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Influence of Radiotherapy and Tamoxifen on Contralateral Cancer Risk in Women with Hereditary Breast Cancer

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Women with breast cancer arising as a consequence of germline mutations in BRCA1 or BRCA2 are known to be at significant risk of contralateral breast cancer (CBC). Our group has reported that approximately 25% of Ashkenazi women undergoing breast conserving treatment for hereditary breast cancer develop CBC within 10 years. Examination of factors influencing contralateral risk will provide insight into prevention strategies for unaffected women with BRCA mutations at risk for hereditary breast cancer. To evaluate these factors, the funded study is evaluating the impact of tamoxifen and radiotherapy on CBC risk. In this reporting period, the human subjects protocol was developed and approved by the local IRB and the relevant DOD authority. Tamoxifen treatment data were acquired and analyzed for the 305 women in the original 1980-1990 dataset. Mutation carriers taking tamoxifen were found to have a non-significant reduction in contralateral risk (0.57 [95% CI: 0.07-4.57; P=0.6]). These data will be presented at the 2002 Era of Hope meeting. Dataset expansion continues per the SOW. 422 additional Ashkenazi women with invasive breast cancer (1990-1992) and available tissue have been identified, and clinical data collection is underway. Further cases are being identified in the 1992-1994 time period. (196 words)

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Introduction

Although women with BRCA1 or BRCA2 mutations constitute a small minority of breast cancer patients overall, in some populations (e.g. Ashkenazi Jewish women with breast cancer before age 50), an appreciable proportion of cancers are BRCA-related. Women with germline mutations are at substantially increased risk of breast cancer, both de novo and contralaterally after a first cancer diagnosis. The study of factors influencing the development of contralateral cancer in such women may provide important clues as to the risks and benefits of certain prevention strategies for unaffected individuals. Exposures that promote the development of contralateral disease should likely be avoided by both affected and unaffected heterozygotes, while interventions that reduce contralateral risk are obvious candidates for deployment in the primary prevention arena. Unfortunately, survival and selection biases may confound the study of variables modulating contralateral risk in prevalent groups of women with BRCA mutations, who are usually identified through familial cancer clinics. The present study, employing a retrospective anonymized design, circumvents those biases and allows the collection of a relatively unselected group of women with BRCA mutations for the examination of factors influencing contralateral risk.

Body

To accomplish the aims of this project, we are extending our previous work examining outcomes in Ashkenazi women with invasive breast cancer. In our original publication, we reported local and systemic outcomes in Ashkenazi women with hereditary breast cancer (associated with BRCA founder mutations) treated with lumpectomy and adjuvant radiotherapy between 1980 and 1990. These women were compared to Ashkenazi women without mutations undergoing breast conserving therapy in the same time period. A retrospective, anonymized design was employed to address the difficult human subjects issues relevant to germline predisposition research.

As the first step in the current investigation, local IRB and Department of Defense HSRRB approval was obtained for extension of the original protocol to allow records review and tissue acquisition from Ashkenazi women receiving treatment (either lumpectomy and radiation, or mastectomy with or without adjuvant radiation) for invasive breast cancer between 1990 and 1995 at Memorial Sloan-Kettering. Final approval to initiate this expansion was received at the end of August 2001, and contracting was completed by 30 October of that year. In accordance with the Statement of Work agreed upon, from October 2001-March 2002, institutional databases were reviewed to identify women diagnosed with invasive breast cancer in that interval from 1990-
1992. Hospital registration databases were cross-referenced to identify women of self-reported Jewish religious preference (an effective surrogate for Ashkenazi ancestry in our patient population). Since March 2002, in accordance with the Statement of Work, clinical data are being gathered by review of medical records, and tissue specimens are being identified through review of pathology databases. Over 800 Jewish women were treated for invasive breast cancer at Memorial Sloan-Kettering in 1990, 1991, and the first half of 1992 (approximately half of the proposed study period). Of these, 422 have pathology material available, the remainder having received primary surgical therapy elsewhere. To date, medical records review has been completed on 100 of these subjects. As per the approved anonymized design, genetic testing and data analysis will not take place until the last 9 months of the funding period, and therefore information regarding the outcomes of women with or without mutations in the expanded ascertainment is not yet available.

