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Ranitidine Use and Cancer Risk: Results from UK Biobank

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INTRODUCTION

Ranitidine (brand name Zantac) is an H_2-receptor antagonist (H_2-blocker) commonly used to treat gastroesophageal reflux and peptic ulcer disease. After recent studies demonstrated ranitidine degrades to form high levels of N-Nitrosodimethylamine (NDMA), a potent carcinogen in animal models and probable human carcinogen,[1,2] the US Food and Drug Administration (FDA) requested ranitidine sales be halted.[3] As the implications for human carcinogenesis remain unclear, we evaluated the association between ranitidine use and cancer risk in UK Biobank.

METHODS

UK Biobank is a prospective cohort of 502,506 men and women residing in the UK.[4] At baseline (2006-2010), participants completed a detailed questionnaire (assessing lifestyle and health history, among other factors); participants' information was also linked with

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health records and registries. We excluded those with prior history of invasive cancer, except non-melanoma skin cancer (n=27,666), and those missing exposure (n=10,134) or covariates (n=5,489), leaving 459,204 persons aged 38-73 for analysis.

The baseline questionnaire asked participants to indicate regular use of “ranitidine (e.g. Zantac)” and “omeprazole (e.g., Zanprol).” Regularly was defined as “most days of the week for the last 4 weeks.” Exposure was defined two ways: 1) a binary yes/no variable, and 2) use of ranitidine vs active comparator, omeprazole---a proton pump inhibitor (PPI) with similar indications of use. In active comparator analyses, persons reporting use of neither (n=424,221) or both (n=820) were excluded.

Primary outcomes include overall cancer (diagnosis with any invasive cancer, excluding non-melanoma skin cancer), and cancers of the colorectum, lung, breast and prostate. We also explored less-common malignancies of *a priori* interest (liver, kidney, bladder, and ovary).

Participants were followed until date of cancer diagnosis, death, loss-to-follow-up or end-of-study (10/31/15). For site-specific analyses, participants were censored at date of first invasive cancer. Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% cancer risk in UK Biobank. CIs). Minimally-adjusted and multivariable models are detailed in Table 1 footnotes and Supplemental Methods.

Analyses of overall cancer were stratified by sex, median age, BMI, and smoking status, with statistical significance of interaction assessed using a likelihood ratio test.

Sensitivity analyses (for overall cancer) were stratified by follow-up time, providing effect estimates in the first 5 years of follow-up vs thereafter.

UK Biobank was approved by the North West Multicenter Research Ethics Committee in the United Kingdom. The Memorial Sloan Kettering Cancer Center Institutional Review Board determined this analysis did not require oversight. Analyses were conducted using R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Of 459,204 study participants, 26,230 were diagnosed with cancer (median follow-up=6.7 years). Cases include cancers of the colorectum (n=2,728 cases), lung (n=1,833), breast (n=5,099), and prostate (n=5,164). Exploratory analyses examined associations pertaining to cancers of the liver (n=262), kidney (n=700), bladder (n=554), and ovary (n=483).

Overall, 8,844 (1.9%) study participants reported regular ranitidine use, whereas 26,959 (5.9%) reported omeprazole. Factors associated with use of ranitidine and omeprazole were generally comparable, with some small differences (Supplemental Table 1).

Regular use of ranitidine (yes/no) was not associated with overall cancer risk (HR=1.01; 95% CI=0.93-1.09) (Table 1). Active comparator results were similar (HR=0.94; 95%

CI=0.85-1.04). No significant associations were observed for cancers of the colorectum, lung, breast or prostate.

In exploratory analyses, regular ranitidine use (yes/no) was associated with 91% higher risk of liver cancer (HR=1.91; 95% CI=1.09-3.36) (Table 1); no association was observed in active comparator analyses (HR=1.15; 95% CI=0.58-2.26). Regular ranitidine use (yes/no) was associated with a non-significant decreased risk of kidney cancer (HR=0.53; 95% CI=0.27-1.02); this association strengthened to statistical significance in active comparator analyses (HR=0.39; 95% CI=0.19-0.82). No associations were observed for bladder or ovarian cancer.

