

Problems (and solutions) in the study of male breast cancer

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Abstract

Owing to its rarity, large-scale retrospective studies in male breast cancer have suffered from the small numbers of cases available for study from any one center. Here we describe our experience in establishing a large collection of male breast cancers in tissue microarray format suitable for biomarker analysis by immunohistochemistry.

Male breast tissue lies posterior to the nipple on the chest wall. It is generally considered non-functional; while lactation is physiologically possible it is very rare, requiring specific hormonal cues.¹ Although not exposed to the same cyclical hormones as the pre-menopausal female breast, male breast epithelium is not immune to DNA damage, and with the acquisition of both oncogenic activation and compromised DNA repair mechanisms, carcinoma formation can occur. Breast cancer in men is rare however, accounting for about 1% of all breast cancers. Current estimates put this at around 300 cases in the U.K.² and 1900 in the U.S.³ annually. The most common type of breast cancer in men is ductal carcinoma of no specific type (NST) followed by papillary carcinoma, the latter being an uncommon female breast cancer subtype.⁴ Lobular carcinoma is uncommon, an observation originally thought to be a consequence of the scarcity/lack of lobules in most male breasts; however, given modern understanding of the genesis of the lobular carcinoma morphology through inactivation of E-cadherin,⁵ the explanation is likely to be more subtle. Retrospective studies of male breast cancer, in particular those defining prognosis, have suffered from the small numbers of cases available from any one center. Our research institute in the U.K. is affiliated to the Leeds Teaching Hospital NHS Trust, currently the largest teaching hospital in Europe, yet we generally see no more than five cases of male breast cancer annually. Thus a significant problem in studying male breast cancer is accruing sufficiently large numbers to allow robust biological studies. Although reasonably large numbers of male breast cancer cases have been identified from tumor registries; for example, 241 in the Veterans Administration tumor registry⁶ and 111 from the archives of the Mayo Clinic,⁷ only 65 and 72 patients, respectively, had complete follow-up

data and pathology blocks available for immunohistochemistry. The largest male breast cancer series evaluated 778 cases collected over 40 years from the U.S. Armed Forces Institute of Pathology.⁴ This descriptive study investigated frequencies and distribution of histopathological subtypes compared to female breast cancer. Large collections like this would be a very valuable resource to study male breast cancer but contact with the corresponding author revealed that the group has since dispersed and the blocks were not available (personal communication). To tackle this problem, we adopted a co-ordinated multi-center approach. Following ethical approval from the Leeds (West) Research Ethics Committee, Leeds, U.K. (06/Q1205/156), we identified 129 cases from our local archive. In addition to these cases, we approached pathologists within the U.K. and overseas and named this the Male Breast Cancer Study Consortium. We have experienced a tremendous amount of goodwill toward accruing this collection with all of the groups we contacted willing to provide cases. Throughout this process a key element has been direct engagement with histopathologists. On receipt in our laboratory, cases were anonymized and hematoxylin-eosin sections prepared. Following inspection of these sections, 0.6 mm cores were removed from the most representative tumor area and assimilated into tissue microarrays (TMAs). This provided a means of preserving the longevity of the resource, thus maximizing the amount of information that can be obtained. Donor blocks were returned promptly to the original centers. To date we have collected a total of 386 cases from six different countries. In addition we have collected comprehensive clinical details from as many cases as possible, including: date of diagnosis and surgical procedure, age, tumor size, grade, type, TNM stage, type of treatment (chemo/endocrine therapy, adjuvant/neoadjuvant), nodal status, recurrence, family history, and survival. We have used our TMAs to analyze over 25 biomarkers including those associated with hormone receptors, proliferation, angiogenesis, apoptosis, tumor taxonomy, and therapeutic markers. Publications are in the pipeline. A collection of this nature has allowed a much-needed, large-scale study of male breast cancer. As male breast cancer is rising,⁸ our collection represents an important resource for future testing of new biomarkers that may have prognostic or predictive significance, as well as for comparative studies with matched female breast cancer, something that has not been possible with smaller collections owing to the well-recognized heterogeneity of breast cancer. Finally, it has been reported recently that the Breast International Group and North American Breast Cancer Group have joined forces to develop an International Male Breast Cancer Program to pool specimens, and clinical and epidemiological data, with the long-term goal of facilitating clinical trials for male breast cancer.⁹ We applaud

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Key words: male breast cancer.

Acknowledgements: we are very grateful to members of the Male Breast Cancer Consortium who have kindly donated material, which has made this collection possible. Our male breast cancer program is supported by the Breast Cancer Campaign.

Received for publication: 15 April 2010.

Accepted for publication: 15 April 2010.

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Rare Tumors 2010; 2:e28

doi:10.4081/rt.2010.e28

this initiative. With male breast cancer prognosis and treatment derived exclusively from female breast cancer studies, together these collections should increase our knowledge of male breast cancer and potentially identify factors that might affect outcome, and may also inform treatment selection.

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