Cancer Risk Management Decisions of Women with BRCA1 or BRCA2 Variants of Uncertain Significance

To the Editor:

One possible result of BRCA1 and BRCA2 genetic testing is a variant of uncertain significance (VUS). VUS are changes in the BRCA genes that have unknown clinical significance and it is unknown if these gene changes are associated with an increased risk of cancer. Overall, approximately 7% of individuals who undergo BRCA1 and BRCA2 genetic testing will be found to have a VUS. However, this frequency varies depending on the patient’s ethnicity and can be as low as 5–6% among individuals of European ancestry and as high as 21% among individuals of African-American ancestry (personal communication with Myriad Genetic Laboratories). Although there are some strategies to aid clinicians in determining the clinical significance of a VUS, including cosegregation studies, co-occurrence with a deleterious mutation, evolutionary data, and protein function studies (1), often no real definitive conclusions can be made. This means that the patients and their providers must make decisions regarding risk management for cancers that the patient may or may not be at increased risk for. The objectives of this study were to characterize the risk management strategies undertaken by women who are found to have a BRCA1 or BRCA2 VUS.

Women who underwent genetic testing for the BRCA1 and BRCA2 genes at M. D. Anderson Cancer Center between 1997 and 2007 and were found to have a VUS were included in the study. Medical records were reviewed retrospectively to determine the patients’ personal and family history of breast and ovarian cancer. If the patient had a personal history of breast or ovarian cancer, her cancer treatment decisions, including surgery and hormone therapy were noted. Chemotherapy and radiation decisions were not included, as currently these decisions are not influenced by genetic test results. Breast and ovarian cancer screening practices, tamoxifen use, and breast and ovarian prophylactic surgery decisions were also recorded. Cancer screening and prophylactic surgery decisions were noted only after the patient received their BRCA1/2 VUS test result.

Screening and prophylactic surgery decisions were compared with the patients’ family history of cancer to determine whether the patients elected to pursue procedures that would not otherwise be recommended based on their family history. Family history was defined as a first, second, or third degree relative with breast and/or ovarian cancer. All patients included in the study had BRCA1 and BRCA2 genetic testing through Myriad Genetic Laboratories, which is responsible for determining whether a result will be classified as positive, negative, or VUS. The institutional review board at The University of Texas M.D. Anderson Cancer Center (Houston, TX) approved the study protocol.

Of the 58 women identified for inclusion in the study, one had a personal history of breast and ovarian cancer, 42 had a personal history of breast cancer, 7 had a personal history of ovarian cancer, and 8 had no personal history of breast or ovarian cancer. The median age at genetic testing was 50 years (range 31–77 years) for women with a personal history of breast cancer, 62 years (range 50–71) for women with a personal history of ovarian cancer, and 41 years (range 33–50) for women with no personal history of breast or ovarian cancer. The median age of cancer diagnosis was 45 years (range 27–67) among women with breast cancer and 59 years (range 43–63) among women with ovarian cancer. The majority (29 of the 43; 67%) of the breast cancer diagnoses were stage 0, I, or II, whereas the majority (6 of the 8; 75%) of the ovarian cancer diagnoses were stage III or IV. Finally, the majority (49 of the 59; 83%) of the women included in the study had some family history of breast and/or ovarian cancer.
The breast and ovarian cancer risk management decisions of the study population can be seen in Table 1. Of the women with a personal history of breast cancer, 11% underwent contralateral prophylactic mastectomy and 8% underwent prophylactic TAH/BSO after receiving their VUS genetic test result. Only 33% of the patients who chose to have prophylactic TAH/BSO had any family history of ovarian cancer. Thirty-nine percent of the women with a personal history of breast cancer and intact ovaries underwent ovarian cancer screening, to include at least annual CA-125 blood tests, while only 14% of those undergoing the screening had any family history of ovarian cancer.

Overall, these data indicate that 35% (15 of the 43) of the women with a personal history of breast cancer chose to undergo risk management procedures that would not otherwise be recommended based on their family history. This is significant compared to women with a personal history of ovarian cancer or with no personal history of breast or ovarian cancer who chose risk management strategies that would otherwise be recommended based on their family history (p = 0.02).

