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# **Cardiac glycosides and breast cancer risk: A systematic review and meta-analysis of observational studies**

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Keywords: Epidemiology; Meta-analysis; Breast cancer; Cardiac glycosides.

Abbreviations used: HR: Hazard ratios; CIs: Confidence intervals; ER: Estrogen receptors; Mesh: Medical subject headings; OR: Odds ratio; HR: Hazard ratio; SIR: Standardised incidence ratio; RR: Rate ratio; NOS: Newcastle Ottawa scale; BMI: Body mass index; HRT: Hormone replacement therapy; C-C: Case –Control; NC-C: Nested case-control; CPRD: Clinical practice research datalink; CG: Cardiac glycosides; PM: Postmenopausal; NR: Not reported; FCR: Finnish cancer registry; SII: Social insurance institution; pop: population; HT: Hypertension; ER: Estrogen; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs.

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Novelty and Impact: Cardiac glycosides are phytoestrogens and their use has been associated with increased risk of estrogen sensitive cancers. However, the association between their use and risk of breast cancer remains unclear. We investigated the association between cardiac glycosides use and the risk of breast cancer by systematically reviewing the published literature and performing meta-analyses. This study is the first comprehensive systematic review and meta-analysis to investigate the association between cardiac-glycosides use and risk of breast cancer.

## Abstract

Cardiac glycosides are phytoestrogens and have been linked to the risk of estrogen sensitive cancers such as uterus cancer. However, the association between use of cardiac glycosides and risk of breast cancer remains unclear. We investigated the association between cardiac glycosides use and the risk of breast cancer by systematically reviewing the published literature and performing meta-analyses. A comprehensive literature search was performed using MEDLINE, EMBASE, Web of Science and SCOPUS to identify all relevant articles published up to November 2015. Risk estimates, and accompanying standard errors, for the association between cardiac glycoside use and breast cancer were extracted from identified studies. Meta-analysis models were used to calculate a combined hazard ratio (HR), and 95% confidence interval (CI), and to investigate heterogeneity between studies. In total, 9 studies were identified investigating cardiac glycosides use and risk of developing breast cancer. Overall, there was evidence to suggest an association between cardiac glycosides use and breast cancer risk (HR=1.34; 95% CI 1.25, 1.44;  $p < 0.001$ ) with little variation in the association between studies ( $I^2 = 16\%$ ,  $p$  for heterogeneity = 0.30). Results were little altered when analysis was restricted to studies with high quality scores or cohort studies. Overall, there was a 34% increase in breast risk with use of cardiac glycosides but it is unclear whether this association reflects confounding or is causal. Further observational studies are required to examine this association particularly for estrogen receptor positive breast cancer and to explore the role of potential confounding variables.

## **Introduction**

Cardiac glycosides (digoxin and digitalis) are phyto-estrogens <sup>1</sup> and are used to treat heart failure and supra-ventricular arrhythmias (atrial fibrillation/flutter) <sup>2</sup>. Early animal studies indicate that cardiac glycosides may bind to estrogen receptors (ER) and have estrogenic effects <sup>1</sup>. In support of this, digoxin has been found to be associated with estrogen sensitive cancers such as uterus cancer <sup>3,4</sup> and to induce gynecomastia in men <sup>5,6</sup>.

It has long been recognised that estrogen therapy increases breast cancer risk <sup>7-10</sup>, therefore the effect of cardiac glycosides on breast cancer risk is of some concern. Research into the association between cardiac glycosides and breast cancer risk began in the 1970s <sup>11</sup>. Since then numerous additional studies have been conducted. However this research is difficult to interpret because of the number of studies conducted, the different sizes and powers of these studies and the seemingly conflicting results <sup>12,13</sup>. Although an earlier observational study <sup>14</sup>, conducted a brief meta-analysis for digoxin and breast cancer risk, this meta-analysis only searched one bibliographic database (with a literature search which initially identified only 67 articles), did not report detailed characteristics of the included studies, did not investigate study quality and included two overlapping studies <sup>15,16</sup>.

