Short Communication

Cimetidine Use and Risk of Prostate and Breast Cancer

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Abstract

Histamine (H_2) receptor antagonists, such as cimetidine and ranitidine, became available in the late 1970s and presently number among the most commonly used drugs. Cimetidine has been hypothesized to exert a cancer preventive effect on the prostate due to its ability to inhibit the binding of dihydrotestosterone to androgen receptors. Other hormonal effects of this drug include increases in serum prolactin levels and inhibition of 2-hydroxylation of estradiol. We assessed risk of prostate and breast cancers in a cohort of 48,512 members of the Group Health Cooperative of Puget Sound prescribed cimetidine or another H_2 blocker between 1977 and 1995. Standardized incidence ratios were calculated comparing the observed numbers of cancers to those expected based on population rates in western Washington State. Because cimetidine, but not other H_2 blockers, influences hormonal activity and metabolism, we conducted nested case-control studies comparing cancer risk among individuals treated with cimetidine to individuals who used other H_2 blockers. Risks of breast and prostate cancers were identical among users of cimetidine and users of other H_2 blockers (relative risk, 1.0 for both cancers). We observed no trend in risk of breast cancer according to time since first or last cimetidine prescription or number of cimetidine prescriptions filled. For prostate cancer, our findings were similar save for a modest increase in risk among men who had filled ≥21 cimetidine prescriptions (relative risk, 1.4; 95% confidence interval, 1.0–1.9). Our results suggest that use of cimetidine does not influence risk of female breast cancer. Further, these data provide little evidence to support the previously hypothesized preventive effect of cimetidine on risk of prostate cancer.

Introduction

Cimetidine, ranitidine, famotidine, and nizatidine are H_2 receptor antagonists (H_2 blockers) that are widely used for the treatment and prevention of peptic and duodenal ulcers, gastroesophageal reflux disorders, and hypersecretory states (1–4). In 1977, cimetidine was approved for use in the United States, followed in the early 1980s by ranitidine and more recently by famotidine and nizatidine. In 1988, cimetidine was the sixth most commonly prescribed drug in the United States (5). In late 1995, cimetidine and famotidine were approved in the United States for over-the-counter sale for the control of heartburn, acid indigestion, and sour stomach, followed in 1996 by ranitidine and nizatidine.

In contrast to this widespread exposure, the hypothesis that cimetidine, through its effects on androgen binding or estrogen metabolism, may influence the risk of hormonally mediated cancers, has been explored in only a few studies (6–8). Cimetidine, but not the other H_2 blockers, has been suggested to exert a cancer preventive effect on the prostate due to its ability to inhibit the binding of dihydrotestosterone to androgen receptors (9). Other hormonal effects of this drug include increases in serum prolactin levels (1) and inhibition of 2-hydroxylation of estradiol (10, 11).

We examined risk of prostate and breast cancer in users of H_2 blockers within the membership of the GHC[2] of Puget Sound. To reduce the extent to which our results might be influenced by confounding by indications for use of H_2 blockers and because only cimetidine notably influences androgen binding and estrogen metabolism, we assessed the risk of cancer among individuals treated with cimetidine relative to that of individuals who used other H_2 blockers.

Materials and Methods

Computerized records maintained by GHC served as data sources, including the enrollment, pharmacy, demographic, and GHC-specific CSS databases. The pharmacy database includes information on each prescription dispensed at GHC-owned outpatient pharmacies since March 1977. Between 89% and 99% of prescriptions written to GHC members are filled at GHC pharmacies (12). A computerized record is created every time a prescription is filled, and it contains the patient consumer number, the drug number, date dispensed, and quantity dispensed. The drug number links the prescription to the drug form, strength, and other specific drug information. Using this database, we identified individuals prescribed H_2 blockers during the interval of March 1977 through December 1995.

The enrollment data files contain a record for each person ever enrolled at GHC, and they include the beginning and ending dates of all enrollment periods. Information on date of birth and gender are available in a separate demographic file. We used data from these files to calculate the person-time contribution of each eligible individual during enrollment from age 20 through age 84.

Cancers were identified using data provided to GHC by

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[2] The abbreviations used are: GHC, Group Health Cooperative; CSS, Cancer Surveillance System; SEER, Surveillance, Epidemiology, and End Results; SIR, standardized incidence ratio; CI, confidence interval; RR, relative risk; PSA, prostate-specific antigen.

