Relationship between Histamine$_2$-Receptor Antagonist Medications and Risk of Invasive Breast Cancer

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Abstract

Background: **Histamine$_2$-receptor antagonist (H_2 blocker) medications are used to treat heartburn, gastroesophageal reflux disease, and ulcers. Some H_2 blockers, specifically cimetidine and ranitidine, also increase serum prolactin concentrations. Given the positive relationship between prolactin levels and postmenopausal breast cancer risk, use of H_2 blockers is a potential breast cancer risk factor. The few previous studies evaluating this association have been null but have been limited by small sample sizes, and none have evaluated risk by either histologic type or estrogen receptor/progesterone receptor status.**

Methods: **Combining data from two population-based case-control studies conducted in western Washington, we assessed the relationship between use of H_2 blockers and risk of different types of breast cancer among 1,941 cases and 1,476 controls 55 to 79 years old. Odds ratios and 95% confidence intervals (95% CI) were calculated using polytomous logistic regression.**

Results: **Current use of H_2 blockers overall, cimetidine, and famotidine was not associated with an increased risk of either invasive ductal or invasive lobular breast cancer. Current users of ranitidine had a 2.2-fold (95% CI, 1.1-4.3) increased risk of ductal carcinoma that was confined to a 2.4-fold (95% CI, 1.2-4.9) increased risk of estrogen receptor–positive/progesterone receptor–positive ductal carcinoma.**

Conclusions: **Use of H_2 blockers in general is not associated with an increased risk of breast cancer, although current use of ranitidine may increase risk of hormone receptor–positive ductal carcinoma. Further studies to confirm this finding are warranted.** (Cancer Epidemiol Biomarkers Prev 2008;17(1):67–72)

Introduction

Histamine$_2$-receptor antagonist (H_2 blocker) drugs are used to treat gastric and duodenal ulcers, gastroesophageal reflux disease, and high levels of gastric acidity. There are four H_2 blocker medications approved for use in the United States: cimetidine, ranitidine, famotidine, and nizatidine. To date, all have been approved for over-the-counter use at relatively low doses, whereas higher doses of these drugs are dispensed by prescription only. Available in the United States as a prescription-only drug from 1977 to 1995 and as an over-the-counter drug after 1995, cimetidine was the first H_2 blocker approved by the Food and Drug Administration. By the late 1980s, cimetidine was one of the most commonly prescribed medications for ulcer in the United States (1). Ranitidine was introduced several years after cimetidine in 1983 and exceeded the popularity of cimetidine in the United States by 1987 (2). Famotidine and nizatidine were developed and marketed in the mid to late 1980s and were also among the top 100 medications in the world in terms of drug sales in the 1990s (2). Although H_2 blockers are still widely used today, they became less commonly used after the introduction of proton-pump medications in the late 1980s and 1990s.

In relation to breast cancer risk, cimetidine has garnered the greatest attention because of its observed effect on hormone levels. Specifically, cimetidine increases serum levels of prolactin, inhibits the binding of dihydrotestosterone to androgen receptors, and inhibits the metabolism of estradiol (3, 4). The other H_2 blocker drugs have not been studied as extensively as cimetidine because it is thought they have less of an effect or no effect on hormonal pathways (3). Ranitidine administered at higher doses has been observed to increase prolactin levels, although this increase is more modest than that induced by cimetidine (5). Famotidine and nizatidine are not thought to affect serum prolactin concentrations.

Plasma prolactin levels have been positively associated with postmenopausal breast cancer risk in prospective observational studies (6, 7). In one such study that evaluated this relationship by breast cancer subtype (7), no statistically significant difference in the relationship between ductal and lobular breast cancer was observed (P = 0.43), although relative risks differed somewhat between these histologies at higher plasma concentrations. Specifically, the relative risk for ductal cancer at prolactin concentrations of 9.4 to 12.3 and >12.3 ng/mL was 1.19 [95% confidence interval (95% CI), 0.89-1.60] and 1.38 (95% CI, 1.04-1.85), respectively, compared with risks of 1.69 (95% CI, 0.90-3.14) and 1.76 (95% CI, 0.95-3.26) for lobular

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cancer at the same prolactin concentrations. This study did find a much stronger difference by estrogen receptor (ER)/progesterone receptor (PR) status, as risk of ER+/PR+ tumors was positively associated with prolactin levels (P for trend < 0.001), whereas risk of ER-/PR- tumors was not (P for trend = 0.28).

