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Spironolactone use and the risk of breast and gynecologic cancers

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ABSTRACT

Spironolactone, an aldosterone-antagonist, is associated with gynecomastia. Digoxin, which can also cause gynecomastia, has been associated with increased incidence of breast and uterus cancers. We therefore postulated that spironolactone use might also increase these cancer risks. Using a nationwide prescription drug registry between 1995 and 2010, we identified use of spironolactone in a cohort of Danish women (≥20 years old). In users and non-users, incidence rate ratios adjusted by age group and calendar-year examined risk of breast and uterus cancers, both estrogen-sensitive, and ovary and cervix cancers, both relatively estrogen-insensitive. As an added control exposure, risk ratios in women who used another diuretic, furosemide, were examined by the same approach. Among 2.3 million women (28.5 million person-years), risks of breast, uterus, ovary, and cervix cancers were generally increased about 10–30% in both spironolactone and furosemide users. In the first year of drug exposure, incidences were increased, especially for ovary cancers. However, incidence increases in the first year of use were not specific for estrogen-sensitive cancers, occurred with both spironolactone and furosemide, and were driven by exposures immediately prior to diagnosis. For drug exposure ≥1 years before cancer diagnosis, incidences of these cancers were not significantly increased. We conclude that associations observed with first use in the year immediately before cancer diagnosis were driven by reverse causality, i.e., because of treatment for symptoms related to the incipient cancer. With respect to breast, uterus, ovarian and cervical cancer, there is no evidence of increased risk with spironolactone or furosemide use.

Spironolactone is a commonly used aldosterone-antagonist diuretic with structural similarity to estrogen [1]. Although it can bind to both estrogen and progestin sex hormone receptors, its predominant affinity is to the androgen receptor [2], However, gynecomastia is a common side effect of use, especially when the drug is given in high dose [3–6]. Spironolactone may induce gynecomastia by anti-androgenic properties, but it also appears to affect androgen/estrogen balance through complex mechanisms involving 17b-hydroxysteroid dehydrogenases [7,8]. Similarly, digoxin binds weakly to estrogen receptors [2] and is also thought to induce gynecomastia [9]. Digoxin use has been associated with developing breast and uterus (corpus uteri) cancers but not the relatively estrogen-insensitive cancers of the ovary or cervix (uterine cervix) [10–12]. Digoxin appears to act via estrogen receptor (ER) stimulation since risk increases are greater for ER+ cancers [9].

Given its potential to cause gynecomastia, we postulated that spironolactone might also increase risks of breast and uterus cancer. Several case reports [13–15] suggest support for this concept, but until recently there have been no large scale studies which examine risks. Therefore, the International Agency for Cancer Research noted the absence of adequate data and classified spironolactone as a drug not classifiable concerning its carcinogenicity in humans in 2001 [16]. In 2012, however, a retrospective cohort evaluation of women was published in which spironolactone was found to have no association with breast cancer risk [17].

We have also evaluated the risk of breast and uterus cancers, both estrogen-sensitive, in a cohort of women older than 20 years born in Denmark who used spironolactone between 1995 and 2010. To address specificity of any observed association, we examined two additional common gynecological tumors, ovary and cervix cancer, both relatively estrogen-insensitive and not expected to show associations, given our hypothesis that effects, if any, would be mediated by interaction with the ER. We recognized that medical care might change as women with symptoms of incipient cancer sought evaluation and therefore stressed evaluations of drug exposures of greater than one year.

Furthermore, we examined risks of these four cancers in women using furosemide, a commonly used loop diuretic that has no similarity to estrogen and no gynecomastia effect [18]. *A priori*, we did not expect use of furosemide to increase risks of these cancers except as a consequence of coming under more intensive medical care.

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1. Methods

Since 1995, prescription drug use records have been maintained by the Danish Register of Medicinal Products Statistics [19], using individual identifiers that permit linkage to other registries. In the current study we examined use of spironolactone (aldactone) and furosemide (lasix) by using the ATC code C03DA01 and C03CA01, respectively (World Health Organization Collaborating Centre for Drug Statistics Methodology, Norwegian Institute of Public Health, P.O. BOX 4404, Nydalen NO-0304, Oslo, Norway). We had no information about the indication for the prescription (not available in registry data).

Following procedures previously used in our studies [11,12], we assumed prescriptions were given for no more than 6 months. Therefore, women were classified as prevalent users if they had a prescription in the first 6 months of registry initiation and as incident users if their first prescription was after the first 6 months of registry initiation. Subjects were assumed to have continued use of the drug for 6 months after their last prescription and thereafter considered former users. If they later obtained another prescription, we considered them restarters. Restarters were included in the current-use category for as long as they continued using the drug (that is, for 6 months after the last prescription, at which point they were former users). To assure accuracy about duration of use, studies of duration were restricted to continuous users with known start dates, excluding prevalent users (duration of use unknown) and including restarters only to the point they first stopped use (to assure continuous use).