Table 1 Risk of breast cancer among female users of H_2 blockers in GHC relative to the general population of western Washington State, 1977–1996

	Observed	Expected	SIR	95% CI
All users	507	518.2	1.0	0.9–1.1
Time since cohort entry (mo)				
0–11	68	76.8	0.9	0.7–1.1
12–59	223	234.8	1.0	0.8–1.1
60–119	154	149.8	1.0	0.9–1.2
120+	62	56.8	1.1	0.8–1.4
By type(s) of H_2 blocker used				
Cimetidine only	267	281.8	0.9	0.8–1.1
Time since cohort entry (mo)				
0–11	30	42.0	0.7	0.5–1.0
12–59	118	122.5	1.0	0.8–1.2
60–119	83	84.3	1.0	0.8–1.2
120+	36	33.0	1.1	0.8–1.5
Cimetidine and other	165	166.3	1.0	0.8–1.2
Time since cohort entry (mo)				
0–11	20	18.2	1.1	0.7–1.7
12–59	62	70.2	0.9	0.7–1.1
60–119	58	54.8	1.1	0.8–1.4
120+	25	23.2	1.1	0.7–1.6
Other only	75	70.0	1.1	0.8–1.3
Time since cohort entry (mo)				
0–11	18	16.6	1.1	0.6–1.7
12–59	43	42.2	1.0	0.7–1.4
60–119	13	10.7	1.2	0.6–2.1
120+	1	0.6	1.7	0.0–9.4

Table 2 Risk of prostate cancer among male users of H_2 blockers in GHC relative to the general population of western Washington State, 1977–1996

	Observed	Expected	SIR	95% CI
All users	403	535.3	0.8	0.7–0.8
Time since cohort entry (mo)				
0–11	47	73.0	0.6	0.5–0.9
12–59	176	230.1	0.8	0.7–0.9
60–119	130	167.3	0.8	0.6–0.9
120+	50	64.9	0.8	0.6–1.0
By type(s) of H_2 blocker used				
Cimetidine only	191	271.7	0.7	0.6–0.8
Time since cohort entry (mo)				
0–11	18	33.8	0.5	0.3–0.8
12–59	92	109.4	0.8	0.7–1.0
60–119	54	91.0	0.6	0.4–0.8
120+	27	37.5	0.7	0.5–1.0
Cimetidine and other	151	180.2	0.8	0.7–1.0
Time since cohort entry (mo)				
0–11	13	17.6	0.7	0.4–1.3
12–59	50	71.8	0.7	0.5–0.9
60–119	65	64.0	1.0	0.8–1.3
120+	23	26.7	0.9	0.5–1.3
Other only	61	83.4	0.7	0.6–0.9
Time since cohort entry (mo)				
0–11	16	21.6	0.7	0.4–1.2
12–59	34	48.9	0.7	0.5–1.0
60–119	11	12.3	0.9	0.4–1.6
120+	0	0.7	0	0.0–5.6[a]

[a] One-sided 97.5% CI.

the CSS, a population-based cancer registry operating as part of the SEER program of the National Cancer Institute. This database contains information on all incident cancers diagnosed among GHC members after 1973, including anatomical site, histology, and stage at diagnosis.

The study was restricted to individuals who filled at least two prescriptions for either cimetidine or another type of H_2 blocker within a 6-month period, and each individual was first considered a "user" of a specific H_2 blocker on the date of the second of these prescriptions. The filling of two prescriptions within this interval gives some assurance that the drug was actually taken. We estimated the extent of cimetidine exposure by summing the total number of cimetidine prescriptions filled, starting this count from the prescription that determined eligible cimetidine use. Entry into the cohort occurred at the time of the prescription fill that determined eligibility (if >20 years of age) or at the first date of enrollment after age 20 (if "eligible" drug use had occurred before 20 years of age). End-of-follow-up was the first of: December 31, 1996; end of enrollment; attaining age 85; or diagnosis of prostate or female breast cancer. Cancers were ascertained throughout follow-up until December 31, 1996.