Despite this observed association between prolactin and breast cancer, four previous epidemiologic studies have been consistent in showing no increase in breast cancer risk among users of cimetidine and other H_2 blockers (8-11). It should be noted that two of these studies (9, 10) used a large cohort of cimetidine users (2,031 and 6,045 women, respectively) but were limited by small numbers of breast cancer cases (58 and 43 cases, respectively). The other two studies that evaluated cimetidine use (8, 11) had a large number of breast cancer cases (6,994 and 507 cases, respectively), although the former study reported a prevalence of H_2 blocker use in only 2% of cases and controls. Moreover, no study evaluated cimetidine use on risk of different subtypes of breast cancer based on histology or hormone receptor status. Only one study has specifically evaluated ranitidine use in relation to breast cancer risk and found no association (9). However, the number of cases who took ranitidine was small (n = 10). No epidemiologic study has evaluated the association between famotidine or nizatidine and risk of breast cancer. The only study that evaluated the collective use of any H_2 blocker on breast cancer risk observed no association (11). We conducted this study to determine if different H_2 blockers are associated with risk of different breast cancer subtypes, particularly hormone receptor–positive tumors.

Materials and Methods

Subjects. Subjects from two population-based case-control studies were used for this analysis. The first study recruited women ages 55 to 74 years diagnosed with invasive breast cancer between 2000 and 2004. Sampling of cancer cases differed by histologic type because the focus of this study was to assess the etiology of lobular carcinomas. Thus, all women with invasive lobular carcinoma (ILC; either pure lobular carcinomas or mixed ductal-lobular carcinomas) were eligible, whereas only a random sample of ductal cases was chosen to participate. Cases were ascertained through the Cancer Surveillance System, a population-based cancer registry that monitors cancer incidence in western Washington. A total of 1,251 eligible cases were identified from King, Pierce, and Snohomish counties and 1,044 (83%) were subsequently enrolled in the study and interviewed. Women without breast cancer were identified from the general population of King, Pierce, and Snohomish counties through random-digit dialing and were frequency matched to cases on age and reference year. A total of 660 eligible controls were identified and 469 (71%) were enrolled and interviewed. Tumor tissue was ascertained and centrally reviewed for 83% (869 of 1,044) of cases. Cases were defined as being either ductal or lobular (including both pure lobular and mixed ductal-lobular carcinomas) based on this centralized review conducted at the Fred Hutchinson Cancer Research Center by experienced breast cancer pathologists. The remaining cases were defined as being either ductal or lobular based on a centralized review of pathology reports. Among the 869 cases whose histology was assessed by both a slide review and a pathology report review, there was 92% agreement between these two methods with a corresponding κ statistic of 0.87. ER/PR status was also centrally evaluated using the tumor tissue specimens collected (n = 792). ER/PR status was ascertained from pathology reports when available for the remaining cases (n = 63), leaving only 14 cases who were excluded from ER/PR analyses because of an unknown status.

The second study included women ages 65 to 79 years diagnosed with invasive breast cancer between 1997 and 1999 regardless of histologic type. Details of the methods used in this study have been published previously (12). Cases were ascertained through the Cancer Surveillance System. A total of 1,210 eligible cases were identified from King, Pierce, and Snohomish counties and 975 (81%) were subsequently enrolled in the study and interviewed. Female controls without breast cancer were identified from the general population of King, Pierce, and Snohomish counties through Centers for Medicare and Medicaid Service records and were frequency matched 1:1 to cases on 5-year age groups, year, and county of residence. A total of 1,365 eligible controls were identified and 1,007 (74%) were enrolled and interviewed. Cases were histologically classified as either ILC (n = 189) or invasive ductal carcinoma (IDC; n = 708) based on a centralized review of pathology reports. The 78 cases with a histology other than lobular or ductal were excluded because tumors with only these two histologies were enrolled in the other study. Data on ER/PR status were also obtained through pathology report reviews and were available for 92% (900 of 975) of cases.

In both studies, all women with a prior history of *in situ* or invasive breast cancer were excluded. A trained interviewer collected data on all cases and controls via a standardized in-person questionnaire that was very similar across the two studies. The Fred Hutchinson Cancer Research Center Institutional Review Board approved the protocols used by both studies, and written informed consent was obtained from all participants.

