Perspective

Risk of asynchronous contralateral breast cancer: multiple approaches for a complex issue

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In 2013, an estimated 232,000 new cases of invasive breast cancer will be diagnosed among women in the US (1). In the past few decades, breast cancer survival has increased significantly, with about 95% of patients still alive 5 years after diagnosis, and 77% alive after 15 years (1). This is due to the development of more sensitive screening methods that detect cancer early as well as improved treatment regimens. In 2012, it is estimated that about 2.9 million women were currently alive that had been previously diagnosed with breast cancer (2). An important health issue for these women involves the risk of being diagnosed with a second cancer. The second cancer could be a recurrence of the initial cancer in the same breast (ipsilateral recurrence), a new cancer in the same breast (ipsilateral second primary cancer) or a new cancer in contralateral breast [asynchronous contralateral breast cancer (CBC)]. CBC accounts for about 50% of all secondary cancers diagnosed among patients with primary breast cancer (3).

In the February 2013 issue of the *Journal of Clinical Oncology*, Reiner *et al.* assessed the risk of CBC among breast cancer patients who had a family history of breast cancer, but who were negative for BRCA 1/2 mutations (4). Study participants were recruited from a population based case-control study (WECARE) using data from four cancer registries in the US and one cancer registry in Denmark. A total of 708 CBC cases were individually matched with 1,399 unilateral breast cancer controls on year of birth, year of diagnosis, cancer registry and race. The women were diagnosed with primary breast cancer between 1985 and 2000, and were 54 years or younger at diagnosis. The study results showed that the 10-year cumulative risk of CBC increased from 4.6% among women without BRCA gene mutation and no family history of cancer to 15.6% among women without a BRCA gene mutation and with a first-degree relative diagnosed with bilateral breast cancer. The 10-year cumulative risk of CBC was 18.4% among women with a BRCA1 or BRCA2 mutation.

This study was very important because it was the first to disentangle the effects of BRCA mutation and family history on risk of CBC; showing that women with a family history of breast cancer were at increased risk for CBC even if they are BRCA 1/2 mutation negative. This is essential to understanding the epidemiology of CBC. Other studies including those using the population based SEER data also found significant increases in the risk of developing CBC among breast cancer patients after 10 years, ranging from 4% in a general population of primary breast cancer cases to 44% among cases with BRCA mutations (5-7). These figures suggest that the risk for developing CBC among primary breast cancer cases, while modest for women without BRCA mutations and/or family history of breast cancer, is not trivial, and multiple approaches will be needed to adequately address the problem. These approaches must include primary prevention by understanding and modifying risk factors, secondary prevention through routine, high quality screening as well as tertiary prevention to maintain quality of life by addressing mental health issues.

First, a significant amount of research has been devoted to characterizing the different options available to women for risk reduction/prevention. Reiner and several other researchers characterized the risk factors associated with developing CBC including young age, family history, BRCA mutation, breast density and treatment modality (4,5,8). Few of these risk factors are modifiable, however several

other options for prevention have been documented. These include contralateral prophylactic mastectomy (CPM), chemoprevention with Tamoxifen or aromatase inhibitors, and prophylactic radiation of the contralateral breast (9-12). Each of these prevention modalities has associated risks, sometimes significant, which must be carefully weighed in relation to its benefit in order to prevent inappropriate use.

For instance, several studies in the US have documented a recent increase in the rates of CPM among women with early stage primary cancer, even among women with no family history and/or BRCA mutation (13,14). Several studies have also documented significant reduction in risk of CBC among women given tamoxifen (15,16), but in other studies the protective effect was observed only in ER-positive tumors (17). More research is needed to identify which group of women will benefit the most from each specific prevention modality. It is also important to quantify the survival advantage as well as financial cost associated with each method. A recent study quantified the mean quality-adjusted life-years (QALYs) associated with contralateral prophylactic mastectomy compared with routine screening and found only minor differences; CPM provides 21.22 QALYs compared with 20.93 for routine surveillance for 45-year old women (18). More research is therefore needed to guide current clinical practice regarding the sub-group of women that can reap the most benefit from specific risk reduction strategies, since not all approaches will be equally beneficial for all women.

Second, women who have been diagnosed with a primary breast cancer will benefit from frequent, systematic high-quality screening to ensure that any subsequent cancer diagnosis is captured early. It is generally accepted that frequent clinical examination is needed together with screening. However there is considerable debate over the most appropriate screening modality (mammography or MRI), the duration of screening (starting at 6 months until 10 years or perpetually after initial diagnosis) or the frequency of screening (yearly or biannually) (19,20). A recent study found that within a year of mammography screening, breast cancer diagnosis among women with prior breast cancer was 10.5 per 1,000 screens compared with 5.8 per 1,000 screens in women without prior breast cancer (21). However, false positives and interval cancers were high among women with prior breast cancer, especially among younger women and those with dense breasts.

A recent meta-analysis on the use of MRI for contralateral breast cancer screening concluded that although contralateral lesions were detected in a significant number of women that was missed by mammography (incremental cancer detection rate for MRI was 4.1%), MRI sometimes could not reliably differentiate benign from malignant changes (22). This may lead to over-treatment, which, in a population of women with a prior cancer diagnosis, may have important implications for survival and quality of life. Regardless of the screening modality, the evidence in support of early and frequent screening is clear. Schootman *et al.* [2006] compared women with CBC diagnosed at early versus late stages, and found that women diagnosed in stages 0-1 had 81% better survival compared with women diagnosed in stages II-IV (23). Therefore, more research is needed to assess the optimal modality, frequency and intensity of screening that will be most effective for detecting true CBC cases at the earliest stages.

Third, some research studies have documented the mental health impact of a primary breast cancer. A recent study observed that 23% of breast cancer patients reported symptoms of post-traumatic stress syndrome related to their cancer diagnosis (24). However, there is no published article assessing any type of mental health issue related to a CBC diagnosis. Despite the lack of attention to this issue, a recent survey of cancer survivors found that about 60% of 1-year survivors had moderate to severe fears about cancer recurrence (25). If the goal is to improve survival while maintaining a decent quality of life among CBC patients, mental health assessment and treatment, including counseling for women at high risk, has to be a part of the strategy.

Finally, a sophisticated approach to primary breast cancer treatment, and increasingly breast cancer prevention, involves the approach of risk stratification. This requires a clear understanding of the epidemiology and pathobiology of the disease, including an assessment of which risk group will benefit from which risk reduction or treatment strategy. The use of genetic analysis to identify susceptibility genes, and the use of biomarkers to provide clues about disease development and progression in CBC are areas where more research is urgently needed.

In summary, as the population of the United States ages and treatment becomes better at keeping women with breast cancer alive for longer, CBC will become an increasingly important public health issue. It is already a reality for women with family history of bilateral breast cancer or BRCA 1/2 mutations. The knowledge gained in the past several decades regarding cancer treatment and prevention must also be applied to better understanding the pathogenesis of CBC. These should drive clinical decisions

about when and how to screen, how to reduce risk, who should get which treatment, and how mental health issues must be integrated into routine CBC clinical care.

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