SIRs and associated 95% CIs were calculated comparing the observed numbers of cancers in the cohort overall and in subgroups by type of drug used to those expected based on the age- (5-year strata), gender-, and calendar year-specific (1-year strata) population rates in western Washington State reported by SEER for the CSS reporting area for 1977–1995 (13) and by the CSS for 1996 (SEER data were not available for 1996). We conducted nested case-control studies using conditional logistic regression to compute odds ratios as estimates of RRs, together with 95% CI, of prostate and female breast cancers associated with cimetidine use within the study cohort. These latter analyses were based on the hypothesis that cimetidine use in particular might influence risk of breast or prostate cancer because of its distinctive hormonal effects; thus, users of H_2 blockers other than cimetidine were considered the "unexposed" group. For each case, we selected 10 controls matched on gender and year of birth (3-year strata) from among those cohort members who had not developed breast or prostate cancer and were under observation at the diagnosis age of the matched case using the survival time to case-control procedure of Stata (Stata Statistical Software, Release 6.0., Stata Corporation, College Station, TX). Cases and controls were assigned a reference date corresponding to the diagnosis date for cases and a comparable date for matched controls. Cases diagnosed before 1984 (and their matched controls) were excluded from these analyses because H_2 blockers other than cimetidine were not used within GHC until that year.

Results

We identified 54,239 individuals who had filled two or more prescriptions for cimetidine or another H_2 blocker within a 6-month interval. We excluded individuals for the following reasons: no GHC enrollment after age 20 or before age 85 (n = 923); first eligible drug use after age 84 (n = 992); missing data on enrollment dates (n = 350) or date of birth (n = 2); inconsistent data in the pharmacy and enrollment data files (n = 713); and one individual with prostate cancer with an unknown diagnosis year. Among individuals with multiple enrollment periods (n = 2746), there was a larger extent of discrepant information among the enrollment, pharmacy, and cancer incidence data files. We therefore restricted our analyses to individuals with only one enrollment period after study entry. Thus, 48,512 individuals (20,709 men and 27,803 women) were included in the analytic cohort.

In all, 253,217 person-years (108,704 in men and 144,513

Table 3 Relation of cimetidine use to risk of breast cancer among female users of H_2 blockers in GHC, 1984–1996

	Controls (N = 4740)		Cases (N = 474)		RR (95% CI)	
	N	%	N	%		
Ever used cimetidine						
No	793	16.7	82	17.3	1.0	
Yes	3947	83.3	392	82.7	1.0	(0.7–1.2)
No. of prescriptions						
Never used	793	16.7	82	17.3	1.0	
1	763	16.1	75	15.8	0.9	(0.7–1.3)
2–3	874	18.4	92	19.4	1.0	(0.7–1.4)
4–10	1146	24.2	110	23.2	0.9	(0.7–1.3)
11–20	590	12.4	53	11.2	0.9	(0.6–1.2)
21+	574	12.1	62	13.1	1.0	(0.7–1.5)
Time since first eligible prescription						
Never used	793	16.7	82	17.3	1.0	
<2 yr	953	20.1	88	18.6	0.9	(0.6–1.2)
2 to <5 yr	1134	23.9	109	23.0	0.9	(0.7–1.2
5 to <8 yr	906	19.1	91	19.2	1.0	(0.7–1.3)
8+ yr	954	20.1	104	21.9	1.1	(0.8–1.4)
Time since last prescription						
Never used	793	16.7	82	17.3	1.0	
≤1 yr	1804	38.1	182	38.4	1.0	(0.7–1.3)
>1 yr to <2 yr	494	10.4	47	9.9	0.9	(0.6–1.3)
2 to <5 yr	941	19.8	82	17.3	0.8	(0.6–1.2)
5+ yr	708	14.9	81	17.1	1.1	(0.8–1.5)

Table 4 Relation of cimetidine use to risk of prostate cancer among male users of H_2 blockers in GHC, 1984–1996

	Controls (N = 3920)		Cases (N = 392)		RR (95% CI)	
	N	%	N	%		
Ever used cimetidine						
No	708	18.1	68	17.4	1.0	
Yes	3212	81.9	324	82.6	1.0	(0.8–1.4)
No. of prescriptions						
Never used	708	18.1	68	17.4	1.0	
1	558	14.2	55	14.0	1.0	(0.7–1.5)
2–3	673	17.2	54	13.8	0.8	(0.6–1.2)
4–10	899	22.9	96	24.5	1.1	(0.8–1.5)
11–20	542	13.8	48	12.2	0.9	(0.6–1.4)
21+	540	13.8	71	18.1	1.4	(1.0–1.9)
Time since first eligible prescription						
Never used	708	18.1	68	17.4	1.0	
<2 yr	681	17.4	54	13.8	0.8	(0.5–1.2)
2 to <5 yr	948	24.2	103	26.3	1.1	(0.8–1.6)
5 to <8 yr	790	20.2	81	20.7	1.1	(0.8–1.5)
8+ yr	793	20.2	86	21.9	1.1	(0.8–1.6)
Time since last prescription						
Never used	708	18.1	68	17.4	1.0	
≤1 yr	1461	37.3	154	39.3	1.1	(0.8–1.5)
>1 yr to <2 yr	407	10.4	36	9.2	0.9	(0.6–1.4)
2 to <5 yr	747	19.1	69	17.6	1.0	(0.7–1.4)
5+ yr	597	15.2	65	16.6	1.1	(0.8–1.6)