Therefore, the aim of this study was to perform a systematic review using a wide and comprehensive search strategy to identify all relevant literature and to conduct a meta-analysis of the association between cardiac glycosides and breast cancer risk.

## **Methods**

### **Search strategy**

Studies were identified by searching four electronic databases; EMBASE (Reed Elsevier PLC, Amsterdam, Netherlands), MEDLINE (US National Library of Medicine, National Institutes of Health, Bethesda, Maryland, USA), Web of Science (Thomson Reuters, New York USA), and SCOPUS (Elsevier B V) from inception to November 2015.

The literature search was made with no restrictions. The MEDLINE search strategy used the following text words or Medical Subject Headings (Mesh): Breast neoplasms, breast, neoplasms, cancer, carcinoma, carcinomas, digoxin, digitoxin, cardiac glycosides, cardiac

glycoside, digitalis, sodium potassium ATPase inhibitors, foxglove, cardiotonic steroid, bufadienolide, bufalin, cardenolide, proscillaridin. The full MEDLINE search is shown in Supplementary Table S1. Similar searches were conducted on the other electronic databases.

### **Eligibility criteria**

Articles were screened independently by two investigators (RK, and CC). Articles were included if they met the following inclusion criteria: they reported a risk estimate (odds ratio (OR), hazard ratio (HR), standardised incidence ratio (SIR), or rate ratio (RR)) for the association between cardiac glycoside use and breast cancer in women. First, the articles retrieved from searches were screened by titles and abstracts and articles were excluded at this stage if they were obviously irrelevant. In cases where eligibility could not be determined via article abstracts, full text papers were requested and assessed. The reference lists of included studies were also hand searched. Finally, using Web of Science articles citing the identified studies were also searched to identify any further relevant articles. Finally, duplicate articles were excluded.

### **Data extraction**

Data was independently extracted from all relevant studies by two investigators (RK, and CC) including information on author, year of publication, location, study population, follow-up in years, exposure ascertainment, type of cardiac glycosides used, classification of cardiac glycosides use (ever, never, former, current), outcome ascertainment, outcome reported and confounders adjusted for. In addition, studies that have provided results by estrogen receptor (ER) status (positive, negative, unknown) were examined. The Newcastle Ottawa Scale (NOS)<sup>17</sup> was used to assess study quality with a cut-off of five used to define higher quality articles.

### **Statistical analysis**

Risk estimates (ORs, HRs, SIRs, or RRs) and accompanying standard errors were extracted from each study for the association between cardiac glycoside use and breast cancer risk. In each study, the risk estimate (and standard error) that was adjusted for the most potential confounders was extracted. If not reported within studies, risk estimates were calculated using information provided where possible. Specifically, in a Swedish study no confidence intervals (CI) were reported and therefore CIs were calculated from data reported in Table 1 of the Stenkvist paper<sup>18</sup>. Also, in the Friedman study CIs were calculated based upon the

observed and expected number of breast cancer cases based upon a Poisson exact confidence interval as calculated by STATA <sup>19</sup>.

By necessity, ORs (from two studies), HRs (from 2 studies), RRs (from 3 studies) and SIR (from 2 studies) were combined. However, the OR should approximate a HR and a RR when the disease of interest is not common <sup>20</sup>. As between study heterogeneity was anticipated, random effects models were used to produce an overall pooled HR with 95% confidence intervals (CI) <sup>21</sup>. Heterogeneity among studies was investigated using a Chi-squared test and I-squared statistic ( $I^2$ ) <sup>22</sup>. Sensitivity analyses were conducted to investigate whether results differed on the basis of study design (case-control or nested case-control/cohort) or quality score (NOS score of five or more). To check for publication bias, funnel plots were produced to investigate evidence for asymmetry. All meta-analyses were conducted in Review Manager version 5.1 (Nordic Cochrane Centre, Copenhagen, Denmark).

