 40.** *Breast* 2004, **13:**297-306.
10. Hindle WH, Davis L, Wright D: **Clinical value of mammography for symptomatic women 35 years of age and younger.** *Am J Obstet Gynecol* 1999, **180:**1484-1490.
11. Kolb TM, Lichy J, Newhouse JH: **Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations.** *Radiology* 2002, **225:**165-175.
12. Mandelson MT, Oestreicher N, Porter PL, White D, Finder CA, Taplin SH, White E: **Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers.** *J Natl Cancer Inst* 2000, **92:**1081-1087.
13. Jackson VP: **The role of US in breast imaging.** *Radiology* 1990, **177:**305-311.
14. Saslow D, Boetes C, Burke W, Harms S, Leach MO, Lehman CD, Morris E, Pisano E, Schnall M, Sener S, Smith RA, Warner E, Yaffe M, Andrews KS, Russell CA; American Cancer Society Breast Cancer Advisory Group: **American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography.** *CA Cancer J Clin* 2007, **57:**75-89.
15. Pediconi F, Catalano C, Roselli A, Dominelli V, Cagioli S, Karatasiou A, Pronio A, Kirchin MA, Passariello R: **The challenge of imaging dense breast parenchyma: is magnetic resonance mammography the technique of choice? A comparative study with x-ray mammography and whole-breast ultrasound.** *Invest Radiol* 2009, **44:**412-421.
16. Malone KE, Daling JR, Neal C, Suter NM, O'Brien C, Cushing-Haugen K, Jonasdottir TJ, Thompson JD, Ostrander EA: **Frequency of BRCA1/BRCA2 mutations in a population-based sample of young breast carcinoma cases.** *Cancer* 2000, **88:**1393-1402.
17. Lakhani SR, Van De Vijver MJ, Jacquemier J, Anderson TJ, Osin PP, McGuffog L, Easton DF: **The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2.** *J Clin Oncol* 2002, **20:**2310-2318.
18. Lidereau R, Eisinger F, Champeme MH, Nogues C, Bieche I, Birnbaum D, Pallud C, Jacquemier J, Sobol H: **Major improvement in the efficacy of BRCA1 mutation screening using morphoclinical features of breast cancer.** *Cancer Res* 2000, **60:**1206-1210.
19. Seynaeve C, Verhoog LC, van de Bosch LM, van Geel AN, Menke-Pluymers M, Meijers-Heijboer EJ, van den Ouweland AM, Wagner A, Creutzberg CL, Niermeijer MF, Klijn JG, Brekelmans CT: **Ipsilateral breast tumour recurrence in hereditary breast cancer following breast-conserving therapy.** *Eur J Cancer* 2004, **40:**1150-1158.
20. Haffty BG, Harrold E, Khan AJ, Pathare P, Smith TE, Turner BC, Glazer PM, Ward B, Carter D, Matloff E, Bale AE, Alvarez-Franco M: **Outcome of conservatively managed early-onset breast cancer by BRCA1/2 status.** *Lancet* 2002, **359:**1471-1477.
21. Metcalfe K, Lynch HT, Ghadirian P, Tung N, Olivotto I, Warner E, Olopade OI, Eisen A, Weber B, McLennan J, Sun P, Foulkes WD, Narod SA: **Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers.** *J Clin Oncol* 2004, **22:**2328-2335.
22. King MC, Marks JH, Mandell JB: **Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2.** *Science* 2003, **302:**643-646.
23. Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Loman N, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, Manoukian S, Eccles DM, Tang N, Olah E, Anton-Culver H, Warner E, Lubinski J, Gronwald J, Gorski B, Tulinius H, Thorlacius S, Eerola H, Nevanlinna H, Syrjäkoski K, Kallioniemi OP, Thompson D, Evans C, Peto J, *et al.*: **Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies.** *Am J Hum Genet* 2003, **72:**1117-1130.
24. Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE: **Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium.** *Lancet* 1994, **343:**692-695.
25. Rebbeck TR, Lynch HT, Neuhausen SL, Narod SA, Van't Veer L, Garber JE, Evans G, Isaacs C, Daly MB, Matloff E, Olopade OI, Weber BL; Prevention and Observation of Surgical End Points Study Group: **Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations.** *N Engl J Med* 2002, **346:**1616-1622.
