Association of Women Surgeons: Review

Review of risk factors for the development of contralateral breast cancer

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Abstract

BACKGROUND: Women treated for breast cancer have an increased risk for developing metachronous contralateral breast cancer (CBC). Patient perception of this risk is often overestimated and has been found to contribute to the decision to undergo contralateral prophylactic mastectomy. An individual’s risk is dependent on both patient and tumor characteristics. This review examines and summarizes the current literature on the factors that affect CBC risk.

DATA SOURCES: English-language publications with the keyword “contralateral breast cancer” were identified through a MEDLINE literature search.

CONCLUSIONS: The global incidence of CBC is decreasing, a trend that is attributed to more effective adjuvant therapies. Patients with BRCA germ-line mutations demonstrate the highest risk for CBC. In the absence of known genetic mutations, patients with strong family histories who are diagnosed at young ages (<35 years) with estrogen receptor–negative index tumors appear to have a higher incidence of CBC.

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The introduction of breast-conserving therapy with lumpectomy and radiation treatment for early-stage breast cancer led to a decrease in use of mastectomy in appropriate women.1–4 However, the past decade has seen an increase in rates of mastectomy and an increased use of contralateral prophylactic mastectomy. Many factors influence an individual woman’s decision, including a perception that better symmetry can be achieved with bilateral mastectomy and immediate reconstruction, the desire to avoid future mammograms and biopsies, and the concern that cancer will develop in the opposite breast. The latter 2 reasons are often stated by patients as a desire “never to have to go through this again.”2

Of all of the reasons that patients may choose bilateral mastectomy, this perception of the risk for developing cancer in the opposite breast may be the one most amenable to detailed analysis and careful counseling by an informed surgeon. The purpose of this review is to examine the current data regarding the various factors affecting contralateral breast cancer (CBC) risk and present them in a format that will facilitate the counseling of individual patients facing breast cancer management decisions.

Overall Risk for Contralateral Breast Cancer

It is well established that women who have had breast cancer in the past are at increased risk for CBC. The
Survival, Epidemiology and End Results (SEER) database reported a 4.2% incidence of CBC from 1973 to 1996. The actuarial incidence rates of developing CBC at 5, 10, 15, and 20 years were 3%, 6.1%, 9.1%, and 12%, respectively, corresponding to .6% annual risk. This is commonly reported as an approximately 1.5-fold to 2-fold increased risk for subsequent CBC compared with the general population. Approximately 40% of CBC diagnoses occurred within 1 to 4 years of the first breast cancer diagnosis, 30% between 5 and 9 years, and 30% at ≥10 years.

However, there is evidence that the population-wide incidence of CBC may be changing, influenced mainly by improvements in management of the index cancer. The updated SEER cancer registry program from 1973 to 2000 demonstrates a clear downward temporal trend in incidence. This is mirrored in tumor registry reports from Sweden, Denmark, and Switzerland noting an almost 30% decrease in incidence over a 10-year period. Furthermore, a particular woman’s risk for contralateral disease may vary depending on her age at diagnosis, the hormone receptor status and treatment of her primary tumor, and her family history, among other factors. Many of these have been investigated individually in the medical literature. Table 1 lists the range of reported annual risk as affected by individual factors. There is great variability in the way in which risk is both calculated and reported, which can make interpretation and application to an individual patient very difficult. In the sections that follow, we consider each of these factors in greater detail.

Hormone Receptor Status of the Primary Tumor and Endocrine Therapy

Patients with estrogen receptor (ER)-positive tumors have been thought to be at decreased risk for the development of CBC. This is attributed mainly to the adoption of adjuvant endocrine therapy as a standard for the treatment of hormone receptor–positive patients. Several large population-based analyses that included patients diagnosed before 1990 noted an equivalent incidence of CBC in women with ER-positive and ER-negative tumors, while a 30-year SEER database analysis found that the rate of CBC has decreased by about 3% per year since 1985, mainly in women with ER-positive index tumors. This corresponds with the timing of widespread adoption of tamoxifen therapy. In a large population-based study in Sweden, the risk for CBC was equivalent for ER-positive and ER-negative patients, but in the ER-positive patients, the increased risk was mitigated by adjuvant endocrine therapy. More recent SEER data from 1992 to 2004, as well as data from the Geneva Cancer Registry over a similar time period, have noted an approximately 1.5-fold to 2-fold increased risk for CBC when the initial tumor is ER negative compared with ER positive. The absolute incidence does vary depending on the population studied and ranges from .2% to .65% annually for patients with ER-negative disease and from .1% to .4% per year in patients with ER-positive tumors.

An Early Breast Cancer Trialists’ Collaborative Group review of randomized adjuvant trials reported that after 15 years of follow-up, the use of tamoxifen for approximately 5 years reduced CBC risk by 39% among women with ER-positive or ER-unknown breast cancer. In women with ER-positive ductal carcinoma in situ, the incidence of CBC was decreased by half by tamoxifen. Aromatase inhibitors appear to confer an even greater protective effect; the 10-year CBC rate was 3.2% in the anastrozole arm of the Arimidex, Tamoxifen, Alone or in Combination trial, compared with 4.9% in the tamoxifen arm. Women who were treated with endocrine therapy ultimately had a lower risk for CBC that all women with breast cancer diagnoses.

