Title
Re: Vitamin A Analogue for Breast Cancer Prevention: a Grade of F or Incomplete?

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CORRESPONDENCE

Re: Vitamin A Analogue for Breast Cancer Prevention: a Grade of F or Incomplete?

We were annoyed by the disparaging title given to the editorial written by S. Piantadosi (1) on our breast cancer prevention trial with fenretinide, which was published in the November 3 issue of the Journal (2). First, we feel that the title is not consistent with the editorial content itself (who gives an F grade to a “well designed and conducted study”?). In addition, the title is in sharp contradiction with Journal policy to publish only articles of major importance. Our disappointment was increased after learning that, as a result of this title, several media outlets have dismissed our study as being one of poor quality. In the current publicity-dominated era, the choice of this title is at best unscrupulous, if not dictated by reasons that have little to do with science.

It is a shame that the irresistible temptation of adding a sensationalist title has overcome a more reasonable review of our study, while we think we have honestly addressed the limitations of our work in the paper. Contrary to Dr. Piantadosi’s doubts, we had clearly stated in the article that, among the dozen possible interactions, we tested only the one between fenretinide treatment and menopausal status because this interaction has strong biologic support. This support came not only from our previous observations that plasma insulin-like growth factor-I (IGF-I) levels behaved with the same pattern following fenretinide treatment [refs. (27) and (28) of our paper], but also from the well-established notion that premenopausal and postmenopausal breast cancer are different diseases that receive different treatments and have different risk factors, some of which, like body mass index, interact in a qualitative manner with menopausal status [refs. (39–41) of our paper].

Since we believe that biologic plausibility should drive statistics and not vice versa, we feel that leaving this interaction untested would have missed some very important information. It is argued that our study was not powered to test such an interaction. Consistently, we have not recommended treating premenopausal women with fenretinide but simply suggested implementing further studies to address the new hypotheses that are generated by our study. Our prudent attitude is demonstrated by the fact that, in contrast to one reviewer’s advice, we have not pooled contralateral breast cancer and ipsilateral breast cancer events in a single figure. While this combination would have certainly provided more powerful statistical support for the benefit of fenretinide in premenopausal women, such a combined analysis had not been planned before the study was conducted.

The bottom line is that the fenretinide trial is one of the few large cancer prevention trials ever performed and is by far the largest clinical study that tests a retinoid for breast cancer prevention. Awarding an F grade to our pioneering study without any sound scientific argument is arrogant, cynical, and useless. Mortifying for the nearly 3000 women who took part in the study for an average of 8 years, for the many investigators and support personnel who gave their time and effort for such a long period of time, for the reviewers who recommended National Cancer Institute funding for three consecutive periods for a total of 9 years, and last, but not least, for the U.S. and Italian taxpayers and contributors who made the resources available.

We thought it appropriate to submit our paper to the Journal in view of the above-mentioned reasons. We are extremely disappointed by the Journal’s decision to publish our paper alongside this destructive editorial without informing us until the moment of its publication. We are sorry the Journal missed an opportunity to begin a fruitful discussion on the complex issues related to cancer prevention trials.

Note

Both the report on the “Randomized Trial of Fenretinide to Prevent Second Breast Malignancy in Women With Early Breast Cancer” and the accompanying editorial impressed me as thoughtful presentations and discussions of the complex results reported (1,2). Why then the sensationalist title for the editorial? If this title was the one chosen by the editorialists, the Journal should have insisted on a more objective title. If the title was selected by the Journal, then shame on the Journal. Certainly the dismissal by the media of this trial as a poorly done study serves no one well. Doing clinical research is hard enough without our most cited (best?) journal in cancer research resorting to “yellow journalism.”

Frank L. Meyskens, Jr.

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Veronesi et al. did. Careful reading, time to digest, and perhaps even e-mail might have prevented their perversion. In any case, I will ignore the ad hominem in their letter in favor of the following comments. Dr. Meyskens objects to the title alone, but oddly didn’t reconsider it, even after finding the content “thoughtful.” His concerns are obviated below.

First, the title. It clearly interrogates “vitamin A analogue” (fenretinide) as a drug, not the fenretinide trial or the work of the authors. Since when is querying the efficacy of a drug considered “sensationalist” and “yellow journalism”? It is only because the trial was well done, as I said explicitly, that one can make inferences about the drug. The reasonableness of this title is further emphasized below.

Second, the methodologic danger as I see it is that the findings of the trial with respect to the treatment—covariate interaction will be dismissed outright by many. This dismissal is because of the small magnitude, marginal significance, and post hoc pedigree of the test. Those who take such a harsh view would rate fenretinide as a proven failure. The editors of the Journal correctly saw this as an issue, which is why a trial statistician was asked to comment. My editorial argued against dismissal, again explicitly.

Third, are Veronesi et al. (or Meyskens) more heavily invested in the reality of a beneficial fenretinide effect than the manuscript suggests? It is hardly proven by the putative biologic mechanism—but it is given support. It is my opinion, a statement of which is the right and purpose of an editorial, that additional empirical data will be required to establish the truth of the observation. Hence, my assessment that the tale of fenretinide is incomplete. Even Veronesi et al. say in their complaint that we need further studies to address the new hypothesis. So, asking if fenretinide is a failure or if the information is merely incomplete captures the essence of the issue.

Finally, I am not responsible for the poor reading habits of journalists. Perhaps with these points emphasized, Veronesi et al. can regain their composure, recognize a serious inferential issue, appreciate a favorable review of their study, and continue with the important work of developing prevention strategies for breast cancer.

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NOTE

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EDITOR’S NOTE

After careful reading, we agreed that the intention of the Piantadosi editorial (1) was not to criticize the authors (Veronesi et al.), the study itself, or the analysis. In fact, the editorial endorsed the analytic methods as well as the written conclusions of the investigators. The editorial, including its title, properly emphasized the evaluation of the drug, fenretinide, based upon what was present in the Veronesi et al. article. We believe that it properly described the evaluation of the primary analysis, as well as the subset analysis of data. We regret that some readers may have misconstrued the editorial title. We hope that the response by Piantadosi, and the editorial itself, will clear up the misunderstanding. Furthermore, we want our readers to know that the Journal neither writes the editorials nor imposes the choices for titles on the editorial writers. Our policy allows only for changes required by our style guide. Beyond that, we give authors of editorials rein to attack issues—not people. We feel that the Piantadosi editorial met that standard. It covered the strengths and pitfalls of subset analysis and interpretations of qualitative interactions clearly, and endorsed the authors’ approach on both counts. We agree with Piantadosi that the study by Veronesi et al. offers important leads for the prevention of breast cancer. We differ with Veronesi et al. regarding the media coverage of their article. We found that the media interpreted this study positively and their coverage was quite favorable. (News citations are available on request.)

Erratum: “Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer,” by Gail et al. [J Natl Cancer Inst 1999;91:1829-46 (Issue 21)]. The column labeled “Relative risk factor” in Table 2 has an error in the eleventh entry from the top, which corresponds to a woman whose first live birth occurred before age 20 and who had one affected first-degree relative. The incorrect relative risk, 1.00, should be replaced by the correct number, 2.61. The Journal regrets the error.

Erratum: “Antiquity of Epstein-Barr Virus, Sjögren’s Syndrome, and Hodgkin’s Disease—Historical Concordance and Discordance” (letter), by Altschuler [J Natl Cancer Inst 1999;91:1512-3 (Issue 17)]. The author’s last name was inadvertently misspelled and should read as above. The Journal regrets the error.