26. Kauff ND, Domchek SM, Friebel TM, Robson ME, Lee J, Garber JE, Isaacs C, Evans DG, Lynch H, Eeles RA, Neuhausen SL, Daly MB, Matloff E, Blum JL, Sabbatini P, Barakat RR, Hudis C, Norton L, Offit K, Rebbeck TR: **Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and**

BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. *J Clin Oncol* 2008, **26:**1331-1337.
27. Domchek SM, Friebel TM, Neuhausen SL, Wagner T, Evans G, Isaacs C, Garber JE, Daly MB, Eeles R, Matloff E, Tomlinson GE, Van't Veer L, Lynch HT, Olopade OI, Weber BL, Rebbeck TR: **Mortality after bilateral salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: a prospective cohort study.** *Lancet Oncol* 2006, **7:**223-229.
28. Li FP, Fraumeni JF Jr: **Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome?** *Ann Intern Med* 1969, **71:**747-752.
29. Li FP, Fraumeni JF Jr, Mulvihill JJ, Blattner WA, Dreyfus MG, Tucker MA, Miller RW: **A cancer family syndrome in twenty-four kindreds.** *Cancer Res* 1988, **48:**5358-5362.
30. Garber JE, Goldstein AM, Kantor AF, Dreyfus MG, Fraumeni JF Jr, Li FP: **Follow-up study of twenty-four families with Li-Fraumeni syndrome.** *Cancer Res* 1991, **51:**6094-6097.
31. Varley JM, McGown G, Thorncroft M, Santibanez-Koref MF, Kelsey AM, Tricker KJ, Evans DG, Birch JM: **Germ-line mutations of TP53 in Li-Fraumeni families: an extended study of 39 families.** *Cancer Res* 1997, **57:**3245-3252.
32. Malkin D, Li FP, Strong LC, Fraumeni JF Jr, Nelson CE, Kim DH, Kassel J, Gryka MA, Bischoff FZ, Tainsky MA, *et al.*: **Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms.** *Science* 1990, **250:**1233-1238.
33. Birch JM, Hartley AL, Tricker KJ, Prosser J, Condie A, Kelsey AM, Harris M, Jones PH, Binchy A, Crowther D, *et al.*: **Prevalence and diversity of constitutional mutations in the p53 gene among 21 Li-Fraumeni families.** *Cancer Res* 1994, **54:**1298-1304.
34. Salmon A, Amikam D, Sodha N, Davidson S, Basel-Vanagaite L, Eeles RA, Abeliovich D, Peretz T: **Rapid development of post-radiotherapy sarcoma and breast cancer in a patient with a novel germline 'de-novo' TP53 mutation.** *Clin Oncol (R Coll Radiol)* 2007, **19:**490-493.
35. Gonzalez KD, Noltner KA, Buzin CH, Gu D, Wen-Fong CY, Nguyen VQ, Han JH, Lowstuter K, Longmate J, Sommer SS, Weitzel JN: **Beyond Li Fraumeni Syndrome: clinical characteristics of families with p53 germline mutations.** *J Clin Oncol* 2009, **27:**1250-1256.
36. Ginsburg OM, Akbari MR, Aziz Z, Young R, Lynch H, Ghadirian P, Robidoux A, Londono J, Vasquez G, Gomes M, Costa MM, Dimitrakakis C, Gutierrez G, Pilarski R, Royer R, Narod SA: **The prevalence of germ-line TP53 mutations in women diagnosed with breast cancer before age 30.** *Fam Cancer* 2009, **8:**563-567.
37. Toguchida J, Yamaguchi T, Dayton SH, Beauchamp RL, Herrera GE, Ishizaki K, Yamamuro T, Meyers PA, Little JB, Sasaki MS, *et al.*: **Prevalence and spectrum of germline mutations of the p53 gene among patients with sarcoma.** *N Engl J Med* 1992, **326:**1301-1308.
38. Speiser P, Gharehbaghi-Schnell E, Eder S, Haid A, Kovarík J, Nenutil R, Sauter G, Schneeberger CH, Vojtesek B, Wiltschke CH, Zeillinger R: **A constitutional de novo mutation in exon 8 of the p53 gene in a patient with multiple primary malignancies.** *Br J Cancer* 1996, **74:**269-273.
