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Contralateral Prophylactic Mastectomy: Mind the Genetics

TO THE EDITOR: In the November 20, 2007, issue of the *Journal of Clinical Oncology*, Tuttle et al¹ delineate the current landscape in the extent of surgery for early-stage breast cancer in the United States. Despite the limitations of lack of genetic testing data, this report has important clinical implications for physicians, patients, society, health systems, and industry. The data of the Surveillance, Epidemiology and End Results database for breast cancer patients treated in the United States are clear. They show a dramatic increase in the rate of contralateral prophylactic mastectomy (CPM) among women with unilateral breast cancer. This rate was significantly increased from 4.2% in 1998 to 11.0% in 2003. In this population-based study, the rate of breast-conserving surgery was also increased from 56.1% in 1998 to 59.7% in 2003, whereas the rate of unilateral mastectomy was decreased. How can this trend be explained? Will this trend impact European and other countries with a high prevalence of breast cancer?

Women who undergo unilateral surgery for early breast cancer are known to live with the fear of increased risk of developing a second primary in the contralateral breast.² This fear led to the introduction of CPM in early 1970s, which gradually gained popularity with the increasing attention to bilateral prophylactic mastectomy in late 1990s.^{3,4} Tuttle et al showed that in the United States, women diagnosed with unilateral early breast cancer increasingly choose CPM to prevent contralateral breast cancer (CBC).¹ However, despite its apparent popularity, there are no randomized controlled trials to support the efficiency of CPM among all patients with unilateral breast cancer, or for the subsets of patients with family history of breast cancer, regardless, the presence of germline *BRCA1/2* mutations. Only in a recently published retrospective cohort study was CPM found to be associated with decreased breast cancer mortality.⁵

It deserves careful consideration that with the generalization of genetic testing in clinical practice, it became evident that the subset of breast cancer patients who carry *BRCA1/2* mutations faces the highest risk of developing CBC, whereas it remains unknown if noncarriers of *BRCA* mutations with a family history of breast cancer face a true increased risk for CBC.^{6,7} Moreover, it has been shown that although CPM can reduce the risk of CBC in women with a *BRCA1* or *BRCA2* mutation and a personal history of invasive breast cancer, it is bilateral prophylactic oophorectomy that can provide a survival benefit.⁷

We want to draw attention to the fact that the inclusion of genetic testing in the pretreatment diagnostic work-up of patients with breast cancer and a family history of breast/ovarian cancer allows rational decision making toward individualized surgical treatment decisions.^{8,9} Today, in the era of evidence based medicine, when cancer management evolves toward more personalized approaches, the option of prophylactic surgery offered to women with a family history of breast cancer should be evidence-driven and rationally guided by genetic testing, with adequately informed patients taking active roles in decision making.^{10,11} Molecular genetics helps tailor treatment decisions to optimize therapeutic results and minimize unnecessary harms, and this complex management should be undertaken by experienced teams.¹²⁻¹⁴

We think it is time to start rethinking the unconditional generalization of radical surgery practices such as CPM without offering patients the opportunity for genetic testing and counseling. Moreover, unbiased prospective studies are definitely needed to evaluate the CPM and precisely define which subsets of patients with inherited predisposition to breast cancer might benefit, and by which type of prophylactic surgery.^{8,15}

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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IN REPLY: Using the Surveillance, Epidemiology, and End Results cancer registry, we reported that the rate of contralateral prophylactic mastectomy (CPM) increased by 150% from 1998 to 2003 in the United States.¹ We appreciate the interest and comments from Briasoulis and Roukos regarding our study. We found that the CPM rate increased through the end of our study period with no diminution in the incline of the curve (Fig 2¹). Based on 2003 data, we estimate that about 10,000 patients with unilateral breast cancer undergo CPM in the United States each year. Also, since we excluded patients whose initial treatment was not CPM, but later underwent CPM, the rate is probably higher than we reported.

We agree with Briasoulis and Roukos that prophylactic surgery should be "rationally guided by genetic testing," but acknowledge that other nongenetic factors should be considered in choosing CPM. For example, for patients who have been treated with chest radiotherapy (eg, Hodgkin's disease) and subsequently develop breast cancer, CPM may be a rational choice because of the marked increased risk of contralateral breast cancer. Moreover, many patients have contraindications for breast-conserving treatment (tumor size, multiple tumors, or contraindications for breast radiotherapy) and require mastectomy. For some mastectomy patients, CPM may be appropriate especially if the contralateral breast is large, creating balance and symmetry difficulties after unilateral mastectomy. Also, a large remaining breast after unilateral mastectomy complicates symmetric reconstructive techniques. Finally, the presence of dense breast tissue on mammography, strong family history without an identified genetic mutation, lobular carcinoma in situ, and atypical hyperplasia may also be considered in the decision-making process.

Although CPM is effective in preventing contralateral breast cancer, it does not improve breast cancer mortality.²⁻⁴ Still, many women with small unilateral breast cancer amenable to breast-conserving treatment request bilateral mastectomy despite the potential risks and

complications. On the other hand, other women with advanced unilateral breast cancer desire CPM when, in fact, their risk of systemic metastases exceeds their risk of contralateral breast cancer. We agree with Briasoulis and Roukos that prospective studies evaluating decision-making processes leading to CPM are lacking. Specifically, research is needed to develop models and instruments to elucidate the decision-making processes among patients with breast cancer and their surgeons. This research is important and timely because it may ultimately provide decision aids for patients and their physicians.

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