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Digitoxin medication and cancer; case control and internal dose- response studies

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An association study of digitoxin use and cancer.

by

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Abstract

Background: Digitoxin, in concentrations therapeutic for treatment of cardiac disease, induces apoptosis in different human malignant cell lines in vitro. Our intention with the present study was to investigate if patients on digitoxin for cardiac disease have different cancer incidence compared to the general population.

Methods: Computer stored data on digitoxin concentrations in plasma in 9271 patients with cardiac disease were used to define a user population. Age and sex matched controls from the Norwegian Cancer Registry were used to calculate the expected cancer cases for the common types of cancer.

Results: The population on digitoxin showed a higher incidence of cancer compared to the control population. However, an additional analysis showed that the population on digitoxin had a general increased incidence of cancer already before start on digitoxin. Thus, the increased cancer incidence among digitoxin users is explained by factors mutual for the occurrence of both cancer and cardiovascular disease and not to the actual use of digitoxin. Smoking is one evident risk factor for both lung cancer, as well as some other cancers, and cardiovascular disease. More intriguingly is that leukemia/lymphoma were the cancer types which stood out with the highest risk in the digitoxin population before start on digitoxin. This indicate that yet unknown

risk factors exists for cardiovascular disease and lymphoproliferative cancer.

An internal analysis revealed a relationship between high plasma concentration of digitoxin and a lower risk for leukemia/lymphoma and for cancer of the kidney/urinary tract.

Conclusion: The morbidity and mortality is high in the population on digitoxin due to high age and cardiac disease and these factors disturb efforts to isolate an eventual anti-cancer effect of digitoxin in this setting. Still, the results indicate an anti-cancer effect of digitoxin for leukemia/lymphoma and kidney/urinary tract cancers.

Prospective clinical cancer trials have to be done to find out if digitoxin and other cardiac glycosides are useful as anti-cancer agents.

Background

Cardiac glycosides have been used in the treatment of cardiac disease for more than 200 years. In most Western countries digitoxin has been replaced by digoxin and other drugs. Digitoxin is still today the most common cardiac glycoside prescribed in Norway [1]. Digoxin has a shorter elimination half life and is often regarded easier to dosage than digitoxin. However, more attention is again paid to digitoxin as a valuable cardiac drug, especially for the elderly, and perhaps its use will increase in the future [2].

Cardiac glycosides also have well known antiproliferative effects on tumor cells [3,4,5]. Some cardiac glycosides have been evaluated in short term animal models. The conclusion from these experiments was that very high probably toxic doses would be needed for obtaining anticancer effects in humans [6]. In contrast, we have found that non toxic concentrations of digitoxin and digoxin inhibits growth and induce apoptosis in different human malignant cell lines, whereas highly proliferating normal cells were not affected [7,8,9]. The apoptosis inducing capability of cardiac glycosides has recently been confirmed in other studies [10,11,12). There is a great difference in susceptibility for cardiac glycosides in different species indicating that one can not extrapolate the results from animal models into humans [4] . In our in

in vitro experiments the apoptosis-inducing effect was more potent for digitoxin than for digoxin, and for digitoxin there was a dose response pattern; the higher concentration the more apoptosis. As previous studies on cancer risk in patients on digitalis more or less exclusively concern digoxin [12,13,14,15] we have studied the possible anti-cancer effect of digitoxin in patients with cardiac disease. Thus, we wanted to examine if the strong anti-cancer effects detected in vitro were evident in vivo in a patient population on the drug for cardiac disease.

Material and Methods

In Norway patients on digitoxin usually have their plasma concentration checked shortly after the initiation of the treatment. The basis of the study is all cardiac patients ($n = 9271$, 5026 women and 4245 men) who had their first digitoxin concentration measurement carried out in the period 1986-96 at the University Hospital of Trondheim. The settlement is very stable for these patients, so our figures are not corrupted by that patients have had their plasma digitoxin measured in another hospital before. The digitoxin concentrations were measured by a radio-immunoassay method (Coat-A-Count Digitoxin, Diagnostic Products Corporation, Los Angeles, USA). The reference range for plasma digitoxin concentration at our laboratory is 15-33 nmol/l (12-25 ng/ml). The mean age for the total digitoxin population was 75.8 years (1 SD = 10.2), for men 73.3 years (1 SD = 10.3) and women 78.0 years (1 SD = 9.5). After approval of the Norwegian Data Inspectorate, the regional ethical committee and the Norwegian Health Inspectorate, the digitoxin data were linked to individual data on cancer in the population based Norwegian Cancer Registry. To study the association between digitoxin use and cancer, three different approaches were used. Firstly, a prospective design was chosen. All the digitoxin users free from cancer formed a basis cohort from the time they have their first digitoxin plasma concentration measurement carried out. This cohort was followed for the occurrence

of cancer until they died or up to December 31, 1996. The expected number of cases for each type of cancer was calculated by applying the national cancer rates matched exactly on year of birth, age and sex. The standardized incidence ratio (SIR) was calculated for all types of cancers having more than 30 expected cases. The 95% confidence intervals were estimated on the basis of the Poisson-distribution.