In the structured in-person interview, women were asked about over-the-counter or prescription medications used for ulcers, heartburn, or stomach problems in the 20 years preceding her reference date. Reference dates were defined as the date of breast cancer diagnosis for cases; for controls, they were assigned based on the expected distribution of case reference dates. For each ulcer medication use of ≥1 week, information was collected on generic or brand name, start and stop dates, and duration of use. A list of both generic and brand names of the major medications (Tagamet/cimetidine, Pepcid/famotidine, Axid/nizatidine, and Zantac/ranitidine) was asked of all subjects to enhance recall. Ever users of H_2 blocker medications were defined as women who used a H_2 blocker for ≥3 months. Duration of H_2 blocker use was assessed by evaluating risk for less than 2 years use and use for ≥2 years. Current users were defined as ever users who continued H_2 blocker use within 6 months before their reference date. Former users are classified as those women who stopped H_2 blocker use more than 6 months before the reference date. In addition to use of any H_2 blocker, we evaluated use of

Table 1. Demographic characteristics and risk factors of breast cancer cases and controls

	Controls (n = 1,390), n (%)	Ductal carcinoma (n = 1,148), n (%)	Lobular carcinoma (n = 688), n (%)
Reference age (y)			
55-59	131 (9.4)	133 (11.6)	153 (22.2)
60-64	117 (8.4)	122 (10.6)	133 (19.3)
65-69	414 (29.8)	323 (28.1)	179 (26.0)
70-74	450 (32.4)	367 (32.0)	172 (25.0)
75-79	278 (20.0)	203 (17.7)	51 (7.4)
Race			
White (non-Hispanic)	1,269 (91.3)	1,065 (92.8)	641 (93.2)
Black	44 (3.2)	23 (2.0)	15 (2.2)
Asian/Pacific Islander	36 (2.6)	35 (3.0)	10 (1.5)
Other/unknown	41 (2.9)	25 (2.2)	22 (3.2)
Education			
Less than high school	161 (11.6)	123 (10.7)	47 (6.8)
High school	493 (35.5)	394 (34.3)	200 (29.1)
Some college	441 (31.7)	383 (33.4)	225 (32.7)
College/college graduate	294 (21.2)	248 (21.6)	216 (31.4)
Missing	1	0	0
Parity			
Nulliparous	122 (8.8)	125 (10.9)	91 (13.2)
Parous	1,268 (91.2)	1,023 (89.1)	597 (86.8)
Age at menopause (y)			
23-39	82 (8.9)	39 (5.2)	10 (2.1)
40-44	123 (13.4)	78 (10.4)	40 (8.4)
45-49	233 (25.3)	206 (27.4)	131 (27.4)
50-54	337 (36.6)	293 (39.0)	193 (40.4)
≥55	146 (15.9)	135 (18.0)	104 (21.8)
Missing	469	397	210
Recency of menopausal hormone therapy use			
Never user	414 (32.7)	312 (30.2)	125 (19.4)
Former user of hormone therapy	234 (18.5)	182 (17.6)	89 (13.8)
Current EHT user	420 (33.2)	280 (27.1)	178 (27.6)
Current CHT user	197 (15.6)	259 (25.1)	252 (39.1)
Missing	125	115	44
First-degree family history of breast cancer			
No	1,094 (83.8)	848 (77.9)	518 (77.3)
Yes	212 (16.2)	241 (22.1)	152 (22.7)
Missing	84	59	18
Body mass index, quartiles (kg/m^2)			
≤23.16	347 (25.7)	263 (23.5)	195 (28.8)
23.17-26.44	349 (25.9)	279 (25.0)	154 (22.8)
26.45-30.82	326 (24.2)	280 (25.0)	180 (26.6)
≥30.83	326 (24.2)	296 (26.5)	147 (21.7)
Missing	42	30	12
History of ulcers			
No	1,239 (89.3)	1,019 (88.8)	614 (89.4)
Yes	149 (10.7)	128 (11.2)	73 (10.6)
Unknown	2	1	1

Abbreviations: EHT, estrogen hormone therapy; CHT, combined hormone therapy.

cimetidine, famotidine, and ranitidine separately. Because few women reported nizatidine use, we did not evaluate it separately.

Women with missing H_2 blocker use data were excluded (n = 31). Additionally, we excluded women who began using H_2 blockers less than 1 year before their reference date (n = 32) or who used H_2 blockers for less than 3 months (n = 142) because such a short duration of use is unlikely to affect breast cancer risk. As a result, the final analytic data set consisted of 1,386 controls, 1,144 IDC cases, and 686 ILC cases.

