Author’s response to reviews

Title: An association study of digitoxin use and cancer.

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Reply to Havlik’s comments:

1. We and others try to elucidate the molecular mechanisms behind apoptosis induction by cardiac glycosides. A recent article compares the anticancer effects of different cardiac glycosides on tumor cell lines and confirms our data that digitoxin seems to have more potent anticancer effects than digoxin. [Anticancer Drugs 2001;Jun12(5):475-83 Cytotoxicity of digitoxin and related cardiac glycosides on human tumor cells.] We include this new article as a reference and we think our present article will lose focus if we start to discuss possible effector mechanisms in dept. In our previous articles molecular mechanisms are discussed and we have them in the reference list. Multiple comparisons always give the risk of finding positive results by chance. However, the positive findings concerning leukemia and lymphoma are supported by very strong anticancer effects of digitoxin on leukemic cancer cell lines in vitro. We have not tested any renal cancer cell lines, but in the article cited above, a renal cell line is tested and found sensitive for digitoxin. We think the results we communicate are real and not chance findings due to that they are supported by other independent observations.

2. To improve the article concerning the possible effects of concomitant use of other drugs we replace reference 24 with a more recent article on the same topic. We have also expanded the discussion about the reversal relationship between table 1 and 2 concerning melanoma and other skin cancers.

3. A Cox regression analysis was performed and the continuous values for the digitoxin variables were used to test for trend. (We have included this note in the article too.

4. The future will show which studies will come. Cardiac glycosides for cancer prophylaxis will perhaps not be actual, but a cardiac glycoside (in the form of oleandrin) have already entered clinical cancer trials (in the USA).

We also thank Havlik for the suggestions to improve the language, which we have adopted.
Reply to Egesten's comments:

1. Egesten states that "the hypothesis of a protective effect from digitoxin against cancer is not supported by the study". In the next sentence he writes "In addition, digitoxin-treated patients had a higher cancer incidence already before the initiation of digitoxin treatment." Evidently, other factors have impact on the cancer risk in patients with cardiovascular disease and a study in this setting is not suitable for firm conclusions about the possible effects of digitoxin on cancer.

2. a. For leukemia/lymphoma the number of cases are: 23 in first tertile (16 ng/ml), 18 in second tertile and 12 in third tertile, the corresponding numbers for kidney/urinary tract cancers are; 33, 12 and 14. The number of cases is not large, but large enough to make as firm conclusions as the p-values indicate. (The statistical analysis used also takes into account the absolute numbers).

   b. All the digitoxin using patients were picked out by the first plasma digitoxin measurement. Some patients have several measurements, others just one or a few. We considered to use the mean value for each patient. However, many factors may contribute to why some have several and others a few measurements. More serious cardiac disease could perhaps increase the efforts to give an optimal dose and lead to more measurements. After careful consideration we chose to just use the first value as we do not think we can isolate the "digitoxin - cancer" effects better by using figures on digitoxin concentration in another way.

3. The basis for the study is information about age, sex, year and date for start on digitoxin and the digitoxin concentration in plasma. Thus, we have no data on smoking. Smoking is one of the most well known and scrutinized risk factors for cancer and we have smoking in mind during the whole work with the study. In fact, in drug - cancer risk studies, data on smoking habits are often lacking. Some of the novel findings in our present study are probably not explained by smoking, as we discuss in the article.

4. We compare digitoxin-treated patients with controls in the regard that the digitoxin treated patients take digitoxin. For the setting of our study it is no weakness that the group on digitoxin is "not well defined" with respect to cardiovascular disease. Naturally, "it is also unlikely that the controls matched for age and sex are healthy with resepect to cardiovascular disease"; actually that is what is characteristic for controls randomly picked out from the general population (extensively used in epidemiology).

5. Just about 1.1% of the cancer diagnoses in the material are based on autopsies so even if there should be difference in performed autopsies in the two groups it should not change the figures.