39. Voogd AC, Nielsen M, Peterse JL, Blichert-Toft M, Bartelink H, Overgaard M, van Tienhoven G, Andersen KW, Sylvester RJ, van Dongen JA: **Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials.** *J Clin Oncol* 2001, **19:**1688-1697.
40. Kurtz JM, Jacquemier J, Amalric R, Brandone H, Ayme Y, Hans D, Bressac C, Spitalier JM: **Why are local recurrences after breast-conserving therapy more frequent in younger patients?** *J Clin Oncol* 1990, **8:**591-598.
41. Freedman GM, Hanlon AL, Fowble BL, Anderson PR, Nicolaou N: **Recursive partitioning identifies patients at high and low risk for ipsilateral tumor recurrence after breast-conserving surgery and radiation.** *J Clin Oncol* 2002, **20:**4015-4021.
42. Kroman N, Jensen MB, Wohlfahrt J, Mouridsen HT, Andersen PK, Melbye M: **Factors influencing the effect of age on prognosis in breast cancer: population based study.** *BMJ* 2000, **320:**474-478.
43. Xiong Q, Valero V, Kau V, Kau SW, Taylor S, Smith TL, Buzdar AU, Hortobagyi GN, Theriault RL: **Female patients with breast carcinoma age 30 years and younger have a poor prognosis: the M.D. Anderson Cancer Center experience.** *Cancer* 2001, **92:**2523-2528.
44. Swain SM, Jeong JH, Geyer CE Jr, Costantino JP, Pajon ER, Fehrenbacher L, Atkins JN, Polikoff J, Vogel VG, Erban JK, Rastogi P, Livingston RB, Perez EA, Mamounas EP, Land SR, Ganz PA, Wolmark N: **Longer therapy, iatrogenic amenorrhea, and survival in early breast cancer.** *N Engl J Med* 2010, **362:**2053-2065.
45. Walshe JM, Denduluri N, Swain SM: **Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer.** *J Clin Oncol* 2006, **24:**5769-5779.
46. Sukumvanich P, Case LD, Van Zee K, Singletary SE, Paskett ED, Petrek JA, Naftalis E, Naughton MJ: **Incidence and time course of bleeding after long-term amenorrhea after breast cancer treatment: a prospective study.** *Cancer* 2010, **116:**3102-3111.
47. Goodwin PJ, Ennis M, Pritchard KI, Trudeau M, Hood N: **Risk of menopause during the first year after breast cancer diagnosis.** *J Clin Oncol* 1999, **17:**2365-2370.
48. Jonat W, Kaufmann M, Sauerbrei W, Blamey R, Cuzick J, Namer M, Fogelman I, de Haes JC, de Matteis A, Stewart A, Eiermann W, Szakolczai I, Palmer M, Schumacher M, Geberth M, Lisboa B; Zoladex Early Breast Cancer Research Association Study: **Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: The Zoladex Early Breast Cancer Research Association Study.** *J Clin Oncol* 2002, **20:**4628-4635.
49. de Haes H, Olschewski M, Kaufmann M, Schumacher M, Jonat W, Sauerbrei W: **Quality of life in goserelin-treated versus cyclophosphamide + methotrexate + fluorouracil-treated premenopausal and perimenopausal patients with node-positive, early breast cancer: the Zoladex Early Breast Cancer Research Association Trialists Group.** *J Clin Oncol* 2003, **21:**4510-4516.
50. Bernhard J, Zahrieh D, Castiglione-Gertsch M, Hürny C, Gelber RD, Forbes JF, Murray E, Collins J, Aebi S, Thürlimann B, Price KN, Goldhirsch A, Coates AS; International Breast Cancer Study Group Trial VIII: **Adjuvant chemotherapy followed by goserelin compared with either modality alone: the impact on amenorrhea, hot flashes, and quality of life in premenopausal patients–the International Breast Cancer Study Group Trial VIII.** *J Clin Oncol* 2007, **25:**263-270.
51. Castiglione-Gertsch M, O'Neill A, Price KN, Goldhirsch A, Coates AS, Colleoni M, Nasi ML, Bonetti M, Gelber RD: **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.