The second approach was a case control design where the cases constituted persons who were identified in the laboratory database to become digitoxin users. For each becoming digitoxin user one control was randomly picked out from the general population. These controls were matched by birthday and gender and they should be alive at the time when the corresponding becoming digitoxin user started on digitoxin. The Odds ratio of cancer cases before start on digitoxin was used as a risk estimate. The 95 % confidence intervals were estimated on the basis of the Mantel-Haenzel chi-square estimation. As the controls are randomly picked out from the general population matched by birthday and gender, we do not know anything about the eventual drug use in the controls. Thus, some of the persons picked out as controls in the general population might use digitoxin and other drugs. However, the frequency of digitalis users in the general population is so low that it did not corrupt our figures significantly.

The third approach was a prospective internal analysis on the cohort on digitoxin users where the risk of cancer was studied by different levels of digitoxin plasma concentration at first measurement divided in tertiles and a Cox regression analysis was carried out. The the lowest plasma digitoxin concentration (< 16 ng/ml) was set as reference in these calculations.

Results

Table 1 demonstrates a general higher cancer incidence in the population on digitoxin compared to what is expected in the general population. However, it is not clear whether the population to become digitoxin using differ from the general population already before start on the drug. Table 2 presents the results of the second approach where we wanted to examine if the persons on digitoxin had an increased risk of cancer already before they had started to take the drug. Here the actual cancer cases in the population not yet started on digitoxin (Digitoxin group) and expected cases calculated from age and sex matched controls in the general population (Control group) are presented with corresponding Odds ratio (OR) for each type of cancer. Thus, more cancer cases were among the patients to become digitoxin users than expected except for melanoma and other skin cancers. Lymphoma and leukemia are presented as a single group in the tables due to the close relationship between them. In the prospective part of the study (as presented in Table 1) for leukemia alone SIR was 1.39 (95% CI: 0.95-1.97) (31 observed versus 22.3 expected). In the comparison between becoming digitoxin users and the controls (as presented in Table 2), the Odds ratio for leukemia was 1.95 (95%CI: 1.42-2.67).

The internal analysis is shown in Table 3. For most types of cancer we could not find any association, neither for all types of cancer combined. However, a test for trend by

level of digitoxin concentration indicated a trend for protective effects of high digitoxin levels for the lymphoma/leukemia group ($p=0.008$) and for kidney/urinary organ cancers ($p=0.05$).

Discussion

The intention with the present study was to investigate whether use of digitoxin induces any changes in the incidence of cancer. One strength in our material is that we use plasma concentration measurements for defining the digitoxin using population. In previous studies drug use has been estimated by employing dispensing data or questionnaires about drug use [12,13,14]. These methods are less reliable than measuring plasma drug concentration, as neither completely account for variations in compliance nor for the existing inter-individual pharmacokinetic variability. As mentioned earlier, digoxin and other cardiac glycosides are more commonly used in many countries and the use in the earlier studies is usually not specified to just one drug, but to the digitalis group.

We found a general higher incidence of cancer among the patients on digitoxin.

This is in agreement with the earlier published studies [12,13,14,16].

These studies have just presented figures on cancer incidence after start up on the drug, as we have done in the prospective part (Table 1). For some types of cancer there are known factors contributing to both cardiovascular disease and cancer such as smoking. The general higher incidence of cancer in the cardiac population on digitoxin thus prompted us to perform the analysis presented in Table 2. These figures show that the population to become digitoxin using has an increased risk of cancer.

Thus there are factors associated with both cancer and cardiovascular disease. For some types of cancer this association may be explained by food habits, smoking and other factors. Intake of food rich in antioxidants and a favorable composition of carbohydrates, fats and proteins as well as vitamins and minerals may reduce morbidity in both cardiovascular disease and cancer [17].

Surprisingly, the leukemia/lymphoma group shows the highest Odds ratio and melanoma, less surprisingly, the lowest (Table 2). Excessive exposition to sunlight shows a positive correlation with the development of skin cancer [18].

The lower Odds ratio (OR) for the development of skin cancer could hypothetically be explained by a different life style, as people who will develop cardiac disease and subsequent become digitoxin users may be more in house and therefore not exposed to sunlight to the same extent. The high risk of lymphoproliferative cancers before start on digitoxin is more intriguing (Table 2). Microbiological agents are associated with some types of cardiovascular disease and also for the development of cancer, but whether mutual agents exists are unclear [19,20]. Our ratios are well in agreement with a previous study focusing on drug use and other factors preceding non Hodgkin lymphoma [14]. This substantiates that yet unknown common risk factors exist for the development of cardiovascular disease and lymphoproliferative cancer. A protective effect of digitoxin here is supported by a dose response pattern in the internal analysis. In addition, human leukemic cell lines in the form of Jurkat (T-cell leukemia) and Daudi (B-cell leukemia) are among the most susceptible for apoptosis induction by digitoxin treatment in vitro [8]. This further support that the SIR - (Odds ratio) ratio for leukemia of 0.70 may be a significant finding, indicating an anti-cancer effect.