in women) were observed in the study cohort, with a mean follow-up of 5.2 years. SIRs were calculated for: users of cimetidine only (n = 29,103; mean follow-up, 5.1 years); users of both cimetidine and other H_2 receptor antagonists (n = 9792; mean follow-up, 7.4 years); and individuals who only used H_2 receptor antagonists other than cimetidine (n = 9,617; mean follow-up, 3.4 years). Breast cancer (including *in situ* and invasive disease) was diagnosed among 507 women, and prostate cancer was diagnosed in 403 men during follow-up. Eleven of these 507 women were known to have had breast cancer diagnosed both before and after study entry; these women were excluded from the case-control analyses.

The risk of breast cancer among women who had taken an H_2 blocker was similar to that of female residents of western Washington State (Table 1), whereas in male users, the risk of prostate cancer was less than that of the general population. This latter reduction in risk was uniformly observed when users of H_2 blockers were separated into subgroups according to the types of drugs used (Table 2). No trend in risk of breast or prostate cancer according to the time since entry into the study was noted. Risk of prostate cancer among users of H_2 blockers was similar to the general population during 1977–1984 (SIR = 0.96; 95% CI, 0.64–1.38) and reduced during later calendar years (SIR for 1985–1989 = 0.82; 95% CI, 0.68–0.99 and SIR for 1990–1996 = 0.71; 95% CI, 0.63–0.80).

Risk of breast cancer in women who took cimetidine was similar to that among women who had only used other H_2 blockers (Table 3). We observed no evidence that risk varied by the number of cimetidine prescriptions filled or by the time since starting or stopping use of this drug. Similar results were observed in subgroups of women aged <50 years and ≥50 years of age at the reference date.

Risk of prostate cancer was also similar in ever-users of cimetidine relative to users of other H_2 blockers (Table 4). Although we observed no clear trend in risk according to the number of cimetidine prescriptions, risk was somewhat increased among men who had filled ≥21 prescriptions (RR, 1.4; 95% CI, 1.0–1.9). Analyses conducted separately among men with localized prostate cancer (n = 224) and men with regional/distant disease (n = 122; stage data missing for 46 cases) and their matched controls yielded similar findings.

Discussion

Strengths of this study include its large size, as well as the availability of an identifiable and relatively stable population base and computerized databases with information regarding dates of GHC membership, use of H_2 blockers, and incidence of cancer. Relative to data collected via an in-person interview, exposure data ascertained from the pharmacy database are likely to be accurate and complete. The time period of the study minimizes exposure misclassification due to over-the-counter availability of H_2 blockers.

Some weaknesses of the study also result from the exclusive use of GHC databases, including the potential for uncontrolled confounding by factors for which no data are available. However, compared with other area residents, GHC enrollees have slightly higher educational levels but are similar with respect to age, race/ethnicity, and marital status (12). Also, our measure of extent of use (number of prescriptions) may be a relatively crude estimate of the length of time cimetidine was used, resulting in a reduced ability to observe any association with duration of cimetidine use. We did not incorporate information regarding the strength of cimetidine dispensed because prescribing instructions were not available for most prescriptions.

To reduce the possibility of confounding by drug indication, we conducted nested case-control studies comparing cancer risk in cimetidine users to users of other H_2 blockers (of these, the most commonly prescribed agent was ranitidine, which accounted for 99.1% of noncimetidine prescriptions in this cohort). Some recent literature suggests that H_2 blockers may impact the progression of some cancers through enhancing

immune response (14, 15), although this has been questioned (16). To the extent that hormonal or immunomodulatory effects on cancer risk may occur similarly in users of cimetidine and other H_2 blockers, our RR estimates may be biased. To address this possibility, we assessed risk of breast and prostate cancers associated with number of cimetidine prescriptions among women and men who only used cimetidine, with individuals with one eligible prescription serving as the referent group. We again observed no association of breast cancer risk with number of cimetidine prescriptions; for prostate cancer, risk among men with >20 prescriptions was 1.4 (95% CI, 0.9–2.0).