Analysis. To compare IDC and ILC cases with controls, unconditional polytomous logistic regression was used to calculate odds ratios (OR) and 95% CI (13). The reference category was never users of H_2 blockers. Variables considered as potential confounders or effect modifiers included race, income, marital status, education, age at menarche, parity, age at first birth, type of menopause, age at menopause, duration of oral contraceptive use, family history of breast cancer, body mass index, smoking status, and average alcohol intake. We evaluated the effect of these potential confounders on ever use and current use of each H_2 blocker separately and all H_2 blockers combined. None of these variables changed our risk estimates by more than 10%, and so none were included in the final statistical models. Because use of menopausal hormone therapy is associated with breast cancer risk and hormone therapy use may be associated with use of H_2 blockers (that is, because these women may be more likely to use prescription medications), use of hormone therapy was considered an *a priori* confounder and was thus controlled for in all analyses. As such, analyses were

Table 2. Relationship between ever use, duration, and recency of H_2 blockers and histologic types of breast cancer

	Controls (n = 1,390)	Ductal carcinoma (n = 1,148)		Lobular carcinoma (n = 688)	
	n (%)	n (%)	OR* (95% CI)	n (%)	OR* (95% CI)
Any H_2 blocker use					
Never use	1,136 (82.0)	939 (82.1)	1.0 (Reference)	543 (79.2)	1.0 (Reference)
Ever use	250 (18.0)	205 (17.9)	0.9 (0.8-1.2)	143 (20.8)	0.9 (0.7-1.2)
<2 y	89 (6.9)	77 (7.2)	1.1 (0.8-1.5)	56 (8.7)	1.2 (0.8-1.8)
≥2 y	67 (5.2)	60 (5.6)	1.0 (0.7-1.5)	42 (6.6)	1.0 (0.6-1.5)
Former	127 (9.7)	105 (9.7)	1.0 (0.8-1.4)	72 (11.1)	1.2 (0.8-1.6)
Current	45 (3.4)	44 (4.0)	1.1 (0.7-1.7)	33 (5.1)	1.0 (0.6-1.7)
Cimetidine					
Never use	1,136 (92.5)	939 (92.1)	1.0 (Reference)	543 (91.6)	1.0 (Reference)
Ever use	92 (7.5)	81 (7.9)	1.1 (0.8-1.5)	50 (8.4)	1.0 (0.7-1.6)
<2 y	56 (4.6)	54 (5.3)	1.2 (0.8-1.8)	26 (4.4)	1.0 (0.6-1.7)
≥2 y	36 (2.9)	27 (2.6)	0.9 (0.5-1.5)	24 (4.0)	1.1 (0.6-1.9)
Former	78 (6.4)	71 (7.0)	1.1 (0.8-1.6)	37 (6.2)	0.9 (0.6-1.4)
Current	14 (1.1)	10 (1.0)	0.9 (0.4-2.0)	13 (2.2)	1.6 (0.7-3.8)
Famotidine					
Never use	1,136 (96.2)	939 (96.4)	1.0 (Reference)	543 (94.8)	1.0 (Reference)
Ever use	45 (3.8)	35 (3.6)	0.9 (0.6-1.5)	30 (5.2)	1.2 (0.7-2.1)
<2 y	34 (2.9)	22 (2.3)	0.8 (0.4-1.4)	19 (3.3)	1.0 (0.6-1.9)
≥2 y	11 (0.9)	13 (1.3)	1.4 (0.6-3.3)	11 (1.9)	1.9 (0.8-4.9)
Former	30 (2.5)	21 (2.2)	0.8 (0.4-1.4)	24 (4.2)	1.5 (0.8-2.7)
Current	15 (1.3)	14 (1.4)	1.2 (0.6-2.4)	6 (1.0)	0.7 (0.2-2.1)
Ranitidine					
Never use	1,136 (93.6)	939 (92.7)	1.0 (Reference)	543 (91.1)	1.0 (Reference)
Ever use	78 (6.4)	74 (7.3)	1.1 (0.8-1.6)	53 (8.9)	1.1 (0.7-1.6)
<2 y	49 (4.0)	39 (3.8)	1.0 (0.6-1.5)	34 (5.7)	1.3 (0.8-2.0)
≥2 y	29 (2.4)	35 (3.5)	1.3 (0.8-2.3)	19 (3.2)	0.8 (0.4-1.6)
Former	63 (5.2)	45 (4.4)	0.8 (0.6-1.3)	38 (6.4)	1.0 (0.7-1.6)
Current	15 (1.2)	29 (2.9)	2.2 (1.1-4.3)†	15 (2.5)	1.3 (0.6-2.8)