Additionally, the types of CBC that the 2 groups develop appear to be different. In the Swedish study, patients with ER-negative first tumors were 4 times more likely to develop ER-negative second tumors than ER-positive tumors. In contrast, patients with ER-positive first tumors had an equal chance of developing either type of subsequent breast cancer. Multiple analyses of other large population databases have corroborated this finding. In ER-positive patients, the use of adjuvant endocrine therapy decreases the incidence of subsequent ER-positive but not ER-negative cancers. This decrease is most pronounced in the first 5 years after diagnosis of the first cancer, raising the possibility that adjuvant hormonal therapy may postpone rather than prevent the development of some CBCs.

Molecular Subtypes and Tumor Characteristics

The variability in reported risk conferred by an ER-negative primary tumor may be partially attributable to the heterogeneity of ER-negative breast cancers, which can...
include triple-negative disease, human epidermal growth factor receptor 2 (HER2)/neu-positive disease, and cancers that are ER negative but progesterone receptor (PR) positive, and thus still amenable to antihormonal therapy. Some studies have attempted to further delineate risk by using hormone receptor status as a proxy for molecular phenotype (ER+/HER2− [luminal-A] vs ER+/HER2+ [luminal B] vs ER−/HER2− [HER2 overexpressing] vs ER−/PR−/HER2− [triple-negative]). Saltzman et al7 found that patients who were ER positive but PR negative had a slightly higher risk for CBC than those who were positive for both. Patients who failed to express both ER and PR and were HER2 negative (so called triple-negative patients) had a 1.4-fold increased likelihood of CBC. Other studies have found triple-negative breast cancer to bestow an almost 2-fold increase in risk compared with hormone receptor–positive disease.19

The role of HER2/neu overexpression as a risk factor for metachronous CBC is less clear. Large prospective trials of trastuzumab for HER2-positive disease report a .25% per year incidence of CBC in the control arms over a 4-year follow-up period.20,21 Data from both SEER and the California Cancer Registry showed that HER2 overexpression was associated with increased risk for CBC only when it was combined with negative ER and PR status, and then it resulted in a 2-fold increased risk for CBC compared with patients with ER-positive and PR-positive tumors.7,19

Lobular histology, medullary histology, positive nodal status, and high histologic grade have all been observed with varying degrees of consistency to confer a mildly increased risk for CBC. The data on invasive lobular carcinoma histology and risk are contradictory.5,9,14,15,22 Invasive lobular carcinoma has traditionally been thought to confer increased risk for CBC, but 2 large recent studies (1 from SEER data) failed to confirm this.5,14 Although medullary histology is rare, a study from the SEER database identified a 60% higher risk for a second primary breast cancer with this histology and postulated that young age at diagnosis might contribute to this observation.22

Analysis of SEER data on inflammatory breast cancer revealed 2-fold to 3-fold higher incidence of CBC in these patients; however, the majority of the difference was seen within the first 2 to 5 years, raising the question of whether these indeed represented new breast cancers or metastatic or recurrent disease.23

With regard to patients diagnosed with ductal carcinoma in situ alone, the incidence of CBC does not appear to differ significantly between these women and patients with invasive cancer.5,15,22

**Family History**

The influence of family history on CBC risk is complex and is affected by the number and degree of involved relatives and the presence of any known genetic mutations. In a study of >8,000 breast cancer survivors in the United Kingdom, having a single second-degree or third-degree affected relative conferred only a minimally increased risk for CBC, while having ≥1 affected first-degree relative increased the risk by 34%.14 There is much variation in the extent to which having a first-degree relative is reported to affects one’s risk, with most studies suggesting a 1.5-fold to 2-fold increase in risk. Having multiple first-degree and second-degree relatives with breast cancer appears to confer a 2-fold to 3-fold increase in risk.14,15,24

The age of both the proband and the affected relative appear to have some influence on the incidence of CBC in these patients. The Women’s Environmental Cancer and Radiation Epidemiology Study evaluated BRCA-negative women aged ≤55 years and found that the 10-year cumulative risk for CBC in patients with any affected first-degree relative was 8.6%. However, in patients aged 30 to 35 years at diagnosis with a similar family history, the 10-year risk was 14.7%.24 In the same vein, data from the German Consortium for Hereditary Breast and Ovarian Cancer found that BRCA-negative women with strong family histories who were diagnosed at ≥50 years of age did not have a higher incidence of CBC than the general population of breast cancer survivors.25

The highest incidence of CBC is seen in when both the relatives and the patient were diagnosed at <45 years of age, a situation that was associated with a 2.5-fold increased risk. Some studies have also found that having any first-degree relative with bilateral disease confers a 10-year cumulative risk of up to 15.6%; however, this association has not been universally demonstrated.10,22,25,26