52. Schmid P, Untch M, Kossé V, Bondar G, Vassiljev L, Tarutinov V, Lehmann U, Maubach L, Meurer J, Wallwiener D, Possinger K: **Leuprorelin acetate every-3-months depot versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant treatment in premenopausal patients with node-positive breast cancer: the TABLE study.** *J Clin Oncol* 2007, **25:**2509-2515.
53. von Minckwitz G, Graf E, Geberth M, Eiermann W, Jonat W, Conrad B, Brunnert K, Gerber B, Vescia S, Wollert J, Kaufmann M: **CMF versus goserelin as adjuvant therapy for node-negative, hormone-receptor-positive breast cancer in premenopausal patients: a randomised trial (GABG trial IV-A-93).** *Eur J Cancer* 2006, **42:**1780-1788.
54. Goel S, Sharma R, Hamilton A, Beith J: **LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women.** *Cochrane Db Syst Rev* 2009:CD004562.
55. Aebi S, Gelber S, Castiglione-Gertsch M, Gelber RD, Collins J, Thürlimann B, Rudenstam CM, Lindtner J, Crivellari D, Cortes-Funes H, Simoncini E, Werner ID, Coates AS, Goldhirsch A: **Is chemotherapy alone adequate for young women with oestrogen-receptor-positive breast cancer?** *Lancet* 2000, **355:**1869-1874.
56. **Ovarian ablation in early breast cancer: overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group.** *Lancet* 1996, **348:**1189-1196.
57. Kaufmann M, Jonat W, Blamey R, Cuzick J, Namer M, Fogelman I, de Haes JC, Schumacher M, Sauerbrei W: **Survival analyses from the ZEBRA study. goserelin (Zoladex) versus CMF in premenopausal women with node-positive breast cancer.** *Eur J Cancer* 2003, **39:**1711-1717.
58. De Placido S, De Laurentiis M, De Lena M, Lorusso V, Paradiso A, D'Aprile M, Pistillucci G, Farris A, Sarobba MG, Palazzo S, Manzione L, Adamo V, Palmeri S, Ferraù F, Lauria R, Pagliarulo C, Petrella G, Limite G, Costanzo R, Bianco AR; GOCSI Cooperative Group: **A randomised factorial trial of sequential doxorubicin and CMF vs CMF and chemotherapy alone vs chemotherapy followed by goserelin plus tamoxifen as adjuvant treatment of node-positive breast cancer.** *Br J Cancer* 2005, **92:**467-474.
59. **Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials.** *Lancet* 2005, **365:**1687-1717.
60. Colleoni M, Gelber S, Goldhirsch A, Aebi S, Castiglione-Gertsch M, Price KN,

Coates AS, Gelber RD: **Tamoxifen after adjuvant chemotherapy for premenopausal women with lymph node-positive breast cancer: International Breast Cancer Study Group Trial 13-93.** *J Clin Oncol* 2006, **24:**1332-1341.
61. Smith IE, Dowsett M, Yap YS, Walsh G, Lonning PE, Santen RJ, Hayes D: **Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines.** *J Clin Oncol* 2006, **24:**2444-2447.
62. Gnant M, Mlineritsch B, Schippinger W, Luschin-Ebengreuth G, Pöstlberger S, Menzel C, Jakesz R, Seifert M, Hubalek M, Bjelic-Radisic V, Samonigg H, Tausch C, Eidtmann H, Steger G, Kwasny W, Dubsky P, Fridrik M, Fitzal F, Stierer M, Rücklinger E, Greil R; ABCSG-12 Trial Investigators, Marth C: **Endocrine therapy plus zoledronic acid in premenopausal breast cancer.** *N Engl J Med* 2009, **360:**679-691.
63. Loibl S, von Minckwitz G, Gwyn K, Ellis P, Blohmer JU, Schlegelberger B, Keller M, Harder S, Theriault RL, Crivellari D, Klingebiel T, Louwen F, Kaufmann M: **Breast carcinoma during pregnancy. International recommendations from an expert meeting.** *Cancer* 2006, **106:**237-246.
64. Litton JK, Theriault RL, Gonzalez-Angulo AM: **Breast cancer diagnosis during pregnancy.** *Womens Health (Lond Engl)* 2009, **5:**243-249.
65. Partridge AH, Gelber S, Peppercorn J, Sampson E, Knudsen K, Laufer M, Rosenberg R, Przypyszny M, Rein A, Winer EP: **Web-based survey of fertility issues in young women with breast cancer.** *J Clin Oncol* 2004, **22:**4174-4183.
