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EDITORIAL – BREAST ONCOLOGY

Contralateral Prophylactic Mastectomy and Survival: An Ongoing Challenge

Isabelle Bedrosian, MD[1] and Kathy Yao, MD[2]

[1]Department of Surgical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX; [2]Pritzker School of Medicine, NorthShore University HealthSystem, University of Chicago, Evanston, IL

As use of contralateral prophylactic mastectomy (CPM) continues to increase, the need to demonstrate oncologic benefit to patients undergoing this procedure becomes ever more important. Whereas CPM has consistently been shown to reduce the incidence of second, contralateral breast cancer events, demonstrating survival benefit from CPM has been more challenging. In this edition of the *Annals of Surgical Oncology,* Kruper et al. report on their attempt to answer this question by using data from SEER, the Surveillance, Epidemiology, and End Results database. They evaluated the outcome of 26,526 women who underwent CPM and 138,826 patients who underwent single mastectomy. After propensity score matched analysis, they found CPM was associated with improved disease-specific survival [hazard ratio (HR) 0.86, 95 % confidence interval (CI) 0.79–0.93] but a much greater improvement in overall survival (HR 0.76, 95 % CI 0.71–0.81); this pattern was seen in almost all subsets of patients examined. Since CPM decreases the risk of contralateral breast cancer, one would expect that CPM would have more of an effect on survival from breast cancer, that is disease-specific survival, as opposed to overall survival, which measures general overall health.

They also found survival benefit to CPM across all stages of disease and across both estrogen receptor (ER)-positive and ER-negative populations.

Additionally, when they removed the women who would have benefitted the most from CPM, those women who had contralateral breast cancer, the HR for disease-specific and overall survival did not change. They conclude that the reported survival benefits seen for CPM are the result of selection bias.

Like many large observational databases, SEER has a number of shortcomings which are reflected in the results presented by Kruper and colleagues. SEER is not a national population registry, and patient movement in and out of registry zones will limit long-term data collection. SEER also does not collect family history and mutation status, thus limiting the ability to adjust for variables that affect the likelihood of contralateral breast cancer. Importantly for this study, SEER does not contain information on adjuvant hormonal therapy or chemotherapy, HER2 status or comorbid conditions; therefore, patients were not matched on several important variables that affect survival. Consequently, regardless of the use of propensity score matched analysis to balance the cohorts, the inability to account for known prognostic and therapeutic variables in the model limits the ability to minimize bias and distinguish subsets where survival association with CPM may be present.

The conclusion that Kruper et al. put forward, namely, that bias is a key issue in the selection of patients for CPM, has also been raised in prior publications similarly using large observational databases.[1,2] In a retrospective study from the Cancer Research Network, Herrinton et al. reported that CPM was associated with a 4 % absolute decrease in breast cancer mortality compared with women not undergoing CPM.[2] However, much like the Kruper study, Herrinton and colleagues showed CPM to also improve overall survival, with a 7 % absolute decrease in all-cause mortality, thus raising concern that the CPM cohort represented a healthier group of women. Such women would have been more likely to also receive more aggressive treatment for their index malignancy, and this aggressive treatment, rather than the CPM, could have

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I. Bedrosian, MD
e-mail: ibedrosian@mdanderson.org

accounted for the improvement seen in breast cancer related mortality. In our own work using both SEER and the National Cancer Data Base, effects of bias can clearly be seen. Using the National Cancer Data Base, where only overall survival data are available, the unadjusted HR was 0.55 but increased to 0.88 once multiple patient and treatment factors were adjusted for.[1] Working in SEER, we were able to demonstrate the effect of health bias by stratifying cohorts by age and examining the association between CPM and noncancer mortality.[3] In women between 50 and 60 years of age, we noted CPM to be associated with both improvement in cancer-specific survival and noncancer survival, and in women over age 60, we saw CPM-associated improvement in noncancer survival but not in cancer-specific survival. Collectively, these data clearly underscore the health selection that occurs as women seek out CPM and the challenges of carving out meaningful associations between CPM and cancer outcomes using large observational datasets.

