

Author's response to reviews

Title: Factors Associated with Testicular Self-Examination among Unaffected Men from Multiple-Case Testicular Cancer Families

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Author's response to reviews: see over

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Dear Editor and Reviewers,

Thank you very much for your thorough and thoughtful review of our manuscript entitled, "Factors Associated with Testicular Self-Examination among Unaffected Men from Multiple-Case Testicular Cancer Families" (MS# 1288265450247833). As appropriate, we have indicated where in the text the changes can be found after each response and have also highlighted these changes in yellow in the revised manuscript. We appreciate your further consideration of our manuscript and look forward to hearing back from you.

A handwritten signature in black ink, appearing to read 'Susan T. Vadaparampil', followed by a vertical line.

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Reviewer 1

Introduction section

Comment (Introduction): In the introduction section more than two pages are dedicated to pointing out the relevance of this study, unfortunately with little success. What one expects is that the introduction section ends with one or more hypotheses to be tested or, in a more orienting study, one or more clear research questions to be answered. Although three numbered 'aims' are mentioned, this is however not the case.

Response: The current study was intended to be an exploratory study of psychosocial and behavioral variables associated with TSE among a high risk group of individuals. The original behavioral sub study from which these data were obtained was not powered specifically to conduct hypothesis testing; rather, it was designed as a pilot data collection in a previously-unstudied population to provide some initial insights into this group of individuals that could serve as the basis for future studies that are adequately powered to conduct hypothesis testing. We apologize for the confusion related to the aims of the study. Those aims relate to the larger multidisciplinary protocol of which this study was one small part. We hope that addition of the words "We present an analysis of a *subset of data*...."; "The primary aims *of the larger study* include...." and the phrase "*current exploratory sub-study*" help to convey the relationship of the current study to the larger protocol.

Comment (Methods): This study is done in a selected group men of certain high risk TC. How they are selected to participate in the described NCI study stays unclear. This means there is potentially a firm selection bias.

Response: As described in our methods section, participants were recruited through a variety of mechanisms: "Participants were ascertained through multiple referral mechanisms: 62/99 (63%) from healthcare providers (primarily physicians and genetic counselors), in response to mailed recruitment letters; 15/99 (15%) from the Testicular Cancer Resource Center (TCRC) (<http://tcrc.acor.org/>), a patient advocacy group,; 13/99 (13%) self-referred through our study website (<http://familial-testicular-cancer.cancer.gov>); and 9/99 (10%) from other sources." (page 6, paragraph 1)

We agree that these recruitment methods may contribute to selection bias. In the Discussion Section we have elaborated on this issue by addressing how this group may differ from those who did not participate in such a study: "Additionally, men **volunteering** to participate in a study of familial TC may be more aware of and concerned about TC. Thus, the rates of TSE may be higher in this study population than men with a similar history not participating in such a study. Similarly, these men may be more knowledgeable about TC and have differing beliefs and psychological responses to TC." (page 17, paragraph 1). We have added the word volunteering to emphasize that the source of bias may be directly related to the voluntary nature of participation in the study. The fact remains, however, that ours is a unique study population. No one has, either previously or presently, assembled a cohort of multiple-case testicular cancer families of this size and studied it in a comprehensive, systematic, multi-disciplinary fashion. We do not claim that the families we enrolled are representative of all such families in the United States, but until someone develops a practical strategy for accomplishing that goal, our study population is, and will remain, the gold standard.

Comment: As TC-patients do their TSE about 2-3 times a year, it caused surprise that was chosen for the dichotomy in men with TSE 6 or more times a year, and men who do it less than 6 times a year. This means there is potentially a firm medical bias.

Response: In our review of the literature, we have not been able to find a citation that provides a definitive estimate for the frequency of TSE among TC patients. As discussed below in response to Reviewer 2's comment, we performed a sensitivity analysis using various cut points including $\leq 3x$ a year versus $\geq 4x$ a year, and $\leq 7x$ versus $\geq 8x$ a year, and our results remain essentially unchanged.

Comment: Somatic variables; in this ethological-focused design only genes were considered, leaving out (considerable) occupational carcinogenic exposures like solvents, known to be expressed in family occupational patterns as well.

Response: The majority of items regarding risk perception (e.g., perceived susceptibility) were not specifically worded to identify or imply genetics as the cause of the TGCT case-clustering in the family. Our team felt that, in considering psychosocial and behavioral factors related to TSE, it does not matter whether a familial cluster is caused by genes, environmental exposures or some interaction of the two. Operationally, members of these families are aware that there is a "familial predisposition," and we are simply asking whether that knowledge alters their screening behavior.

Comment (Psychological variables): An enormous amount of psychosocial variables were evaluated by means of self report questionnaires. Although in the introduction the Health Belief Model (HBM) is mentioned, it is not clear how this theoretical framework is related to the testing of all these variables.