It is evident that tracking anticancer effects in a population of patients with serious

cardiac disease is hampered by several factors. The mean time of digitoxin use before cancer diagnosis is just about 3 years in our material. In general studies on cancer incidence in relation to drug use may be biased by that the cancer, before detected, induces symptoms treated by the drug of study. Moreover, as patients seek medical advice for cardiac problems they are also subjected to a more careful physical examination and a tumor may therefore be detected and diagnosed soon after the start of treatment for cardiac disease, thus leading to the false impression that the drug induced the cancer. This can be avoided by introducing lag times in the analysis. However in view of the mostly unknown time course for the occurrence and initial progression of solid tumors before they become detected, the lag time applied will be arbitrary chosen. One year lag time did not have any major impact on our figures indicating that this effect has not corrupted the presented results.

Another potential confounding factor is the use of other cardiac drugs in the digitoxin group. Most likely, the use of drugs such as angiotensin converting enzyme (ACE) inhibitors, calcium antagonists and warfarin is higher in the digitoxin group than in the control group. The use of ACE inhibitors and warfarin have been associated with a decreased risk of cancer [21,22], whereas the use of calcium antagonists has been associated with an increased risk of cancer in some studies, but not in all [23]. Thus, use of these drugs might have affected the results in both directions. Unfortunately, information on concomitant drug use was not available in the database.

Chemotherapy, especially in the form of anthracyclines, may induce cardiac congestion and thus subsequent use of digitalis [24,25]. However, it seems that it is just a small fraction of all patients on digitalis who has had the cardiac disease as a result of chemotherapy, so this should not corrupt our figures too much (Table 2), but still it will counteract an eventual anti-cancer effect of digitoxin to some extent in the

analysis.

Based on theoretical assumptions it may be that the cancer incidence is not dramatically changed in patients on digitalis, but that the survival nevertheless could be affected. Our material was not suited for survival analyses due the high age of the patients and the correspondingly high mortality due to cardiac disease. Cancer patients are also prone to get their cancer diagnosis on the death certificate, even if other conditions are the direct cause of death. To make a fair analysis with focus on survival time, autopsy data for most of the patients would be required, and such data are not available [26].

Conclusion

It is evident from the present study that too many disturbing factors exist in a population with serious cardiac disease for making proper examination of possible anticancer effects of cardiac glycosides. However, our study gives some support to data from previous studies indicating a higher incidence of cancer detected in patients treated with digitalis, but this association should be referred to underlying factors inducing and/or promoting both cancer and cardiovascular disease and not the actual use of digitalis.

The possible role for cardiac glycosides in cancer treatment has to be evaluated in prospective clinical studies with cardiac glycosides as primary anticancer agents.

Acknowledgement

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Figure legends

Table 1:

Standardized incidence ratio

The standardized incidence ratio (SIR) is presented for all types of cancers having more than 30 expected cases. The cancer types are divided in the groups according to ICD-10 (International Code of Disease).

Observed = cancer cases in the population on digitoxin after start on the drug, no lag times applied.

Expected = expected cancer cases calculated by applying the national cancer rates matched exactly on year of birth, age and sex.

Table 2:

Case control study.

Digitoxin group = the cancer cases among the 9271 patients constituting the database just before start on digitoxin medication.

Control group = for each cancer case in the digitoxin group one control was randomly picked out from the general population. These controls were matched on birthday and

gender and should be alive at the time when the corresponding becoming digitoxin user started on digitoxin.

For further information see Materials and Methods

Table 3:

Internal analysis

Age-adjusted relative risks of specific types of cancer by concentration levels (tertiles) of digitoxin. A Cox regression analysis was used.

Table 1.

ICD-10	Site	Sex	Observed	Expected	SIR (95 % CI)
C50	Breast	F	57	45.7	1.25 (0.95, 1.62)
C61	Prostate	M	108	86.7	1.25 (1.03, 1.50)
C18-21	Colo-rectal	M + F	127	98.5	1.29 (1.06, 1.51)
C32-34	Lung	M + F	63	46.4	1.35 (1.04, 1.74)
C64,C65,C67,C68	Kidney, urinary	M + F	59	51.8	1.14 (0.87, 1.47)
C43,C44	Melanoma, other skin	M + F	61	49.7	1.23 (0.94, 1.58)
C81-C85,C88-C92	Leukemia/Lymphoma	M + F	53	37.5	1.41 (1.06, 1.85)
C00-C97	All sites	M + F	641	502.8	1.27 (1.18, 1.37)

Table 2.