66. Rippy EE, Karat IF, Kissin MW: **Pregnancy after breast cancer: the importance of active counselling and planning.** *Breast* 2009, **18:**345-350.
67. Azim H, Santoro L, Pavlidis N, Peccatori F: **Safety of pregnancy in breast cancer survivors: a meta-analysis.** *Eur J Cancer Suppl* 2010, **8:**207.
68. Sankila R, Heinavaara S, Hakulinen T: **Survival of breast cancer patients after subsequent term pregnancy: "healthy mother effect".** *Am J Obstet Gynecol* 1994, **170:**818-823.
69. Botelho F, Clark DA: **How might pregnancy immunize against breast cancer?** *Am J Reprod Immunol* 1998, **39:**279-283.
70. Guzman RC, Yang J, Rajkumar L, Thordarson G, Chen X, Nandi S: **Hormonal prevention of breast cancer: mimicking the protective effect of pregnancy.** *Proc Natl Acad Sci U S A* 1999, **96:**2520-2525.
71. de Bree E, Makrigiannakis A, Askoxylakis J, Melissas J, Tsiftsis DD: **Pregnancy after breast cancer. A comprehensive review.** *J Surg Oncol* 2010, **101:**534-542.
72. Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, Beck LN, Brennan LV, Oktay K: **American Society of Clinical Oncology recommendations on fertility preservation in cancer patients.** *J Clin Oncol* 2006, **24:**2917-2931.
73. Oktay K, Sonmezer M, Oktem O, Fox K, Emons G, Bang H: **Absence of conclusive evidence for the safety and efficacy of gonadotropin-releasing hormone analogue treatment in protecting against chemotherapy-induced gonadal injury.** *Oncologist* 2007, **12:**1055-1066.
74. Oktay K, Cil AP, Bang H: **Efficiency of oocyte cryopreservation: a meta-analysis.** *Fertil Steril* 2006, **86:**70-80.
75. Donnez J, Dolmans MM, Demylle D, Jadoul P, Pirard C, Squifflet J, Martinez-Madrid B, van Langendonckt A: **Livebirth after orthotopic transplantation of cryopreserved ovarian tissue.** *Lancet* 2004, **364:**1405-1410.
76. Meirow D, Levron J, Eldar-Geva T, Hardan I, Fridman E, Zalel Y, Schiff E, Dor J: **Pregnancy after transplantation of cryopreserved ovarian tissue in a patient with ovarian failure after chemotherapy.** *N Engl J Med* 2005, **353:**318-321.
77. Demeestere I, Simon P, Buxant F, Robin V, Fernandez SA, Centner J, Delbaere A, Englert Y: **Ovarian function and spontaneous pregnancy after combined heterotopic and orthotopic cryopreserved ovarian tissue transplantation in a patient previously treated with bone marrow transplantation: case report.** *Hum Reprod* 2006, **21:**2010-2014.
78. Oktay K: **Spontaneous conceptions and live birth after heterotopic ovarian transplantation: is there a germline stem cell connection?** *Hum Reprod* 2006, **21:**1345-1348.
79. Azim AA, Costantini-Ferrando M, Oktay K: **Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study.** *J Clin Oncol* 2008, **26:**2630-2635.
80. Lohrisch C, Paltiel C, Gelmon K, Speers C, Taylor S, Barnett J, Olivotto IA: **Impact on survival of time from definitive surgery to initiation of adjuvant chemotherapy for early-stage breast cancer.** *J Clin Oncol* 2006, **24:**4888-4894.
81. Cold S, During M, Ewertz M, Knoop A, Moller S: **Does timing of adjuvant chemotherapy influence the prognosis after early breast cancer? Results of the Danish Breast Cancer Cooperative Group (DBCG).** *Br J Cancer* 2005, **93:**627-632.
82. Shapiro CL, Manola J, Leboff M: **Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer.** *J Clin Oncol* 2001, **19:**3306-3311.
83. Kanis JA, McCloskey EV, Powles T, Paterson AH, Ashley S, Spector T: **A high incidence of vertebral fracture in women with breast cancer.** *Br J Cancer* 1999, **79:**1179-1181.