## **Results**

### **Literature search**

The initial database search ascertained 1,171 articles, of which 1,113 were excluded after screening of titles and abstracts (Figure 1). The remaining 58 potentially relevant articles were screened by full text for inclusion. Duplicate articles (n=37), conference abstracts (n=1) and review articles (n=6) were excluded. Additional exclusions included those studies that included male breast cancer patients (n=2), and that reported relapse/recurrence (n=2) or mortality (n=2) outcomes. A further 2 studies were identified from hand searching the reference list of included articles <sup>12,23</sup>. Two articles were based upon the one study <sup>15,16</sup> and so the later larger study was retained <sup>15</sup>. Therefore 9 studies met the inclusion criteria <sup>12-15,18,19,23-25</sup>.

### **Study characteristics**

Characteristics of the included studies are shown in Table 1. There were three case-control studies, including one nested case-control study, and an additional six cohort studies. Five studies originated in Europe; one in the UK <sup>13</sup>, four in Scandinavia (Denmark, Norway, Finland and Sweden) <sup>15,18,23,25</sup>. Three were conducted in the USA <sup>12,14,24</sup> and for one study the

origin was not reported<sup>19</sup>. Breast cancer cases were ascertained through cancer registries in four articles.

Methods of exposure ascertainment varied across studies (Table 1). Eight of the 9 studies solely used medical records, register data, or questionnaire. Only one study used a combination of questionnaire and medical records. Digoxin use was investigated in three studies, while digitalis was the main exposure in five studies and the remaining study investigated digitoxin (Table 2). Quality scores calculated for each study are shown in table 1. Seven studies had high quality scores ( $\geq 5$ )<sup>13–15,18,23–25</sup>.

All but one of the cohort studies accounted for age in their analyses<sup>12</sup> and all of the case–control studies matched controls to cases by age. The confounders accounted for in analyses varied markedly across studies with some adjusting for few or no confounders whilst others adjusted for a wide range of confounders including body mass index (BMI), hormone replacement therapy (HRT), and medication use (see Table2).

### **Main findings**

Overall there was an increase in rate of breast cancer among cardiac glycosides users compared with non-users (HR= 1.34; 95% CI 1.25, 1.44;  $p < 0.00001$ ) with little evidence of heterogeneity ( $I^2 = 16\%$ ,  $p$  for heterogeneity = 0.30) (Figure 2). Funnel plots revealed no evidence of asymmetry which would be indicative of publication bias (Supplementary Figure S1).

The association was similar in studies which investigated digoxin (pooled HR= 1.29; 95% CI 1.11, 1.51;  $p = 0.0009$ ) or studies which investigated digitalis (pooled HR= 1.42; 95% CI 1.23, 1.63;  $p < 0.00001$ ). Repeating the analysis in higher quality studies (ie. removing two studies that scored less than five on the NOS) the main finding was little altered (pooled HR= 1.31; 95% CI 1.19, 1.44;  $p < 0.00001$ ) and the heterogeneity increased slightly ( $I^2 = 30\%$ ,  $p$  for heterogeneity = 0.02). When restricting the analysis to cohort studies the estimate was slightly more marked (HR=1.39; 95% CI 1.33, 1.46;  $p < 0.00001$ ) with no heterogeneity observed ( $I^2 = 0\%$ ,  $p$  for heterogeneity = 0.95).

Only two of the 9 studies investigated estrogen receptor status. Digoxin users appeared to have stronger associations with estrogen receptor positive breast cancer (RR = 1.35; 95% CI 1.26, 1.45 and HR = 1.46; 95% CI 1.10, 1.95) than estrogen receptor negative breast cancer (RR = 1.20; 95% CI 1.03, 1.40 and HR = 1.12; 95% CI 0.52, 2.37) respectively<sup>14,15</sup>.

## Discussion

Our study provides evidence that women using cardiac glycosides have increased breast cancer risk by 34% (95% CI 1.25, 1.44). This association was fairly consistent across studies and most of the inconsistency reflected the magnitude of the increase, as all studies observed increased risks of breast cancer in cardiac glycoside users, though in some this increase was small and not significant. These findings were little altered when investigating cohort studies or higher quality studies.