Cimetidine, but not ranitidine or other H_2 blockers, inhibits the binding of dihydrotestosterone to androgen receptors and may decrease the synthesis of testosterone (10, 17, 18). For these reasons, cimetidine has been hypothesized to exert a cancer preventive effect on the prostate (9). Cimetidine also increases serum concentrations of prolactin (1), and recent evidence suggests that higher prolactin levels may be associated with an increased risk of postmenopausal breast cancer (19). At commonly administered dose levels, cimetidine inhibits cytochrome P-450-dependent metabolism of estradiol at the C-2 but not the C-16α position (10, 11). Results of some studies support the theory that increased 16α-hydroxylation of estrogens is a risk factor for breast cancer (20), whereas others suggest that catechol estrogens resulting from 2-hydroxylation are a cause of this disease (21). However, in a recent study (22), the urinary 2-hydroxyestrone:16α-hydroxyestrone ratio was not associated with risk of breast cancer in postmenopausal women.

Cancer incidence or mortality among cimetidine users has been examined in two European cohorts: one is a cohort of 10,694 men and 6,045 women in Denmark who were first prescribed cimetidine between 1977 and 1981; the other is a group of 5890 men and 3487 women in England who were first prescribed cimetidine between 1978 and 1980. To date, the effect of cimetidine on risk of prostate cancer has been examined only in the Danish cohort (6). In that population, the incidence of prostate cancer was increased in the first year after starting cimetidine use (RR, 1.84; 95% CI, 1.09–2.90) and reduced in the following years (RR excluding the first year of follow-up, 0.85; 95% CI, 0.65–1.09). To some extent, the observed reduction in risk may reflect the impact of increased cancer detection during the initial follow-up when increased risk was observed.

Risk of breast cancer in the Danish study was lower than that of the general population in the first year of follow-up, similar to that of the general population during years 2–5, and again reduced from 6 to 8 years after initiation of cimetidine use (7). In the English cohort, after an initial increased occurrence of breast cancer death in the first year of follow-up, breast cancer mortality rates resembled those of the general population for years 2–7, followed by a reduced risk of breast cancer mortality in years 8–10 (8). None of these associations was statistically significant.

In the present study, SIR analyses indicated that risk of breast cancer in women who used H_2 blockers was similar to that in the general population. Breast cancer risk among users of cimetidine was identical to that among users of other H_2 blockers and did not vary appreciably according to time elapsed since first or last cimetidine prescription or with number of cimetidine prescriptions. These results suggest that use of cimetidine does not influence the risk of female breast cancer.

Also, SIR analyses indicated that risk of prostate cancer among men in the study cohort was reduced relative to rates in western Washington State. The observations that this reduction in risk was (1) observed among users of various types of H_2 blockers and (2) was most evident during later calendar years suggest that this finding may reflect less frequent use of procedures such as transurethral resection of the prostate and PSA testing among GHC members relative to the western Washington population. Nationwide increases in prostate cancer incidence rates have been attributed to increased identification of asymptomatic cancers through transurethral resection of the prostate in the 1970s and 1980s and through PSA testing in the late 1980s and 1990s (23). In October 1991, the GHC Department of Medical Education conducted a review of the evidence and thereafter initiated a program to discourage PSA testing in asymptomatic men, after which the occurrence of such testing declined rapidly within GHC (24).

Relative to users of other H_2 blockers, users of cimetidine had a similar risk of prostate cancer, save for a modest elevation in risk among men who had filled ≥21 cimetidine prescriptions. This latter result is opposite to the hypothesized reduction in risk associated with reduced androgenic stimulation of the prostate among cimetidine users, and we know of no biological basis for the observed association. Conceivably, screening practices may differ among long-term users of cimetidine, leading to increased diagnosis of asymptomatic prostate cancers among this group. However, among men with ≥21 cimetidine prescriptions, risks of localized and regional/distant stage prostate cancer were similar (relative to never users, RR, 1.3; 95% CI, 0.8–2.2 and RR, 1.4; 95% CI, 0.8–2.6, respectively). Our results provide little evidence to support the previously hypothesized preventive effect of cimetidine on risk of prostate cancer and do not exclude the possibility that prostate cancer risk may be increased among long-term users of the drug.

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