Does a particular subgroup derive a survival benefit from CPM? Those who potentially stand to benefit are patients with a high risk of contralateral breast cancer and few competing risks for their survival from either their index malignancy or from other comorbid conditions. It is relatively easy to obtain information on a patient's comorbidities and cancer relapse rates, but estimating a patient's contralateral breast cancer risk is more difficult. Many factors influence this risk, including family history, presence of a germline mutation, and age at index diagnosis, as well as the hormone receptor status of the index tumor, underscoring the role of adjuvant endocrine therapy for both treating the primary malignancy and reducing risk for a second breast cancer. Many of these risk factors are interdependent, creating additional complexity when trying to predict for the risk of contralateral breast cancer, and no model is available that considers all of these risk factors, thus making accurate prediction of contralateral breast cancer risk a real clinical challenge.

In a recent SEER study, the estimated 5 year risk of contralateral breast cancer for a 50 year old woman with an ER-positive tumor was 1.3 per 100 women, compared with 6.5 per 100 women for a 25 year old woman with an ER-negative tumor.[4] The effect of age and hormone receptor status on contralateral breast cancer risk were also reported by Kurian et al.[5] who showed that women with a hormone receptor–negative index cancer had a nearly tenfold increase in risk of having a second hormone receptor negative cancer compared with the general population. This risk increased to 169-fold over the general population if the woman was also under age 30 at diagnosis. These associations among age, ER status, and breast cancer risk, however, are not consistent across the literature. According to the Early Breast Cancer Trialists' Collaborative Group analysis, the annual risk of contralateral breast cancer among women who did not receive endocrine therapy was 0.5 %, which would mean that the expected cumulative 5 year risk of contralateral breast cancer for patients with ER-negative breast cancer would be 2.5 %.[6] Also, a SEER study from 2003 reported essentially the same 5- and 10 year actuarial rate of contralateral cancer for <45 year-olds compared with >55 year-olds, approximately 3 and 6 %, respectively.[7] These discrepancies across the literature likely reflect differences in controlling for the many variables that drive contralateral breast cancer risk and underscore the importance of risk models that consider the breadth of variables known to influence this risk.

The role of family history in estimating contralateral risk is even less well studied than the effect of age or ER status, particularly for young women who have been diagnosed with cancer. In the WECARE study, estimates for 10 year contralateral breast cancer risk were influenced by age of diagnosis and degree of relationship to an affected relative and ranged from 5.4 to 23.7 %.[8] These data included women with both ER-positive and ER-negative first cancer cases, thus making it challenging to determine the contralateral breast cancer risk independently of the use of adjuvant endocrine therapy.

In our evaluation of the SEER data, when we considered some of the factors that increase contralateral breast cancer risk and used approaches to try to minimize health bias, we were able to show that young women with early-stage, hormone receptor negative breast cancer have improved cancer-specific survival associated with CPM, with no benefit of CPM noted on noncancer mortality.[3] This subset comprised less than 10 % of the breast cancer population, illustrating the fact that most women do not derive a survival benefit from CPM. Similarly, Brewster et al., using data from The University of Texas M.D. Anderson Cancer Center and matching patients across treatment, prognostic, and health variables, reported a disease-free survival association with CPM in women with hormone receptor negative, but not those with hormone receptor positive, breast cancer.[9] Although both these studies are retrospective, and thus with obvious limitations, they suggest there may be small subsets of women who do benefit from CPM. Ideally, this question would be resolved prospectively in a randomized clinical trial. However, given the ethical considerations of such a trial, it is not likely to occur in the near future, if at all.

Considering the complexity of the issues surrounding CPM and survival, the paucity of unbiased, prospective data on the subject, and the widespread media attention to "double mastectomies," it is easy to see why many women have misperceptions of their contralateral cancer risk and believe that CPM will improve their survival.[10,11] These observations highlight the need for accurate patient-

centered decision tools and models that will facilitate shared decision-making between the patient and physician about the decision to undergo CPM. These tools/models need to adequately inform patients about the risk of contralateral cancer, the fact that surgical choices do not influence the risk of distant relapse and overall survival, and the risks associated with CPM, such as operative complications, negative effects on body appearance, and longer recovery. They will need to integrate a breadth of factors, including patient age, comorbidities, tumor stage and phenotype, number and degree of affected relatives, and opportunities for nonsurgical risk reduction, with the ultimate goal of providing much greater accuracy of potential survival benefit for CPM for each individual breast cancer patient. Most importantly, these tools/models need to align patient goals with objective data so that patients can make truly informed decisions that provide the most decisional satisfaction and lessen anxiety and stress for patients. Such efforts to reduce CPM where it is not warranted, coupled with attempts at identifying the small subsets at highest risk for contralateral breast cancer and who thus might potentially benefit from surgical prophylaxis, are important next steps to move the field forward.

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