One possible explanation for the increased uptake of risk management procedures is that the patients may be interpreting their VUS test result to mean that they have an increased risk of cancer. Two previous studies demonstrated that while the majority of patients correctly recalled receiving uncertain results, many still interpret the result as a genetic predisposition for cancer (2,3). One of these studies also reported that the patients who interpret their VUS test result to mean that they have an increased risk of cancer are more likely to undergo prophylactic surgery (3), but in contrast to the present study the authors did not describe what type of prophylactic surgery was performed, nor did they look for differences in risk management decisions between breast and ovarian cancer patients and the patients with no history of breast or ovarian cancer. Our study demonstrates that there are differences in the risk management decisions of these groups, which cannot be fully explained by the misinterpretation of the test result.

The discrepancy in risk management decisions observed between breast cancer patients compared with ovarian cancer patients may be explained by cancer stage and prognosis. Seventy-five percent (six of the eight) of the women included in this study were diagnosed with stage III or IV ovarian cancer, which only has an 18–51% 5-year-survival rate (4), whereas 68% of the women with a personal history of breast cancer had stage 0, I or II breast cancer, which has an 81–100% 5-year-survival rate (5). Given their poor prognosis, ovarian cancer patients with a BRCA1 or BRCA2 VUS may be less likely to worry about future cancer risks and screening and surgery for those risks when compared to breast cancer patients with a BRCA1 or BRCA2 VUS.

### Table 1. Breast and Ovarian Cancer Risk Management Decisions

| Risk management decisions | Cancer history | Breast (N = 43) (%) | Ovarian (N = 8) (%) | None (N = 8) (%) | p |
|---------------------------|---------------|---------------------|-------------------|-----------------|---|
| **Breast**                |               |                     |                   |                 |   |
| Contralateral prophylactic mastectomy or bilateral mastectomies | 3 (3/27; 11)* | 0 | 0 | – | |
| Family history of breast cancer | 1 (1/3; 33) | NA | NA | – | – |
| Prophylactic mastectomy, not otherwise indicated | 2 (2/26; 8) | 0 (0/7) | 0 (0/6) | 1.0 | – |
| Chemoprevention (tamoxifen) | NA | 0 | 1 (1/8; 13) | – | – |
| Family history of breast cancer | NA | NA | 1 (1/1; 100) | – | – |
| Chemoprevention, not otherwise indicated | NA | 0 | 0 | 1.0 | – |
| **Ovarian**               |               |                     |                   |                 |   |
| Prophylactic BSO | 3 (3/39; 8)* | NA | 2 (2/8; 25) | – | – |
| Family history of ovarian cancer | 1 (1/3; 33) | NA | 2 (2/2; 100) | – | – |
| BSO, not otherwise indicated | 2 (2/38; 5) | NA | 0 (0/6) | 0.74 | – |
| Patients with ovaries intact | 36 (36/43; 84) | NA | 6 (6/8; 75) | – | – |
| Ovarian cancer screening | 14 (14/36; 39) | NA | 2 (2/6; 33) | – | – |
| Family history of ovarian cancer | 2 (2/14; 14) | NA | 2 (2/2; 100) | – | – |
| Ovarian cancer screening, not otherwise indicated | 12 (12/34; 35) | NA | 0 (0/4) | 0.20 | – |
| Any, not otherwise indicated | 15 (15/43; 35)* | 0 | 0 | 0.02 | – |

*Three women had bilateral mastectomies for bilateral breast cancer and 13 women had surgery before they received their genetic test result.

†Four women had BSO before they received their genetic test result.

Does not equal total number of incidences of screening or prophylactic surgery not otherwise indicated, as one individual underwent both contralateral prophylactic mastectomy and ovarian cancer screening.
In summary, our analysis of the cancer risk management decisions of women with a BRCA1 or BRCA2 VUS revealed that women with a personal history of breast cancer appear to engage in screening and risk reduction options that would not otherwise be recommended based on their family history of cancer, while women with a personal history of ovarian cancer or no personal history of breast or ovarian cancer do not engage in this same behavior. Prospective studies are needed to determine possible causes for this difference.

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