NOTE: Eleven controls, 11 IDC cases, and 8 ILC cases reported ever use of nizatidine. Seven controls, 4 IDC cases, and 3 ILC cases reported current use of more than one H_2 blocker.
*ORs adjusted for age (continuous), reference year, hormone therapy use, and study.
†$P < 0.05$.

adjusted for age (continuous), reference year, recency of hormone therapy use (never user, former user of hormone therapy, current user of estrogen therapy, and current user of combined estrogen and progestin therapy), and study. We assessed effect modification using likelihood ratio testing. All analyses were conducted using Stata 9.2 (Stata Corp., College Station, TX).

Results

Compared with controls, ILC cases were more likely to be younger, have a college degree, nulliparous, and be older at menopause (Table 1). Both IDC and ILC cases were more likely than controls to be current users of combined estrogen and progestin hormone therapy and

Table 3. Relationship between H_2 blockers and histologic types of breast cancer among ever users of cimetidine, famotidine, and ranitidine

	Controls (n = 202)	Ductal carcinoma (n = 169)		Lobular carcinoma (n = 117)	
	n (%)	n (%)	OR* (95% CI)	n (%)	OR* (95% CI)
Cimetidine					
Never use	110 (54.5)	88 (52.1)	1.0 (Reference)	67 (57.3)	1.0 (Reference)
Ever use	92 (45.5)	81 (47.9)	1.1 (0.7-1.7)	50 (42.7)	1.0 (0.6-1.6)
Former	78 (38.6)	71 (42.0)	1.1 (0.7-1.8)	37 (31.6)	0.8 (0.5-1.5)
Current	14 (6.9)	10 (5.9)	0.9 (0.4-2.1)	13 (11.1)	1.5 (0.6-3.8)
Famotidine					
Never use	173 (79.4)	156 (81.7)	1.0 (Reference)	91 (75.2)	1.0 (Reference)
Ever use	45 (20.6)	35 (18.3)	0.9 (0.5-1.4)	30 (24.8)	1.3 (0.7-2.3)
Former	30 (13.8)	21 (11.0)	0.7 (0.4-1.4)	24 (19.8)	1.5 (0.8-2.9)
Current	15 (6.9)	14 (7.3)	1.1 (0.5-2.3)	6 (5.0)	0.8 (0.3-2.4)
Ranitidine					
Never use	117 (60.0)	99 (57.2)	1.0 (Reference)	60 (53.1)	1.0 (Reference)
Ever use	78 (40.0)	74 (42.8)	1.0 (0.7-1.6)	53 (46.9)	0.9 (0.5-1.5)
Former	63 (32.3)	45 (26.0)	0.8 (0.5-1.3)	38 (33.6)	0.9 (0.5-1.6)
Current	15 (7.7)	29 (16.8)	2.0 (1.0-4.2)	15 (13.3)	1.1 (0.5-2.6)

*ORs adjusted for age (continuous), reference year, hormone therapy use, and study.

have a family history of breast cancer. A similar proportion of cases and controls reported a history of ulcers (12.8% for IDC cases, 11.1% for ILC cases, and 11.9% for controls).

Women who ever used any H_2 blocker had similar risks of ductal and lobular breast cancer compared with never users (OR, 0.9; 95% CI, 0.8-1.2 and OR, 0.9; 95% CI, 0.7-1.2, respectively; Table 2). Duration and recency of use also did not alter risk. Ever users of cimetidine did not have elevated risks of IDC or ILC tumors (OR, 1.1; 95% CI, 0.8-1.5 and OR, 1.0; 95% CI, 0.7-1.6, respectively) irrespective of duration. Current users of cimetidine had a nonsignificant elevated risk of ILC (OR, 1.6; 95% CI, 0.7-3.8). No elevations in risk of IDC or ILC were observed among ever users of ranitidine or famotidine compared with never users. A nonsignificant elevated risk of ILC was observed among women who were users of famotidine for more than 2 years (OR, 1.9; 95% CI, 0.8-4.9), but no elevation in risk was observed among current users of famotidine. Current users of ranitidine had a 2.2-fold risk of IDC (95% CI, 1.1-4.3).