The cause of the increased breast cancer risk in women using cardiac glycosides is unclear. As with all observational studies, we cannot rule out the effect of confounding. Our meta-analysis is based upon the adjustment for confounders conducted within each original study but these adjustments were not consistent across studies and a number of studies<sup>15,18,19,23–25</sup> adjusted for few confounders. Only one study used methods based upon restriction<sup>13</sup>, that have been recommended to reduce the risk of confounding<sup>26</sup>. In that study<sup>13</sup>, the cohort was restricted solely to patients with cardiac glycoside indications (in particular congestive heart failure, atrial fibrillation, atrial flutter, and other supra-ventricular tachycardia) and there was no association between digoxin and breast cancer risk (OR=1.07; 95% CI 0.90, 1.26). This is arguably a better analysis because there are shared risk factors between cardiovascular disease and breast cancer which may have less effect on this comparison as digoxin users are compared with non-users with similar indications. Alternatively, the association may not reflect confounding but could be real. Cardiac glycosides are phyto-estrogens<sup>1</sup> and may have estrogenic effects<sup>27,28</sup>, although the evidence that digoxin and digitoxin act through an estrogen-receptor mediated mechanism is limited, as noted in recent IARC monographs<sup>29</sup>. If real this estrogenic effect of cardiac glycosides could increase breast cancer risk similar to increases seen for estrogen hormone therapy<sup>7–10</sup>. In support of this, there were stronger associations for digoxin users with estrogen receptor positive breast cancer compared with estrogen receptor negative breast cancer<sup>14,15</sup>. However, there is a lack of such information available and future studies should include ER receptor status of breast cancer patients in cardiac glycosides users. Moreover, there is a need for further observational studies with comprehensive investigation of methods to adjust for confounding, for instance by restricting the population to patients with cardiac glycoside indications, to investigate whether the increased risks observed in our meta-analysis are real or reflect confounding. Another weakness was that studies reported different measures of association (including ORs, HRs,



RRs), but by necessity these were combined. However, it is reassuring that despite this there was little heterogeneity<sup>20</sup>.

Our meta-analysis results are similar to the brief meta-analysis conducted by Ahern et al. which observed a 37% increase in breast cancer risk with digoxin use<sup>14</sup>, but their study searched only one database and only included 6 articles, and erroneously included two studies which overlapped<sup>15,16</sup>. Furthermore, their study did not report in detail characteristics of the individual studies (such as confounders), conduct quality scoring, or investigate funnel plots. Our findings are also similar to the conclusion of the narrative review contained in the most recent IARC monograph<sup>29</sup> but it is worth noting that our review includes five additional studies and this IARC monograph did not contain a formal meta-analysis.

In conclusion; in this systematic review and meta-analysis, women using cardiac glycosides had an increased risk of developing breast cancer. However, additional studies are required to examine this association particularly for estrogen receptor positive breast cancer and to explore whether this increased risk would persist after additional adjustment for potential confounding.

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#### Disclosures:

The authors declare that they have no conflict of interest.

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**Tables titles:**

**Table 1** Characteristics of studies of cardiac glycosides use and breast cancer risk

**Table 2** Summary of included studies of cardiac glycosides use and breast cancer risk

**Figure titles:**

**Fig 1** Flow chart of study selection

**Fig 2** Forest plot of the cardiac glycosides and breast cancer risk

**Supplementary material:**

**Supplementary material 1 (PDF 107 KB) Table S1** Presenting the Medline search string

**Supplementary material 2 (PDF 109 KB) Figure S1** Showing the Funnel plot for cardiac glycosides use and risk of breast cancer.

