Molecular Pathways:  Digoxin use and estrogen-sensitive cancers: risks and possible therapeutic implications

Invited review

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Running Title:  Digoxin and estrogen-sensitive cancer risk

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Abstract

Digoxin, a phyto-estrogen, binds with estrogen receptors (ERs) and can cause gynecomastia. Among women currently using digoxin, breast and uterus cancers incidences are significantly increased (approximate risk ratios: 1.3 to 1.5). Both cancers are often estrogen-sensitive. In contrast, ovary and cervix cancers are relatively estrogen-insensitive, and incidence is unaffected by digoxin exposure. When digoxin use stops, incidence rapidly reverts to that in non-uses. These patterns parallel those of estrogen, suggesting that digoxin works via ER-stimulated proliferation of ductal/acinar cells, accelerating the growth of nascent cancers. Also consistent with an estrogenic effect, men using digoxin have a small but significant reduction in prostate cancer (risk ratio: 0.76). Other estrogen-like drugs, particularly spironolactone, should be investigated for similar effects. The effect of digoxin use in women being treated for breast cancer or in survivors is unknown. Women with estrogen-sensitive cancers on adjuvant therapy may take tamoxifen, which blocks ERs. However, post-menopausal patients may use aromatase inhibitors, which block estrogen production while leaving ERs susceptible to digoxin. If adverse effects are found, tamoxifen may be preferred over aromatase inhibitors in patients receiving estrogen-mimicking drugs. Alternatively, other cardiotropic drugs might be considered in women with or at high risk of developing estrogen-sensitive cancers.
BACKGROUND

Digitalis, a medicinal extract of the plant foxglove, has a powerful inotropic effect on cardiac muscle. Chemically, two forms are used as medications in patients with heart disease, digoxin and, less commonly, digitoxin. Both forms are phyto-estrogens, or plant estrogens. Recent studies have shown that use of digoxin significantly increases the risk of breast and uterus cancer\textsuperscript{1-3}. Both cancers are often estrogen-sensitive. In contrast, no changes in risk were seen for two ovary and cervix\textsuperscript{3} cancers, both relatively estrogen-insensitive.

Chemistry and physiology

The principal effect of digitalis drugs is to inhibit the sodium-potassium pump, which regulates the flux of ions across the cell membrane, calcium being of particular importance in cardiac conditions\textsuperscript{4}. However, the basic structure of digitalis compounds is similar to that of estradiol, the principal estrogen (Figure 1). Several studies have indicated that digitalis drugs have the capacity to bind to estrogen receptors (ERs), although with less affinity than estrogen itself\textsuperscript{5,6}. Stimulation of ERs induces proliferation of ductal and acinar tissue. Thus, it is not surprising that chronic use of digitalis induces gynecomastia in men\textsuperscript{7,8}, just as will estrogen excess in men. The effect on female breast tissue is likely similar, although enlargement would be less noticeable.

Estrogen and cancer risk
The vast literature on estrogen use and cancer risks in women is beyond the scope of this review. Briefly, exogenous estrogens given as menopausal hormone therapy have been documented to increase the incidence of breast cancer in many studies see reference 9, particularly when given with progestins10. Generally, breast cancer incidence increases soon after initial exposure remained above expected levels for the duration of use, possibly increasing slightly over time. However, when estrogen exposure ceases, the incidence of breast cancer promptly declines as well. This pattern is consistent with a pathway in which current use of estrogen accelerates the growth of nascent breast cancers rather than inducing them de novo11. Similarly, for the uterus, both hyperplasia12 and endometrial cancer incidence13 increase with estrogen use, an effect decreased by including progestins in the formulation of hormone therapy. For ovary cancer, there appears to be a slight increase in risk with estrogen use14-16 but not to the risk ratios seen with breast cancer. Use seems not to impact cervical cancer risk17.

**Digitalis and cancer risk**

The potential for digitalis to increase cancer risk was appreciated decades ago. Three studies specifically examined this hypothesis, all concluding there was no significant increase in risk18-20. However, in each study, the point estimate of incidence was increased about 30% above non-users. With hindsight, there was inadequate power to detect low risks with statistical confidence, given their limited size. In two case-control studies, men with breast cancer were significantly more likely (2-fold) to use digitalis than expected21,22. These studies ignored or dismissed the importance of these associations.
Recently, two studies in Denmark re-examined breast cancer risk in women using digoxin\textsuperscript{1,2}, the only digitalis drug in the Danish formulary. Using large datasets, both studies reached similar conclusions: the risk was significantly increased. In a regional case/control study\textsuperscript{1}, women with breast cancer (N=324 cases) had an odds ratio of 1.30 (95\% confidence interval (CI) 1.14-1.48) for being a current digoxin user compared to non-users (N=2,546). The association was robust even after adjustment for prior exposure to menopausal hormone therapy and was not confounded by indications for use of hormonal therapy. In a nationwide cohort, risk was examined in 2.1 million women (25.5 million person-years of follow-up through 2008; N=49,016 breast cancers). Digoxin exposure was obtained through a national prescription database\textsuperscript{28} initiated in 1995. The breast cancer incidence rate ratio was 1.39 (95\% CI: 1.32-1.46) in women currently using digoxin, compared to exact age- and calendar-year-adjusted non-using women. Incidence increased within the first year of digoxin use and continued for the duration of exposure. Risk in continuing users was high in the first year of exposure, and then dropped to a nadir at 3 years before rising again. Rate ratio for ER+ (1.35) and untested (1.51) breast cancers were significantly increased, but for ER- breast cancers (1.20), confidence intervals included unity. In former users, incidence declined significantly below expected levels in the first year but rose to expected levels thereafter.