ICD-10	Site	Sex	Digitoxin group	Control group	Odds Ratio (95% CI)
C50	Breast	F	275	232	1.19 (1.11, 1.28)
C61	Prostate	M	370	296	1.25 (1.08, 1.45)
C18-21	Colo-rectal	M + F	430	325	1.32 (1.15, 1.52)
C32-34	Lung	M + F	163	112	1.46 (1.15, 1.86)
C64,C65,C67,C68	Kidney, urinary	M + F	201	180	1.06 (0.95, 1.17)
C43,C44	Melanoma, other skin	M + F	154	191	0.81 (0.66, 0.99)
C81-C85,C88-C92	Leukemia/Lymphoma	M + F	198	117	1.69 (1.35, 2.11)
C00-C97	All sites	M + F	2435	2017	1.21 (1.15, 1.28)

Table 3.

ICD-10	Site	Digitoxin concentration ng/ml		
		<16	16-22	>22
C50	Breast	1.00 (reference)	1.04 (0.59, 1.84)	0.90 (0.48, 1.67)
C61	Prostate	1.00 (reference)	0.79 (0.51, 1.22)	0.89 (0.56, 1.40)
C18-C21	Colo-rectal	1.00 (reference)	0.97 (0.66, 1.42)	0.92 (0.61, 1.40)
C32-C34	Lung	1.00 (reference)	1.25 (0.71, 2.22)	1.06 (0.57, 2.00)
C64, C65	Kidney, urinary	1.00 (reference)	0.30 (0.15, 0.57)	0.45 (0.24, 0.83)
C67, C68	organs			
C43,C44	Melanoma, other skin	1.00 (reference)	1.16 (0.60, 2.25)	1.29 (0.65, 2.57)
C81-C85	Leukemia and	1.00 (reference)	0.67 (0.38, 1.18)	0.57 (0.30, 1.08)
C88-C92	Lymphoma			
C00-C97	All sites	1.00 (reference)	0.84 (0.71, 0.99)	0.86 (0.72, 1.02)

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Reviewers' reports

Digitoxin medication and cancer; case control and internal dose- response studies

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Arne Egesten

The background for the present study is the *in vitro* finding that digitoxin can induce apoptosis in malignant cell lines. The hypothesis was that patients under treatment with digitoxin would have a change in cancer incidence (i.e. e. protection from digitoxin against cancer) compared to controls. The hypothesis is interesting, especially in the light of previously published experimental data. The manuscript is well written and the text is easy to follow. However, there are several major concerns about the study in its present form.

Major points

1. The study shows that patients under treatment with digitoxin have a higher incidence of cancer compared to controls. Therefore, the hypothesis of a protective effect from digitoxin against cancer is not supported by the study. In addition, digitoxin-treated patients had a higher cancer incidence already before initiation of digitoxin treatment.
2. In a subgroup of digitoxin-treated patients, that is patients with a high serum-digitoxin, a decreased risk for leukemia/lymphoma ("trend for protective effect", $p=0.008$) and kidney-/urogenital cancer ($p=0.05$) was seen. Two important questions can be raised concerning these findings:
(a). How large is the group of patients having a high serum-digitoxin? How many cases of leukemia/lymphoma or kidney-/urogenital cancer could be expected in this size of group? Is the size of the group large enough to make firm conclusions with regard to statistical power?
(b). The group of patients with a high serum-digitoxin was picked out by one single measurement. Did these patients have a high serum-digitoxin continuously? Could there be other factors influencing morbidity in the group of patients with high serum-digitoxin?
3. The investigated groups have been matched for age and sex. However, other factors may increase the risk for both cancer and cardiovascular disease. Was smoking a factor taken into account in the study?

4. The study also compared digitoxin-treated patients with controls in the regard that digitoxin-treated patients have cardiovascular disease. However, treatment with digitoxin does not make this group well defined with respect to cardiovascular disease. It is also unlikely that the controls matched for age and sex are healthy with respect to cardiovascular disease.
5. Not all deceased patients were subject to autopsy. Therefore, there are likely subclinical malignancies that have not been detected in the study. Is the number of performed autopsies the same in both groups?

I believe that the paper, in its present form, is of limited interest.

Advice on publication: major revision.

Quality of written English: Acceptable

I do not have any competing or financial interests relevant to the present manuscript.

Richard Havlik

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".

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

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

Quality of written English: Acceptable

Competing interests: none declared.

4 July 2001

Authors' response to reviewers

Digitoxin medication and cancer; case control and internal dose- response studies

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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 loose 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 comparisions 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 senitive 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 regresssion 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 respect 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.