84. Gnant M, Mlineritsch B, Luschin-Ebengreuth G, Kainberger F, Kässmann H, Piswanger-Sölkner JC, Seifert M, Ploner F, Menzel C, Dubsky P, Fitzal F, Bjelic-Radisic V, Steger G, Greil R, Marth C, Kubista E, Samonigg H, Wohlmuth P, Mittlböck M, Jakesz R; Austrian Breast and Colorectal Cancer Study Group (ABCSG): **Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy.** *Lancet Oncol* 2008, **9:**840-849.
85. Hershman DL, McMahon DJ, Crew KD, Cremers S, Irani D, Cucchiara G, Brafman L, Shane E: **Zoledronic acid prevents bone loss in premenopausal women undergoing adjuvant chemotherapy for early-stage breast cancer.** *J Clin Oncol* 2008, **26:**4739-4745.
86. Aviles A, Nambo MJ, Neri N, Castaneda C, Cleto S, Huerta-Guzman J: **Antitumor effect of zoledronic acid in previously untreated patients with multiple myeloma.** *Med Oncol* 2007, **24:**227-230.
87. Daubine F, Le Gall C, Gasser J, Green J, Clezardin P: **Antitumor effects of clinical dosing regimens of bisphosphonates in experimental breast cancer bone metastasis.** *J Natl Cancer Inst* 2007, **99:**322-330.
88. Mystakidou K, Katsouda E, Parpa E, Kelekis A, Galanos A, Vlahos L: **Randomized, open label, prospective study on the effect of zoledronic acid on the prevention of bone metastases in patients with recurrent solid tumors that did not present with bone metastases at baseline.** *Med Oncol* 2005, **22:**195-201.
89. Santini D, Vincenzi B, Galluzzo S, Battistoni F, Rocci L, Venditti O, Schiavon G, Angeletti S, Uzzalli F, Caraglia M, Dicuonzo G, Tonini G: **Repeated intermittent low-dose therapy with zoledronic acid induces an early, sustained, and long-lasting decrease of peripheral vascular endothelial growth factor levels in cancer patients.** *Clin Cancer Res* 2007, **13:**4482-4486.
90. Ha TC, Li H: **Meta-analysis of clodronate and breast cancer survival.** *Br J Cancer* 2007, **96:**1796-1801.
91. Adami HO, Bergstrom R, Hansen J: **Age at first primary as a determinant of the incidence of bilateral breast cancer. Cumulative and relative risks in a population-based case-control study.** *Cancer* 1985, **55:**643-647.
92. Healey EA, Cook EF, Orav EJ, Schnitt SJ, Connolly JL, Harris JR: **Contralateral breast cancer: clinical characteristics and impact on prognosis.** *J Clin Oncol* 1993, **11:**1545-1552.
93. Hislop TG, Elwood JM, Coldman AJ, Spinelli JJ, Worth AJ, Ellison LG: **Second primary cancers of the breast: incidence and risk factors.** *Br J Cancer* 1984, **49:**79-85.
94. Kollias J, Ellis IO, Elston CW, Blamey RW: **Clinical and histological predictors of contralateral breast cancer.** *Eur J Surg Oncol* 1999, **25:**584-589.
95. Rosen PP, Groshen S, Kinne DW, Hellman S: **Contralateral breast carcinoma: an assessment of risk and prognosis in stage I (T1N0M0) and stage II (T1N1M0) patients with 20-year follow-up.** *Surgery* 1989, **106:**904-910.
96. McDonnell SK, Schaid DJ, Myers JL, Grant CS, Donohue JH, Woods JE, Frost MH, Johnson JL, Sitta DL, Slezak JM, Crotty TB, Jenkins RB, Sellers TA, Hartmann LC: **Efficacy of contralateral prophylactic mastectomy in women with a personal and family history of breast cancer.** *J Clin Oncol* 2001, **19:**3938-3943.
97. Peralta EA, Ellenhorn JD, Wagman LD, Dagis A, Andersen JS, Chu DZ: **Contralateral prophylactic mastectomy improves the outcome of selected patients undergoing mastectomy for breast cancer.** *Am J Surg* 2000, **180:**439-445.