The sodium-potassium pump regulates the transport of a variety of products across the cell membrane\textsuperscript{4}, providing alternative pathways by which digoxin might affect cancer risk. To evaluate if the digoxin-associated risk was likely mediated through its effect on ERs, the incidences of cancers of corpus uteri (uterus), ovary and uterine cervix were compared in digoxin-exposed and never-exposed women\textsuperscript{3}. Uterus cancers are predominately estrogen-
sensitive ER+ endometrial cancers, whereas ovarian and cervix cancer are relatively estrogen-insensitive (with uncommon exceptions). The incidence rate ratio of uterus cancers was increased 1.48-fold (95% CI: 1.32-1.65) in current digoxin users. In contrast, risks of ovary and cervix cancers were not increased in current digoxin users (1.06; 0.92-1.22 and 1.00; 0.79-1.25, respectively). Furthermore, the higher risk of uterus cancer decreased when use of digoxin use ended.

Risk factors for uterus cancer\textsuperscript{23} include obesity, a potentially confounding risk factor because it is shared with cardiovascular disease. However, endometrial cancer risk is decreased in smokers\textsuperscript{24}, and furthermore, no association was seen between uterus cancer and drugs used for angina\textsuperscript{3}, which argues against the digoxin effect being related to shared risk factors for cardiovascular disease. That current digoxin increased the risk of only the estrogen-sensitive cancers of the breast and uterus, both approximately 1.3- to 1.5-fold, but not ovary or cervix cancer supports a mechanism mediated by its effect on the ERs.

Estrogen retards the growth on prostate cancer. By analogy, so might digoxin. In drug screening, digoxin was found to be among the most potent of commonly used drugs in inhibiting growth of prostate cancer cell lines\textsuperscript{25}. In the same study, the investigators examined risk in men using digoxin, finding a lower prostate cancer incidence (0.76 (95% CI: 0.61–0.95) compared to non-users\textsuperscript{25}. Further studies are needed to confirm this result, but the result is consistent with digoxin exerting an estrogenic effect.

**CLINICAL-TRANSLATIONAL ADVANCES**
Other estrogen-mimicking drugs

Other common drugs resemble estrogen. Of most interest is spironolactone, a synthetic 17-lactone steroid used as a potassium-sparing diuretic in patients with heart failure, cirrhosis, hypertension and primary aldosteronism, often for prolonged periods. Spironolactone binds to and inhibits aldosterone receptors but also to ERs. Functionally, it is an estrogen agonist, but it may also interfere with estrogen metabolism. Gynecomastia is a common side effect, occurring in 10% with conventional doses and up to 50% with high doses. In case reports patients on spironolactone have been reported to have developed breast cancer, but with common cancers, case reports have limited value. In one small case-control study (N=302 women with breast cancer), no significant association with spironolactone use was observed. This finding should be re-examined in a study with more power. Both digoxin and spironolactone may be used together in patients with heart disease, complicating analysis.

However, this possibility also raises the prospect of overlapping stimulatory effects on breast tissue cells and perhaps even higher risks.

One clue to an estrogenic drug effect might be an association of the drug with gynecomastia. However, gynecomastia may have different causes. Estrogen acts directly on ductal or acinar tissue. Presumably, digoxin and possibly spironolactone act similarly. However, gynecomastia may also occur indirectly, via prolactin release from the pituitary. Antipsychotic and rauwolfia drugs can cause gynecomastia by blocking dopamine and alpha-adrenergic receptor sites in the hypothalamus (e.g., phenothiazine derivatives, and opiate derivatives) or by depleting pituitary catecholamine (e.g., reserpine). In the 1980s, considerable concern was raised about reserpine.
and breast cancer risk, but the association was inconclusive\textsuperscript{e.g.,36}. In recent years the risk has been dismissed as unimportant\textsuperscript{37} but despite this, reserpine is no longer widely used. A review of neuroleptic drugs found no increase in breast cancer risk\textsuperscript{38}. Chemically, these drugs differ from estrogen. With pituitary-induced gynecomastia, galactorrhea may occur\textsuperscript{7}, suggesting that ductal/acinar cells may differentiate further with hypothalamic/pituitary stimulation than with estrogen, which might affect differentiation and malignant potential. Finally, drugs such as cimetidine, a commonly used H2-receptor antagonist, and some (but not all) other anti-ulcer drugs used to control gastric acidity, may interfere with estrogen metabolism\textsuperscript{39} and chronic use has been associated with gynecomastia\textsuperscript{40}. However, but two studies found no association between cimetidine and breast cancer\textsuperscript{41,42}.