Response: For each HBM variable presented in the introduction, we have specifically explained how the variable was operationalized, and described how the final scores were calculated in the Measures Section (pages 6-10). This is a standard approach used in the behavioral and psychological literature to present how study variables are related to a proposed theoretical model. To further illustrate how HBM variables were operationalized, we have added examples of questions specific to each HBM variable assessed in the current study (page 8)

Comment (Design): The testing of so many variables without clear hypotheses, is what is usually referred to as a fishing expedition. One may catch some significant results but it is impossible to draw sound conclusions.

Response: This aspect of the study was carefully planned prior to data collection to assess the association of HBM variables with TSE behavior in a unique population that had never before been investigated. Our design provides important evidence that this was our intent from the outset of this study. For example, all of our measures related to benefits and barriers were specific to TSE (e.g., "I am too busy to do TSE"). Had this been a fishing expedition, these questions would have been asked in a more general way to allow their use in additional analyses with other behavioral outcome variables of interest. Furthermore, as noted above, we never anticipated and do not claim that the results we have identified are "sound conclusions." This was a pilot study aimed at collecting the data required to inform subsequent, hypothesis-driven research. Given that design, we do not believe it appropriate to hold our report to the higher standards expected of a more rigorous research strategy.

Reviewer 2

Comment: As the authors acknowledge, the definition of “regular TSE” is problematic and the authors’ choice to use 6 months as the cutoff seems reasonable. However, would the results have been different if you had used a slightly different cutoff? Some comment on this, including examination of the data and reporting of these results would be helpful to give credibility to the outcome.

Response: As suggested by the reviewer, we have re-run our analyses using two additional cutoffs ($\leq 3x$ vs. $\geq 4x$) and ($\leq 7x$ vs. $\geq 8x$), and the results of the bivariate analyses and the multivariable logistic regression models are statistically unchanged compared with the original model (i.e., $x < 5x$ vs. $\geq 6x$). The only difference noted was that in the $\leq 3x$ vs. $\geq 4x$ comparison, Internal Locus of Control was significant at the bivariate level. However, it was no longer significant in the in the final logistic model. The $\leq 7x$ vs. $\geq 8x$ analyses show that the pattern of bivariate results was similar to the original model. However, only one variable (physician recommendation) remained significant in the final logistic model. We have included this information in the Discussion Section (pages 18-19, paragraph 2).

Comment: The point that cancers found by TSE, rather than by symptoms, would be more amenable to treatment should be better substantiated. Using evidence from other cancers may be necessary. This would strengthen the argument for looking at this outcome, given there are no strong recommendations for TSE or defined screening interval.

Response: Based on our review of the literature, we could not find data that directly support the belief that TSE-detected cancers are more amenable to treatment compared with cancer detected due to symptoms. However, our rationale for examining TSE behaviors in this group is that high-risk individuals are often placed in the challenging situation of making health care decisions in the absence of viable general population guidelines. We have argued by analogy to the hereditary breast and ovarian cancer literature, in which breast self examination is recommended, despite the absence of data proving that cancers detected by self-examination are more amenable to treatment:

“In addition, the American Cancer Society recommends that men with known risk factors such as family history seriously consider performing TSE regularly. This approach to modifying general population early cancer detection practices for high-risk populations is not unique to men with a familial risk of TC. For example, the National Comprehensive Cancer Network recommends routine breast self-examination (BSE) for women at increased risk of hereditary breast and ovarian cancer (HBOC) [17], despite randomized controlled trial data refuting the efficacy of BSE in reducing breast cancer mortality [18]. In addition to the possibility that TSE recommendations may reduce chemotherapy-related morbidity if it increased the proportion of early-stage TC diagnosed in high-risk men, there may also be further benefit in providing at-risk individuals with a management strategy that involves them directly in their own care, and gives them an enhanced sense of control over their lives [6].” (page 4, paragraph 2)

Comment: What are the implications of the fact that HBM variables (other than physician recommendation) were not predictors in the multivariate model? Should other

approaches are considered? Might knowledge, benefits and barriers be related to having received a physician recommendation?

Response: We have added more information specific to the utility of the HBM in understanding TSE in the Discussion Section (page 15, paragraph 1). We have also added discussion about the possibility of using other theoretical frameworks in the Discussion Section (page 17, paragraph 1). It is possible that receiving a physician recommendation may be associated with knowledge, benefits, and barriers. However, from a theoretical perspective, and in much of the cancer screening literature to date, physician recommendation is generally considered to be a potent factor that is independently and positively associated with enhanced screening behavior.

Comment: Missing from Cancer Worry in Table 3.

Response: We have included Cancer Worry in Table 3.

Comment: Ensure formatting is consistent throughout.

Response: We have reviewed the entire manuscript for formatting.

Comment: The MHLC as used consists of 3 scales, not scale items (p.8).

Response: We have corrected this mis-statement.