98. Herrinton LJ, Barlow WE, Yu O, Geiger AM, Elmore JG, Barton MB, Harris EL, Rolnick S, Pardee R, Husson G, Macedo A, Fletcher SW: **Efficacy of prophylactic mastectomy in women with unilateral breast cancer: a cancer research network project.** *J Clin Oncol* 2005, **23:**4275-4286.
99. Tuttle TM, Habermann EB, Grund EH, Morris TJ, Virnig BA: **Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment.** *J Clin Oncol* 2007, **25:**5203-5209.

100. Arrington AK, Jarosek SL, Virnig BA, Habermann EB, Tuttle TM: **Patient and surgeon characteristics associated with increased use of contralateral prophylactic mastectomy in patients with breast cancer.** *Ann Surg Oncol* 2009, **16:**2697-2704.
101. Lostumbo L, Carbine N, Wallace J, Ezzo J: **Prophylactic mastectomy for the prevention of breast cancer.** *Cochrane Database Syst Rev* 2004:CD002748.
102. Bedrosian I, Hu CY, Chang GJ: **Population-based study of contralateral prophylactic mastectomy and survival outcomes of breast cancer patients.** *J Natl Cancer Inst* 2010, **102:**401-409.
103. van Sprundel TC, Schmidt MK, Rookus MA, Brohet R, van Asperen CJ, Rutgers EJ, Van't Veer LJ, Tollenaar RA: **Risk reduction of contralateral breast cancer and survival after contralateral prophylactic mastectomy in BRCA1 or BRCA2 mutation carriers.** *Br J Cancer* 2005, **93:**287-292.
104. Barton MB, West CN, Liu IL, Harris EL, Rolnick SJ, Elmore JG, Herrinton LJ, Greene SM, Nekhlyudov L, Fletcher SW, Geiger AM: **Complications following bilateral prophylactic mastectomy.** *J Natl Cancer Inst Monogr* 2005:61-66.
105. McTiernan A, Irwin M, Vongruenigen V: **Weight, physical activity, diet, and prognosis in breast and gynecologic cancers.** *J Clin Oncol* 2010, **28:**4074-4080.
106. Goodwin PJ, Ennis M, Pritchard KI, Koo J, Hood N: **Prognostic effects of 25-hydroxyvitamin D levels in early breast cancer.** *J Clin Oncol* 2009, **27:**3757-3763.
107. Wenzel LB, Fairclough DL, Brady MJ, Cella D, Garrett KM, Kluhsman BC, Crane LA, Marcus AC: **Age-related differences in the quality of life of breast carcinoma patients after treatment.** *Cancer* 1999, **86:**1768-1774.
108. Ganz PA, Moinpour CM, Pauler DK, Kornblith AB, Gaynor ER, Balcerzak SP, Gatti GS, Erba HP, McCoy S, Press OW, Fisher RI: **Health status and quality of life in patients with early-stage Hodgkin's disease treated on Southwest Oncology Group Study 9133.** *J Clin Oncol* 2003, **21:**3512-3519.
109. Broeckel JA, Thors CL, Jacobsen PB, Small M, Cox CE: **Sexual functioning in long-term breast cancer survivors treated with adjuvant chemotherapy.** *Breast Cancer Res Treat* 2002, **75:**241-248.
110. Schain WS, d'Angelo TM, Dunn ME, Lichter AS, Pierce LJ: **Mastectomy versus conservative surgery and radiation therapy. Psychosocial consequences.** *Cancer* 1994, **73:**1221-1228.
111. **Young Survival Coalition** [http://www.youngsurvival.org]
112. Chompret A, Abel A, Stoppa-Lyonnet D, Brugieres L, Pages S, Feunteun J, Bonaiti-Pellie C: **Sensitivity and predictive value of criteria for p53 germline mutation screening.** *J Med Genet* 2001, **38:**43-47.
113. Chompret A, Brugières L, Ronsin M, Gardes M, Dessarps-Freichey F, Abel A, Hua D, Ligot L, Dondon MG, Bressac-de Paillerets B, Frébourg T, Lemerle J, Bonaïti-Pellié C, Feunteun J: **P53 germline mutations in childhood cancers and cancer risk for carrier individuals.** *Br J Cancer* 2000, **82:**1932-1937.

doi:10.1186/bcr2647
Cite this article as: Gabriel CA, Domchek SM: **Breast cancer in young women.** *Breast Cancer Research* 2010, **12:**212.