Dietary and over-the-counter phyto-estrogen formulations are sometimes taken for menopausal symptoms. Compared to prescription medications, they are used in much weaker preparations and often taken only episodically. There is little evidence they are effective as menopausal therapy\textsuperscript{43} but also no evidence that they affect breast\textsuperscript{44} or uterus cancer risk\textsuperscript{45}.

**Public health impact**

Despite concern about increasing the risk of breast cancer, digital drugs have important roles in patient care. Any reconsideration of their use would likely conclude that the benefits of digoxin for heart disease outweigh the cancer risks. Digoxin use is primarily in the elderly, and hence this discussion largely concerns post-menopausal breast cancer risk in older women. In approximately 350,000 Danish women \( \geq 70 \) years old, breast and uterus cancer annual
incidences are approximately 350 and 90 per 100,000 per year, respectively (data from the Danish Cancer Registry\textsuperscript{46}). The higher rate ratios for breast and uterus cancers apply only to 2.2\% of these women currently using digoxin (data from the Danish Register of Medicinal Products Statistics\textsuperscript{23}). Thus, in 100,000 women \( \geq 70 \) years old, 2200 women would be current digoxin users, among whom approximately 11 breast (8 expected, based on non-users) and 3 uterus (2 expected) cancers would be observed. The net cancer increase is therefore about 3 breast and 1 uterus cancer cases per 100,000 elderly women per year. While this is only 1\% of all breast cancers in this age group, women using digoxin remain at increased risk for every year of digoxin use.

**Digoxin use in women with cancer**

The above presentation focused on cancer incidence. A further concern is the use of digoxin in women with a history of estrogen-sensitive cancers. Most physicians consider exogenous estrogen contraindicated in such patients but an absolute prohibition remains controversial\textsuperscript{47-48}. Digoxin use in women with estrogen-sensitive cancers has not been rigorously examined. While incidence risk is increased with digoxin exposure, this increase may not translate to risk of death from breast cancer. Mortality from cancer is similar in women who develop breast cancer while on estrogens and those not on estrogen\textsuperscript{49-50}. Perhaps better medical surveillance is provided or possibly the biology of the cancers differs. If digoxin-cancer patterns of mortality parallel those of estrogen, as might be predicted, there may be no direct impact on mortality from breast cancer, but even so, having both breast cancer and heart disease is likely to cause increased mortality overall. Similar considerations likely apply to uterus cancer.
Complicating any analysis will be the use of adjuvant therapy, in particular tamoxifen. Tamoxifen and other drugs of its type bind to the ER with complex results. They inhibit attachment of estrogen on ductal and acinar cells\textsuperscript{51} and thus could also block digoxin effect on mammary tissue. However, effects of different drugs within this class vary. In particular, tamoxifen increases the proliferation of endometrial cells and increases the risk of endometrial cancer and sarcomas of the uterus, whereas other drugs in the same class apparently do not\textsuperscript{52-53}. In recent years, aromatase inhibitors, a different class of drug, have become widely used in the treatment of post menopausal patients. These agents block estrogen production but leave the ERs unaffected and without competition by natural estrogens\textsuperscript{54}. Thus, digoxin would have full license to interact with the ER and stimulate proliferation, assuming its effect is mediated through ER binding. If digoxin use is shown to affect breast cancer prognosis adversely, then use of tamoxifen as adjunct therapy might be considered.

In conflict with concern about an increasing risk, some investigators hypothesize digoxin might benefit women with breast cancer. In vitro, it inhibits cell adhesion or proliferation in breast cancer cell cultures\textsuperscript{55,56} and several different molecular pathways have been proposed\textsuperscript{e.g.57-58}. One retrospective study (32 women on digoxin with mortality as the outcome) suggested it might be beneficial\textsuperscript{59}. Regarding cell culture systems, drug doses may be well in excess of those physiologically tolerated by human subjects and hence toxic both to cells and the patient. However, estrogen itself, at very high doses, can also inhibit breast cancer cell lines \textit{in vitro}\textsuperscript{50}.

\textbf{Summary}
Current digoxin use increases the incidence of estrogen-dependent breast and uterus cancers, with rate ratios reverting to the null when exposure stops. Since only current use increases the incidence, the mechanism may be that of a promoter, i.e., digoxin enhancing proliferation of nascent tumors rather than inducing new tumors. On theoretical grounds (and anecdotal data), other estrogen-mimicking drugs may have similar effects. Of particular concern are the potassium-sparing diuretics. Despite cancer risks, the use of digital drugs may be medically indicated because their cardiac benefits likely exceed cancer risks. However, the impact of digoxin use on women with active estrogen-sensitive cancers has yet to be evaluated. It is possible that digoxin, and perhaps other estrogen-mimicking drugs, could affect extant breast and uterus cancers adversely. Physicians treating women with existing cancers may wish to consider using alternative therapies, where possible, and should be especially alert to possible breast or uterus cancer symptoms when digoxin use is clinically indicated.

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References


Figure 1. Speculation concerning the pathogenesis by which estrogen and estrogenic compounds might affect estrogen-sensitive tissues, including nascent cancer cells.
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