**Table 1.** Characteristics of studies of cardiac glycosides use and breast cancer risk

Author (year), location	Design	Exposure period (years)	Study population	Breast cancer ascertainment	Exposure source	NOS score
Couraud et al (2014), UK [13]	NC-C	22	CPRD (CG related indication) <sup>a</sup>	Medical records	Medical records	8
Ahern et al (2014), US [14]	Cohort	16	Nurses' Health study (PM)	Questionnaires & medical records	Biennially self-reported questionnaires	7
Hartz et al (2013), US [12]	Cohort	13	Women's health initiative (PM)	Self-administered self-report	Self-administered self-report	3
Biggar et al (2011), Denmark [15]	Cohort	13	Danish Prescription Database	Danish cancer registry	Prescription registry	8
Haux et al (2001), Norway [23]	Cohort	10	Norwegian population	Norwegian cancer registry	Digitoxin lab database	5
Friedman (1984) [19]	Cohort	4	NR	NR	Computer stored pharmacy records	2
Danielson (1982), US [24]	Cohort	3	Group health cooperative (PM)	NR	Group health records	5
Stenkvist (1980), Sweden [18]	C-C	NR	Swedish Population	Computerized population register	Questionnaire and hospital records	5
Aromaa et al (1976), Finland [25]	C-C	NR	FCR & SII's pop. register (HT)	Finnish cancer registry	Register for HT prescriptions	5

Abbreviations: C-C: Case –Control; NC-C: Nested Case-Control; CPRD: Clinical Practice Research Datalink; CG: Cardiac Glycosides; PM: Postmenopausal; NR: Not Reported; FCR: Finnish Cancer Registry; SII: Social Insurance Institution; pop: population; HT: Hypertension; NOS: Newcastle-Ottawa Scale.

<sup>a</sup> patient with a diagnosis of congestive heart failure, atrial fibrillation or atrial flutter, or supra-ventricular tachycardia

**Table 2.** Summary of included studies of cardiac glycosides use and breast cancer risk

Author (year), location	Comparison	No. of breast cancer cases <sup>a</sup>	No. of non-breast cancer controls <sup>b</sup>	Risk measurement (95% CI)	Adjustments
Couraud et al (2014), UK [13]	Digoxin user vs never user	898	52,556	OR=1.07 (0.90, 1.26)	(Matched on Age, date of cohort entry, and duration of follow-up), smoking, BMI, CG-related indication, HRT, estrogen-based contraceptive drug, statins, aspirin, oral anticoagulants and anti-platelets, NSAIDs, Anti-hypertensive drugs, and anti-diabetic drugs.
Ahern et al (2014), US [14]	Digoxin current user vs. never	4,576	70,394	HR=1.40 (1.18, 1.65)	Age, height, BMI, age (at menarche, menopause, first

	user					birth and parity), alcohol, postmenopausal hormones use, family history, personal history of benign breast disease, mammography screening in the past 2 years, aspirin, ibuprofen, cholesterol-lowering drugs, and tamoxifen.
Hartz et al (2013), US [12]	Digitalis ever user vs. non-user	NR	NR	HR=1.46 (1.24, 1.72)	NR	
Biggar et al (2011), Denmark [15]	Digoxin current user vs. never user	49,016	2,067,013	RR=1.39 (1.32,1.46)		Age, calendar period
Haux et al (2001), Norway [23]	Digitoxin user versus non-user (based upon expected breast cancer from national cancer rates)	57	4,969	SIR=1.25 (0.95, 1.62)		Matched on age, year of birth
Friedman (1984) [19]	Digitalis ever user vs. expected user	20	143,371	SIR=1.21 (0.74,1.87)		Age-sex standardised
Danielson (1982), US [24]	Digitalis glycosides user vs. non-user	302	NR	RR=1.30 (0.7, 2.2)		Age
Stenkvist (1980), Sweden [18]	Digitalis ever user vs. non-user	179	179	OR=1.39 (0.76, 2.57)		Matched on age
Aromaa et al (1976), Finland [25]	Any digitalis ever user vs non-user	109	109	RR=1.33 (0.73, 2.48)		Matched on age, geographic area, and duration of Hypertension treatment

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Abbreviations: NR: not reported; BMI: Body Mass Index; CG: Cardiac glycosides; HRT: Hormone Replacement Therapy; ER: Estrogen; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs.

<sup>a</sup> Number of cases in study population regardless of medication use.

<sup>b</sup> Number of controls in study population regardless of medication use.