Although not specifically included in the funded proposal, we have also taken this opportunity to return to the original group of 305 patients, incorporate their tamoxifen treatment data into the study database, and perform a preliminary analysis of the effect of tamoxifen on contralateral risk in this subset of the final study group. The abstract, which is included in the Appendix, has been accepted for a platform presentation at the upcoming Era of Hope meeting in September 2002. Briefly, of the 28 mutation carriers identified in that group of women, information regarding tamoxifen therapy was available for 25. Of 5 mutation carriers taking tamoxifen, 1 developed CBC, compared to 6 of 20 mutation carriers not taking tamoxifen. The hazard ratio for CBC among tamoxifen users compared to non-users was 0.57 [95% CI:0.07-4.57; P=0.6] Thus, in this small number of cases, tamoxifen appeared to decrease the risk of CBC among mutation carriers, but this reduction was not statistically significant. This further illustrates the critical need to expand the dataset and thus include more mutation carriers in the analysis.

In the short time since we have begun the clinical data collection for this project, a number of obstacles have become evident. First, the institution converted to an electronic medical records system in 1998. Although older (pre-1992), paper records are archived at an remote location, the accessibility of these records has been a problem. To date, we have been unable to recover 45/183 (24%) records that we have requested. Records from 1992 on appear to be more reliably available, and we are therefore concentrating our efforts on expanding the dataset using these patients. Although follow-up time may be shortened slightly by this maneuver, and the numbers of contralateral events may be reduced somewhat, we believe that this is the most efficient means by which to gather the
necessary numbers of cases to accomplish the study aims. There have been no other unanticipated difficulties conducting this trial.

Key Research Accomplishments

None as yet

Reportable Outcomes

No outcomes are yet reportable in manuscript form. As described above, the supplemental analysis of the original dataset has been accepted as a platform presentation at the upcoming Era of Hope meeting, but the conclusions are too preliminary to warrant publication.

Conclusions

The research is in progress, and thus conclusions would not be appropriate at this time, although preliminary analysis of a subset of the data is supportive of one of the hypotheses of the study, that tamoxifen may reduce the contralateral breast cancer risk in women with BRCA mutations who are receiving the drug as adjuvant treatment for their first breast cancer.

References

No directly relevant references have been published since the application.

Appendices

1. Abstract for Era of Hope Meeting, September 2002
Impact of Tamoxifen on the Risk of Metachronous Contralateral Breast Cancer (CBC) in Women with Germline Mutations of BRCA1 or BRCA2.
Robson M, Satagopan J, Boyd J, Offit K. Memorial Sloan-Kettering Cancer Center, New York, NY.

Background: Women with hereditary breast cancer due to germline mutations of BRCA1 or BRCA2 are known to be at high risk for second primary cancers, especially CBC. One case-control study has indicated that the risk of CBC is reduced in mutation carriers taking tamoxifen, but a subset analysis of the Breast Cancer Prevention Trial did not clearly indicate such a benefit.

Subjects and Methods: A retrospective anonymized design was employed. Women of Jewish religious preference undergoing breast conservation therapy for invasive breast cancer between 1980 and 1990 were identified from review of clinical databases. Paraffin-embedded tissue and follow-up information was available for 314 women, 305 of whom were successfully genotyped, after anonymization, for the Ashkenazi founder mutations BRCA1 185delAG and 5382insC, and the BRCA2 founder mutation 6174delT. Clinical outcomes in women with or without mutation have previously been reported (JNCI 1999;91:2112-2117). In this report, we describe the impact of tamoxifen on contralateral breast cancer risk in this population.

Results: Germline mutations were detected in 28 women (9.2%). Information regarding tamoxifen use was available for 25 women. Of 5 mutation carriers taking tamoxifen, 1 developed CBC, compared to 6 of 20 mutation carriers not taking tamoxifen. The hazard ratio for CBC among tamoxifen users compared to non-users was 0.57 [95% CI: 0.07-4.57; P=0.6]

Conclusions: In this small series, tamoxifen appeared to decrease the risk of CBC among mutation carriers, but this reduction was not statistically significant. Expansion of the dataset is continuing. Supported by DAMD17-01-1-0325.