We examined the incidence of breast, uterus (corpus uteri), ovary, and cervix (uteri cervix) cancers using data in the Danish Cancer Registry [20], considered complete from 1943. Invasive cancers were identified by International Classification of Diseases—Oncology, 10th edition (ICDO-10: uterus (C54–55), ovary (C56 and C570–574), and cervix cancer (C53) diagnoses) [21]. Only cancers incident since 1995 through 2010 were included, and women with records of prior cancers in the same category were excluded. Follow-up for cancer incidence in women ≥20 years old continued from 1 July 1995 to 31 December 2010, to the first diagnosis of any of these cancer, or to death, emigration or disappearance, whichever came first.

Associations between spironolactone and cancers incidence compared incidence in women with no exposure, using incidence rate ratios (IRR) with 95% confidence intervals (CI) evaluated by STATA (College Station TX). P-values derived from log-linear Poisson regression used person-years in each category of drug exposure (e.g., current use could have shifted to former use). Evaluation of drug exposure examined associations by time-period prior to cancer diagnosis. Detailed presentation of first use within 0–11 months of cancer onset was undertaken after observing the association of IRR and use starting in the year just before diagnosis. To minimize residual confounding, analyses were adjusted for age (≤25 years and in 1-year categories to >95 years) and calendar period, categorized in one-year groups from 1995 to 2008. Women were followed 1 July 1995 or from age 20 years to immigration, cancer onset, death, disappearance or the end of 2008, whichever came first. In former users, last use assumed continuing exposure for six months after the last prescription. Because of an unexpected finding for ovary cancer, we further examined the subset of serous ovary cancers (ICDO-10 morphology codes: 84413, 84603 and 84613). Associations with furosemide exposure were evaluated by the same methods. Because many subjects had exposure to both spironolactone and furosemide, either in combination or in sequence, the interaction was also evaluated. The study was approved by Danish Data Protection Agency prior to initiation.

2. Results

Overall, the study evaluated cancer incidence in 2.3 million women followed for 28.8 million person-years (p-y). From 1995 through 2010, there were 1.3 million prescriptions for spironolactone (follow-up: current and former use: 214,112 and 152,746 p-y, respectively) and 7.4 million prescriptions for furosemide (1,132,983 and 987,053 p-y). Patient characteristics and drug exposures are provided in Table 1. Breast cancers (58,000 cases) were most common, followed by uterus (9386), ovary (7899) or cervix (5602) cancers (Table 1). Compared to women with breast cancer, those with cervical cancer were younger, and those with

Table 1
Use of spironolactone and furosemide among women with breast, uterus, ovary or cervix cancer in a cohort of all women (>20 years old) in Denmark, 1995–2010.

Cancer	Breast	Uterus	Ovary	Cervix
Total	58,000	9386	7898	5602
Median age	62.6	67.0	65.4	48.7
(25–75%)	(53.2–72.5)	(59.0–75.5)	(55.7–74.6)	(37.5–65.7)
Spironolactone exposure				
Unexposed	56,493	9102	7609	5525
Ever exposed	1507 (2.6%)	284 (3.0%)	290 (3.7%)	77 (1.4%)
Age at first exposure (years)[a]				
20–39	10 (0.7%)	0 (0.0%)	0 (0.0%)	5 (6.5%)
40–49	88 (5.8%)	17 (6.0%)	13 (4.5%)	6 (7.8%)
50–59	271 (18.0%)	37 (13.0%)	44 (15.2%)	14 (18.2%)
60–69	396 (26.3%)	77 (27.1%)	77 (26.6%)	17 (22.1%)
70–79	442 (29.3%)	105 (37.0%)	92 (31.7%)	20 (26.0%)
≥80	300 (19.9%)	48 (16.9%)	64 (22.0%)	15 (19.5%)
Furosemide exposure				
Unexposed	50,317	7841	6725	5134
Ever exposed	7683 (13.2%)	1545 (16.5%)	1174 (14.9%)	468 (8.4%)
Age at first exposure (years)[a]				
20–39	146 (1.9%)	19 (1.2%)	12 (1.0%)	38 (8.1%)
40–49	746 (9.7%)	102 (6.6%)	83 (7.1%)	53 (11.3%)
50–59	1482 (19.3%)	288 (18.6%)	188 (16.0%)	70 (15.0%)
60–69	1821 (23.7%)	433 (28.0%)	292 (24.9%)	102 (21.8%)
70–79	2047 (26.6%)	492 (31.8%)	404 (34.4%)	129 (27.6%)
≥80	1441 (18.6%)	211 (13.7%)	194 (16.6%)	76 (16.2%)

[a] First use among incident users only.