BMI, age, sex, or smoking status did not modify the ranitidine-cancer association (not shown). In sensitivity analyses, the association between ranitidine and overall cancer risk was null in the first 5 years of follow-up, and inverse thereafter (Supplemental Table 2).

DISCUSSION

Ranitidine use was not associated with overall cancer risk. It is possible baseline use may not capture exposure in the etiologically-relevant timeframe, and longer follow-up may reveal different associations. When stratified by time, however, there was an inverse association in later years, reducing concern that shorter follow-up may obscure a strong positive association. Ranitidine use was not associated with risk of common cancers (lung, breast, prostate, and colorectum).

We explored associations for less-common cancer sites. Given drug metabolism and patterns of NDMA-induced malignancies in animal models, liver cancer was of particular *a priori* interest.[5] Compared to non-use, ranitidine use was positively associated with liver cancer; however, this association attenuated when directly compared to omeprazole, which may reflect residual confounding by indication (or another jointly-related factor). Alternatively, the association may have attenuated in active comparator analyses if omeprazole independently increases liver cancer risk. These possibilities need follow-up given inconsistent data for PPIs and liver cancer.[6] We explored ranitidine use and kidney cancer risk because of elevated urinary NDMA following ranitidine exposure—revealing an unexpected inverse association. While prior studies suggest PPI use (vs H2 blockers) is associated with increased risk of chronic kidney disease[7], data specific to renal malignancies are needed. Exploratory analyses of less-common cancers were underpowered and should be interpreted cautiously.

We used a large, prospective cohort to address a question of immediate public health relevance about which little is known; there were limitations, however. Exposure was self-reported, with few details; we were unable to examine associations by dose or distinguish long-vs. short-term use. Variables were captured at one timepoint; secular changes in exposure could lead to measurement error, attenuating results, and changes in covariates could lead to residual confounding. We did not capture long term outcomes; some data suggest longer latency between NDMA exposure and cancer.[8] Lastly, this study included adults, most of whom are white, potentially limiting generalizability.

We found no association between ranitidine use and cancers of the breast, prostate, lung or colorectum. The exploratory positive association with liver cancer and inverse association with kidney cancer are compelling for hypothesis-generation, and study findings merit confirmation in other populations. Cohorts with longer follow-up may further elucidate associations, particularly for less common malignancies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Association between Ranitidine and Cancer Risk