To address potential confounding by indication in terms of all the selection factors that result in a woman taking H_2 blockers, we restricted analyses to women who were ever users of cimetidine, famotidine, or ranitidine (Table 3). No association between ulcer medication use and risks of IDC or ILC was observed. We did find that current users of ranitidine had a 2.0-fold (95% CI, 1.0-4.2) increased risk of IDC, but this elevation was within the limits of chance. This result suggests that the elevated risk of IDC among current users of ranitidine is unlikely caused by confounding by indication.

Ever users of any H_2 blocker did not have elevated risks of either ER+/PR+ IDC or ER+/PR+ ILC (Table 4). Current cimetidine users had a 1.9-fold (95% CI, 0.8-4.8) increased risk of ER+/PR+ ILC, although this estimate was based on a small number of cases and was within the limits of chance. Current ranitidine users had an increased risk of ER+/PR+ IDC (OR, 2.4; 95% CI, 1.2-4.9) but not of ER+/PR+ ILC. Neither ever nor current use of any H_2 blocker, cimetidine, famotidine, or ranitidine was associated with risk of either ER+/PR- IDC or ER-/PR- IDC (data not shown). Risks of ER-/PR+ IDC or ILC defined by other categories of ER/PR could not be assessed due to the rarity of these tumor types.

Discussion

There are several limitations of this study. Because data on H_2 blocker use were based on self-reports, recall bias could occur. To minimize this bias, a list of all H_2 blocker names and a life events calendar were presented to every woman interviewed. Ideally, to determine accuracy of reporting, we would compare self-reported use to pharmacy records. However, the H_2 blockers assessed here are now all over-the-counter medications. It should also be noted that only 82.0% of eligible cases and 75.2% of eligible controls were interviewed. If women who were interviewed differed from women who were not interviewed according to use of H_2 blockers, then our results could be biased. We also had no data on the strength or frequency of H_2 blocker use. Such data are relevant given that cimetidine and ranitidine concentration is strongly positively related with serum prolactin levels (3, 5). Finally, our power was limited to detect associations between certain aspects of use of particular types of H_2 blockers, such as recency and duration, in relation to risk of IDC and ILC.

We found no association between ever use of any H_2 blocker and breast cancer risk, which is consistent with the only other study that evaluated breast cancer risk among users of any H_2 blocker. Rossing et al. conducted a study of 48,000 subscribers to the Group Health

Table 4. Relationship between ever use and recency of H_2 blockers to risk of histologic types of breast cancer by ER+/PR+ status

	Controls (n = 1,390)	Ductal carcinoma (n = 812)		Lobular carcinoma (n = 525)	
	n (%)	n (%)	OR* (95% CI)	n (%)	OR* (95% CI)
Any H_2 blocker use					
Never use	1,136 (82.0)	666 (82.2)	1.0 (Reference)	413 (79.0)	1.0 (Reference)
Ever use	250 (18.0)	144 (17.8)	0.9 (0.7-1.1)	110 (21.0)	1.0 (0.7-1.2)
Former	127 (9.7)	69 (9.0)	0.9 (0.6-1.3)	52 (10.5)	1.1 (0.7-1.6)
Current	45 (3.4)	33 (4.3)	1.1 (0.7-1.8)	28 (5.7)	1.1 (0.6-1.9)
Cimetidine					
Never use	1,136 (92.5)	666 (92.2)	1.0 (Reference)	413 (91.4)	1.0 (Reference)
Ever use	92 (7.5)	56 (7.8)	1.0 (0.7-1.5)	39 (8.6)	1.1 (0.7-1.7)
Former	78 (6.4)	49 (6.8)	1.1 (0.7-1.6)	28 (6.2)	0.9 (0.6-1.6)
Current	14 (1.1)	7 (1.0)	0.9 (0.3-2.2)	11 (2.4)	1.9 (0.8-4.8)
Famotidine					
Never use	1,136 (96.2)	666 (96.5)	1.0 (Reference)	413 (94.1)	1.0 (Reference)
Ever use	45 (3.8)	24 (3.5)	0.9 (0.5-1.5)	26 (5.9)	1.4 (0.8-2.4)
Former	30 (2.5)	14 (2.0)	0.7 (0.4-1.4)	21 (4.8)	1.7 (0.9-3.4)
Current	15 (1.3)	10 (1.4)	1.1 (0.5-2.6)	5 (1.1)	0.6 (0.2-2.1)
Ranitidine					
Never use	1,136 (93.6)	666 (92.5)	1.0 (Reference)	413 (91.0)	1.0 (Reference)
Ever use	78 (6.4)	54 (7.5)	1.0 (0.7-1.5)	41 (9.0)	1.0 (0.7-1.6)
Former	63 (5.2)	30 (4.2)	0.7 (0.4-1.2)	28 (6.2)	1.0 (0.6-1.6)
Current	15 (1.2)	24 (3.3)	2.4 (1.2-4.9)†	13 (2.9)	1.2 (0.5-2.7)

