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Commentary

Male Breast Cancer: A Study in Small Steps

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Disclosures of potential conflicts of interest may be found at the end of this article.

In this issue of ***The Oncologist***, two articles discuss the management of men with breast cancer or a predisposition to breast cancer. Masci et al. describe clinicopathologic characteristics, treatment, and outcomes of 91 men with invasive breast cancer diagnosed between 2000 and 2013 [1]. Mitri et al. describe *BRCA* mutation testing results and BRCAPRO modeling in 146 men presenting for genetic evaluation at the MD Anderson Cancer Center between February 1997 and September 2011 [2]; 48 of the men studied had a history of breast cancer.

Male breast cancer (mBC) is understudied because of its rarity. Consequently, management of mBC is based largely on extrapolation of data from studies of female breast cancer. Emerging data, from the study by Masci et al. [1] and others [3, 4] suggest that there are several unique characteristics of male breast cancer compared with female breast cancer, including a higher rate of hormone positivity, lower HER2 positivity, and more advanced presentation at diagnosis. A large retrospective international study of male breast cancer, presented at the San Antonio Breast Cancer Symposium in December 2014, included 1,483 patients and noted rates of ER and HER2 positivity comparable to the analysis presented by Masci et al., as well as a similar distribution of grade and nodal status. Interestingly, in both studies, although a majority of patients had stage I or II disease, relatively few patients underwent lumpectomy (9% in the series by Masci et al. and 4% in the international series).

Of note, Masci et al. described both treatment patterns and patient outcomes [1]. In their study, 22% of patients received therapy with an aromatase inhibitor. Of 14 patients who received an aromatase inhibitor as adjvuant therapy, 6 (42%) developed recurrent disease. In addition, in men treated with aromatase inhibitors in the metastatic setting, only 1 of 9 patients had stable disease for more than 12 months. None of the patients received concomitant therapy with a gonadotropin-releasing hormone (GnRH) agonist. Preclinical data suggest that men do not have as complete suppression of estrogen with aromatase inhibitors as seen in women. Furthermore, aromatase inhibitors may increase circulating testosterone, leading to an increase in androgen available for conversion to estrogen. Consequently, although aromatase inhibitors are the treatment of choice for postmenopausal female breast cancer, it is generally not considered the standard for mBC. Clinical data suggest lower efficacy for aromatase inhibitors as sole hormonal therapy [5, 6], although the addition of GnRH analogs may be beneficial. In the absence of clinical trial data supporting the efficacy of aromatase inhibitors in mBC, tamoxifen should be considered the standard of care.

Masci et al. also noted a high rate of second cancers among men with breast cancer in their series [1], a finding also seen in other studies [7, 8]. Eighteen percent of patients developed a second malignancy, most commonly prostate cancer (31%) and colon cancer (19%). Although these cancers are both common in elderly men, this finding highlights the issue of hereditary cancer syndromes in men diagnosed with breast cancer. Unfortunately, in this study, only a small percentage of patients studied underwent *BRCA* mutation testing (11 patients were tested; 1 was found to have a mutation in *BRCA1*, one had a *BRCA2* mutation, and one had a *BRCA1* variant of uncertain significance). Although many of these patients were not treated in the modern era, these findings highlight the need for genetic evaluation and counseling for all men presenting with breast cancer.

Clinical practice guidelines currently recommend *BRCA* mutation testing for all men diagnosed with breast cancer. Also in this issue of ***The Oncologist***, Mitri et al. described their work validating the BRCAPRO model in men presenting for genetic evaluation, including those with a diagnosis of breast cancer [2]. The BRCAPRO model takes into account personal history of cancer, first- and second-degree family history, age at cancer diagnosis, current age or age at death of included individuals, ethnicity (including Ashkenazi Jewish ancestry), and history of risk-reducing surgeries. The BRCAPRO model has been validated as a tool for determining risk of carrying a *BRCA* mutation in multiple settings [9–11] but has not been studied specifically in men. In this series, 33% of the evaluated male patients had a personal history of breast cancer [2]. The cohort also included men with a personal history of prostate and pancreatic cancer, those with a family history of cancer, and those with a known *BRCA* mutation in a family member. This study is the first validation of the BRCAPRO model in men being seen by a medical genetics professional. The authors found that the model had acceptable sensitivity, specificity, and positive and negative predictive value in the study cohort. A valid risk-prediction model could potentially be

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used to more accurately assess which patients should proceed to genetic testing; therefore, these results provide reassurance regarding the validity of BRCAPRO in men and may have clinical implications for some patients, particularly those with a family history of breast cancer or with a personal history of pancreatic or prostate cancer. It should be noted, however, that a large portion of patients included in this study were men with a personal history of breast cancer and with a known *BRCA1* or *BRCA2* mutation in the family; for such patients, genetic testing should be performed regardless of prior probability based on risk modeling.

Although both studies provide valuable information [1, 2], these two papers also serve as a reminder of the gaps in our knowledge about mBC. No randomized clinical trials to date have evaluated treatment of men with breast cancer. We continue to extrapolate from data from female patients to make clinical treatment decisions, despite growing evidence of biological differences between male and female breast cancer. The use of aromatase inhibitors in the treatment of male breast cancer is a case in point. Furthermore, the genetics of male breast cancer remains poorly described. The data show clearly that *BRCA2* and, to a lesser extent, *BRCA1* increase risk of male breast cancer, but a large portion of breast cancer in men remains unexplained by mutations in these genes. Additional genes, such as *PALB2, CHEK2, PTEN*, and *BRIP1* have also been implicated in mBC [11–15], and other risk factors have been described [16]. With the recent advent and availability of multigene panels for genetic testing in those with a suspected hereditary cancer predisposition, it is likely that additional genetic mutations that increase risk of mBC will be identified; however, much remains to be learned about the etiology and genetic basis of male breast cancer. An international consortium of investigators, led by the European Organization for Research and Treatment of Cancer (EORTC) and the Translational Breast Cancer Research Consortium (TBCRC), recently presented the results of a retrospective study in 1,483 patients with male breast cancer that included central pathology review [3]. This group has recently initiated a prospective cohort study of male breast cancer that will include the collection of DNA and tumor samples and hopefully will lead to great strides in our understanding of male breast cancer biology, genetics, treatment, and outcomes. This effort will also provide the infrastructure on which to build future clinical trials in mBC.

In conclusion, much can be learned from small single-institution studies in male breast cancer; however, individual studies represent only small steps toward our understanding of this rare disease. International collaborative efforts are necessary to make the great strides needed to discern the unique biology, genetics, and optimal treatment for male breast cancer and to best serve our patients with this disease.

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Editor's Note: See the related articles on pages 586 and 593 of this issue.