PRIMARY: Overall Cancer and Common Cancer Sites				
	Cohort N (%)	**Case N (%)**	**Minimally-Adjusted[a] HR (95% CI)**	**Multivariable-Adjusted[b] HR (95% CI)**
Overall Cancer[c]				
Regular Ranitidine Use				
No	450,360 (98.1)	25,665 (97.8)	Reference	Reference
Yes	8,844 (1.9)	565 (2.2)	1.06 (0.98, 1.15)	1.01 (0.93, 1.09)
Ranitidine vs Omeprazole				
Regular Omeprazole Use	26,139 (76.5)	1,907 (78.9)	Reference	Reference
Regular Ranitidine Use	8,024 (23.5)	509 (21.1)	0.95 (0.87, 1.05)	0.94 (0.85, 1.04)
Colorectal Cancer[d]				
Regular Ranitidine Use				
No	428,360 (98.1)	2,664 (97.7)	Reference	Reference
Yes	8,281 (1.9)	64 (2.3)	1.17 (0.92, 1.50)	1.12 (0.88, 1.44)
Ranitidine vs Omeprazole				
Regular Omeprazole Use	24,453 (76.4)	167 (74.6)	Reference	Reference
Regular Ranitidine Use	7,537 (23.6)	57 (25.4)	1.26 (0.93, 1.71)	1.25 (0.92, 1.69)
Lung Cancer[e]				
Regular Ranitidine Use				
No	450,360 (98.1)	1,783 (97.3)	Reference	Reference
Yes	8,844 (1.9)	50 (2.7)	1.32 (1.00, 1.75)	0.96 (0.72, 1.27)
Ranitidine vs Omeprazole				
Regular Omeprazole Use	26,139 (76.5)	199 (81.6)	Reference	Reference
Regular Ranitidine Use	8,024 (23.5)	45 (18.4)	0.84 (0.60, 1.16)	0.76 (0.55, 1.06)
Breast Cancer[f,g]				
Regular Ranitidine Use				
No	235,859 (98.1)	4,989 (97.8)	Reference	Reference
Yes	4,677 (1.9)	110 (2.2)	1.08 (0.89, 1.30)	1.04 (0.86, 1.26)
Ranitidine vs Omeprazole				
Regular Omeprazole Use	14,525 (77.3)	324 (76.1)	Reference	Reference
Regular Ranitidine Use	4,267 (22.7)	102 (23.9)	1.09 (0.87, 1.36)	1.08 (0.86, 1.35)
Prostate Cancer[h,i]				
Regular Ranitidine Use				
No	196,195 (98.1)	5,067 (98.1)	Reference	Reference
Yes	3,785 (1.9)	97 (1.9)	0.96 (0.78, 1.17)	1.01 (0.82, 1.23)
Ranitidine vs Omeprazole				

	Cohort N (%)	Case N (%)	Minimally-Adjusted[a] HR (95% CI)	Multivariable-Adjusted[b] HR (95% CI)
PRIMARY: Overall Cancer and Common Cancer Sites				
Regular Omeprazole Use	10,377 (75.2)	309 (78.6)	Reference	Reference
Regular Ranitidine Use	3,424 (24.8)	84 (21.4)	1.00 (0.78, 1.27)	1.02 (0.80, 1.30)
EXPLORATORY: Less-Common Cancer Sites				
Liver Cancer[j]				
Regular Ranitidine Use				
No	450,360 (98.1)	249 (95.0)	Reference	Reference
Yes	8,844 (1.9)	13 (5.0)	2.49 (1.43, 4.35)	1.91 (1.09, 3.36)
Ranitidine vs Omeprazole				
Regular Omeprazole Use	26,139 (76.5)	37 (77.1)	Reference	Reference
Regular Ranitidine Use	8,024 (23.5)	11 (22.9)	1.10 (0.56, 2.16)	1.15 (0.58, 2.26)
Kidney Cancer[k]				
Regular Ranitidine Use				
No	450,360 (98.1)	691 (98.7)	Reference	Reference
Yes	8,844 (1.9)	9 (1.3)	0.63 (0.33, 1.22)	0.53 (0.27, 1.02)
Ranitidine vs Omeprazole				
Regular Omeprazole Use	26,139 (76.5)	74 (90.2)	Reference	Reference
Regular Ranitidine Use	8,024 (23.5)	8 (9.8)	0.39 (0.19, 0.81)	0.39 (0.19, 0.82)
Bladder Cancer[l]				
Regular Ranitidine Use				
No	450,360 (98.1)	538 (97.1)	Reference	Reference
Yes	8,844 (1.9)	16 (2.9)	1.44 (0.87, 2.36)	1.22 (0.74, 2.01)
Ranitidine vs Omeprazole				
Regular Omeprazole Use	26,139 (76.5)	36 (73.5)	Reference	Reference
Regular Ranitidine Use	8,024 (23.5)	13 (26.5)	1.34 (0.71, 2.54)	1.30 (0.69, 2.46)
Ovarian Cancer[f,m]				
Regular Ranitidine Use				
No	225,680 (98.1)	472 (97.7)	Reference	Reference
Yes	4,284 (1.9)	11 (2.3)	1.13 (0.62, 2.06)	1.11 (0.61, 2.02)
Ranitidine vs Omeprazole				
Regular Omeprazole Use	13,156 (77.1)	34 (75.6)	Reference	Reference
Regular Ranitidine Use	3,917 (22.9)	11 (24.4)	1.17 (0.59, 2.31)	1.08 (0.54, 2.15)