*ORs adjusted for age (continuous), reference year, hormone therapy use, and study.
†$P < 0.05$.

Cooperative of Puget Sound, a large health maintenance organization in western Washington, to compare breast cancer rates in ever users of all H_2 blockers with population rates of breast cancer in female residents of western Washington (11). Users of any H_2 blocker were defined as those who filled at least two prescriptions for a specific H_2 blocker within 6 months. They observed a standardized incidence ratio of 1.0 (95% CI, 0.9-1.1) based on 518.2 expected cases and 507 observed cases. Although they could not specifically evaluate current use of H_2 blockers, they did attempt to account for recency of use (that is, ≤1 year since last prescription) and found no association between recency of any H_2 blocker use and breast cancer risk.

We observed that current ranitidine users experience a 2.2-fold increased risk of IDC that was mostly confined to a 2.4-fold increased risk of ER+/PR+ IDC compared with never users of H_2 blockers. To our knowledge, only one other study has specifically evaluated the relationship between ranitidine and breast cancer risk. A cohort study of ~26,000 women identified from two computerized pharmacy databases of medications dispensed by Northern California Kaiser Permanente between 1982 and 1987 showed no altered risk of breast cancer among women with at least one prescription of ranitidine compared with never users (OR, 0.92; 95% CI, 0.49-1.71; ref. 9).

However, the authors could only evaluate time since last prescription and could not specifically evaluate the effect of current ranitidine use on breast cancer risk. Furthermore, this study was limited by a small number of cases who took ranitidine (n = 10). Conversely, the number of breast cancer cases in our study who reported ranitidine use was large (n = 127), thus strengthening our results. Whereas ranitidine has been observed to raise prolactin levels only modestly compared with cimetidine, it is still plausible that it could increase breast cancer risk through this pathway. In the United States, typical over-the-counter ranitidine doses are 75 and 150 mg, whereas prescription doses can range up to 300 mg, and ranitidine doses greater than 200 mg have been shown to increase prolactin concentrations (5).

Our results suggest that cimetidine use does not increase risk of IDC or ILC, which is consistent with prior studies that have observed no association between cimetidine use and risk of breast cancer overall (8-11). Also consistent with these findings, we observed no associations with recency or duration of cimetidine use. Whereas these other studies did not evaluate the relationship between cimetidine use and risk of breast cancer subtypes defined by histology or hormone receptor status, we did not find that this relationship varied by the subtypes assessed here. Prior studies have not evaluated the effect of famotidine use on breast cancer risk separately from other H_2 blockers. We did not observe that famotidine use was related to risk of IDC or ILC, which is not surprising given that famotidine has not been shown to influence hormone levels. However, these analyses were limited by the comparatively few famotidine users included in this study.

In conclusion, our data suggest that current users of ranitidine have a higher risk of hormone receptor–positive ductal carcinoma. However, our data do not support an association between cimetidine use and breast cancer. The reason why ranitidine, but not cimetidine, may be related to IDC risk is unclear, particularly given the greater potency of cimetidine to elevate prolactin levels. It is also unknown why ranitidine would be related to risk of IDC, particularly ER+/PR+ IDC, but not to ILC or ER+/PR+ ILC because in general ILC is more hormonally responsive than IDC. However, we cannot rule out that this observed increased risk of breast cancer among ranitidine users is a chance finding due to the number of statistical tests we did. Whereas these results add to a growing body of evidence that rebuts a hypothesized link between cimetidine use and breast cancer, further study of a possible link between ranitidine use and breast cancer risk is warranted.

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