Reviewer’s report

Title: An association study of digitoxin use and cancer.

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Reviewer: Dr Richard Havlik

Level of interest: A paper whose findings are important to those with closely related research interests

Advice on publication: Accept after revision, which I do not need to see

In this report the authors test a hypothesis concerning digitalis use in patients and less cancer incidence. They utilize a rather unique cohort of those with digitoxin levels measured in the blood paired with available cancer registry data analyzed both after and importantly BEFORE the date of drug initiation. The results of some of the analyses suggest that the relationships found are more likely due to selective factors, because of apparent associations being present before medication use, while prospective results are more consistent with the original hypothesis. However, the addition of more detail about the hypothesis, interpretation of the data, and rationale for the conclusion would strengthen the report.

1. There is quite a nice introduction, which was informative for me, about previous clinical and laboratory research concerning digitalis and cancer. However, what was not well explained is the actual mechanism of why digitoxin should show more of an effect but the more commonly used digoxin form would be less. Also, it was not clear whether certain cancer types would be hypothesized to be more controlled by apoptosis than others and be more sensitive to digitalis. The references refer to prostate and breast cancer. To have designated these cancers a priori would have helped in interpreting the conclusions. My impression of cancer etiological dogma is to see each site as having a separate etiology. In fact, these were not the cancers found to be associated in the results. There is always the potential statistical bias of looking at multiple comparisons and identifying false positive associations. The authors could elaborate more on this aspect in the introduction and discussion.

2. The interpretation of the data analysis would be assisted by some additional considerations. The findings in tables 1-2 about cardiovascular disease (CVD) are very interesting. The idea that there are risk factors common to both CVD and cancer seems possible, especially for smoking, but the relationship with cholesterol or hypertension is not so clear. Reference is made to the initial findings of calcium channel blocker drugs (commonly used in those with CVD) being associated with cancer. However, others and our own group have been unable to replicate the original findings. Also, the understanding of how melanoma (reversal of relationship between tables 1 and 2) would be affected is too conjectural. Sun exposure for melanoma usually occurs many years before the onset of CVD. The discussion on these issues should be expanded.
3. The dose-response data in table 3 could be considered the strongest indication of a possible real association. The statistical test used for the trend analysis should be stated. In fact, there seems to be more of a threshold at 16 ng/ml rather than a trend, especially for kidney and all sites.

4. Finally, in terms of the conclusion it will not be possible to use digitalis in prospective clinical trials in non-CVD cases and randomization in CVD cases would be problematic. So, at best more descriptive clinical data collection will be necessary to understand possible relationships.

There are a few words that might be modified for better meaning. In the Results section of the Abstract start? should be starting?. There is a sentence that should be: This indicates that yet unknown factors exist... Also, an internal analysis, I think is better described as a dose-response analysis. In the Conclusion better to say: should be ascribed? rather than referred?. Table 1 should be: International Classification? not Code?.

Competing interests:

None declared.