[a]Adjusted for age (time axis of analysis), sex, race (white, non-white)

[b]Adjustment variables depend on the outcome of interest

[c]Analyses of overall cancer adjusted for factors listed in footnote a above, as well as household income (<£18,000; £18,000-30,999; £31,000-51,999; £52,000-100,000; >£100,000; Do not know/prefer not to answer/missing),BMI (12.1-25 kg/m^2; 25-<30 kg/m^2; 30-<35 kg/m^2; 35-74.7 kg/m^2), history of smoking status (Never; Former; Current), packyears (0/Non-smokers,0.05-12.5, >12.5-26.3, >26.3-301.0); alcohol

intake (Never; Special occasions only; One to three times a month; One to four times a week; Daily or almost daily);physical activity (None; Any moderate; Any vigorous; Do not know/prefer not to answer/missing); diabetes (No; Yes)

[d]Analyses of colorectal cancer adjusted for factors listed in footnote c above as well as history of bowel screening (No; Yes), fruit intake (0-<2.0 servings per day; 2.0-2.9 servings per day; 3.0-3.9 servings per day; 4.0-65.0 servings per day), vegetable intake (0-<2.0 servings per day; 2.0-2.9 servings per day; 3.0-3.9 servings per day; 4.0-50.0 servings per day), red meat intake (0-<1 time per week; 1.0-1.9 times per week; 2.0-2.9 times per week; 3.0-21.0 times per week), processed meat intake (Never; <1.0 time per week; 1.0 time per week; >=2.0 times per week – 1.0 or more times per day, aspirin intake (No; Yes), non-aspirin NSAID intake (No; Yes), and menopause status and post-menopausal hormone use (Pre-menopausal/Men; Post-menopausal w/ No PMH; Post-menopausal w/ PMH; Do not know/missing)

[e]Analyses of lung cancer adjusted for factors listed in footnote c above. We additionally adjusted for history of pre-existing lung disease (No; Yes)

[f]Analyses restricted to women

[g]Analyses of breast cancer adjusted for factors listed in footnote c above, except for sex. We additionally adjusted for history of screening/ mammogram (No; Yes), age at menarche (5-<11, 11-12, 14-15, 16-25), menopause status and post-menopausal hormone use (Pre-menopausal; Post-menopausal w/ No PMH; Post-menopausal w/ PMH; Do not know/missing), and parity (0; 1-2; 3-22).

[h]Analyses restricted to men

[i]Analyses of prostate cancer adjusted for factors listed in footnote c above, except for sex, as well as prostate specific antigen screening (No; Yes).

[j]Analyses of liver cancer adjusted for factors listed in footnote c above, as well as history of pre-existing liver disease (No; Yes)

[k]Analyses of kidney cancer adjusted for factors listed in footnote c above. We additionally adjusted for NSAID use (No; Yes), and hypertension/ hypertension meds (No; Yes – unmedicated; Yes - medicated).

[l]Analyses of bladder cancer adjusted for factors listed in footnote c above

[m]Analyses of ovarian cancer adjusted for factors listed in footnote c above, except for sex. We additionally adjusted for parity (0; 1-2; 3-22), NSAID use (No; Yes), oral contraceptive use (No; Yes), menopause status and post-menopausal hormone use (Pre-menopausal; Post-menopausal w/ No PMH; Post-menopausal w/ PMH; Do not know/missing), history of tubal ligation (No; Yes), and history of hysterectomy (No; Yes). Women with history of bilateral oophorectomy were excluded from this analysis.