**BRCA Mutation**

It is well known that the BRCA1 and BRCA2 germ-line mutations confer an increased lifetime breast cancer risk of 56% to 84%.27,28 These patients are also at increased risk for metachronous contralateral cancer.29 The cumulative risk for CBC 25 years after first breast cancer was reported to be 47.4% among >2,000 patients from families with BRCA1 or BRCA2 mutations in the German Consortium for Hereditary Breast and Ovarian Cancer.30 Members of families with BRCA1 mutations had a 1.6-fold higher risk for CBC than members of families with BRCA2 mutations. However, more rigorous analysis of this population has found that the magnitude of this risk is modified by age at diagnosis of the first breast cancer. For BRCA-positive women diagnosed at ≥50 years of age, the 10-year CBC rate was found to range from 8.4% to 10.8%. In contrast, the 10-year CBC rate for carriers aged <40 years was as high as 28.3%.31 Importantly, unlike for BRCA-negative breast cancer survivors, the CBC risk does not appear to level off over time, so that at 25 years, the cumulative risk in women diagnosed with their first breast cancer at <40 years of age is 62.5%.30,31 Prophylactic oophorectomy is thought to reduce CBC risk by half.32
Age at Diagnosis

Younger age of diagnosis has been demonstrated to be a risk factor for CBC in a number of population-based studies.6,8,9,15,22,33 In a study of SEER data from 1975 to 2006, Nichols et al8 noted early and late incidence peaks near ages 30 and 70 years, respectively, with higher incidences noted in young patients with ER-negative tumors. The highest risk was seen in patients diagnosed at <30 years of age, with estimated annual CBC rates of .45% and 1.26% after ER-positive and ER-negative cancers, respectively. Between 40 and 50 years of age, the estimated annual rates fall significantly to .24% to .26% per year for ER-positive and .45% to .53% per year for ER-negative primary tumors, although they remain elevated above baseline. The rates do not remain constant for individual patients but fall by about .5% with each yearly increase in age.8,34 Furthermore, it appears that young women with ER-negative tumors are almost twice as likely to develop new ER-negative tumors (vs ER-positive ones) than their older counterparts.9

These estimates represent the higher end of the spectrum, however. Because older data do not take into account BRCA mutation status, analysis of young patients during time periods before routine testing was performed inevitably produces higher estimates of risk. Furthermore, many of these patients did not benefit from risk-reducing adjuvant therapies that have since become standard. Indeed, SEER reports from 1998 to 2003 reveal a cumulative 5-year CBC rate of only .5% for young women (aged <50 years) with ER-positive first primary tumors and a .9% rate for young women with ER-negative cancers.6,33 A recent estimate based on data from 4 cancer registries demonstrated a cumulative CBC risk of 4.5% over 10 years in known BRCA-negative women aged <55 years.24

Race and Ethnicity

Although African American women are known to have a lower baseline risk for breast cancer, multiple population-based analyses have found that once diagnosed with an index breast cancer, this group has a 20% to 50% higher incidence of metachronous contralateral disease than Caucasian women, when corrected for age and hormonal status.5,6,9,19,22 The CBC risk in Asian/Pacific Islander and Hispanic women is noted to be increased in some studies and decreased in others, so the influence of race in these situations is less clear.5,6,19

Chemotherapy

The Early Breast Cancer Trialists’ Collaborative Group meta-analysis of chemotherapy trials found the 10-year CBC rate to be only 2.2% among the 14,250 women who received multiple-drug chemotherapy, but the reduction in incidence attributable to chemotherapy was small. In subgroup analysis, the benefit was seen maximally in women aged <50 years, in whom the incidence was decreased by 25%.16

Although fewer long-term data are available on HER2/neu-directed therapy, the results from the Herceptin Adjuvant Breast Cancer trial, NSABP31, and NCTCG N9831 found that at 5 years, the incidence of CBC was halved in the treated group.20,21 As with hormonally directed therapy, only long-term studies will show whether this is a true decrease in incidence or simply a postponement.

Contralateral Breast Cancer in Men

Men with primary diagnoses of breast cancer are at significantly higher risk for developing new contralateral malignancies compared with the general population, although it is unclear whether their risk is higher than that of a woman with primary breast cancer. SEER data from 1973 to 2000 found that men who were diagnosed with their first cancers before age 65 years were twice as likely as their older counterparts to develop new breast cancer, as were men who had received radiation. This is likely to reflect the high rate of genetic mutation in this population, which is not evaluated in the SEER database.9

Conclusions

The incidence of CBC has decreased both in the United States and Europe over the past 30 years, and this is at least partially attributed to advances in adjuvant therapy of the primary cancer. Annual risk for the typical postmenopausal woman with ER-positive breast cancer is estimated at .1% to .4%. Age, hormone receptor status, family history, and adjuvant treatment all affect risk, and it is unclear exactly how all those factors interact to influence an individual woman’s chances of developing contralateral metachronous disease. Additionally, it does not appear that a woman’s lifetime risk remains constant but may be attenuated by time, especially in patients who are young (aged <50 years) at diagnosis. It is important to consider genetic testing in appropriate patients, because this has significant implication for risk management. In the absence of genetic mutation, women who are younger (aged <35 years) at diagnosis, with a strong family histories and ER-negative primary tumors, appear to be at the highest risk for CBC.

References