

Supplemental Table 1. Population Characteristics, by Regular Use of Ranitidine and Omeprazole

	Total	Regular Ranitidine Use		Regular Omeprazole Use	
	N= 459,204 N (%)	No N= 450,360 (98.1%)	Yes N= 8,844 (1.9%)	No N= 432,245 (94.1%)	Yes N= 26,959 (5.9%)
Age^a					
< 50	111,021 (24.2)	109,201 (98.4)	1,820 (1.6)	107,597 (96.9)	3,424 (3.1)
50-60	154,284 (33.6)	151,433 (98.2)	2,851 (1.9)	146,399 (94.9)	7,885 (5.1)
60-70	191,801 (41.8)	187,685 (97.9)	4,116 (2.2)	176,374 (92.0)	15,427 (8.0)
≥ 70	2,098 (0.5)	2,041 (97.3)	57 (2.7)	1,875 (89.4)	223 (10.6)
Sex					
Female	248,338 (54.1)	243,540 (98.1)	4,798 (1.9)	232,988 (93.8)	15,350 (6.2)
Male	210,866 (45.9)	206,820 (98.1)	4,046 (1.9)	199,257 (94.5)	11,609 (5.5)
Race					
White	433,602 (94.4)	425,620 (98.1)	8,342 (1.9)	408,150 (94.1)	25,452 (5.9)
Non-white	25,602 (5.6)	25,100 (98.0)	502 (2.0)	24,095 (94.1)	1,507 (5.9)
Household Income (£)					
< 18,000	87,290 (19.0)	84,950 (97.3)	2,340 (2.7)	79,512 (91.1)	7,778 (8.9)
18,000 to 30,999	99,687 (21.7)	97,839 (98.2)	1,848 (1.9)	93,528 (93.8)	6,159 (6.2)
31,000 to 51,999	104,003 (22.6)	102,297 (98.4)	1,706 (1.6)	99,249 (95.4)	4,754 (4.6)
52,000 to 100,000	81,983 (17.9)	80,716 (98.5)	1,267 (1.6)	79,127 (96.5)	2,856 (3.5)
> 100,000	21,867 (4.8)	21,549 (98.6)	318 (1.5)	21,138 (96.7)	729 (3.3)
Missing	64,374 (14.0)	63,009 (97.9)	1,365 (2.1)	59,691 (92.7)	4,683 (7.3)
BMI (kg/m²)^b					
< 25	152,339 (33.2)	150,439 (98.8)	1,900 (1.3)	146,946 (96.5)	5,393 (3.5)
25 - <30	195,394 (42.6)	191,641 (98.1)	3,753 (1.9)	183,799 (94.1)	11,595 (5.9)
30 - <35	79,987 (17.4)	77,843 (97.3)	2,144 (2.7)	73,223 (91.5)	6,764 (8.5)
≥ 35	31,484 (6.9)	30,437 (96.7)	1,047 (3.3)	28,277 (89.8)	3,207 (10.2)
Smoking Status					
Never	252,663 (55.0)	248,663 (98.4)	4,000 (1.6)	239,888 (94.9)	12,775 (5.1)
Former	158,082 (34.4)	154,542 (97.8)	3,540 (2.2)	146,900 (92.9)	11,182 (7.1)
Current	48,459 (10.6)	47,155 (97.3)	1,304 (2.7)	45,457 (93.8)	3,002 (6.2)
Packyears (tertiles among smokers)^c					
0/Non-smokers	320,758 (69.9)	315,467 (98.4)	5,291 (1.7)	304,036 (94.8)	16,722 (5.2)
Tertile 1	46,293 (10.1)	45,372 (98.0)	921 (2.0)	43,772 (94.6)	2,521 (5.5)
Tertile 2	45,227 (9.8)	44,085 (97.5)	1,142 (2.5)	41,913 (92.7)	3,314 (7.3)
Tertile 3	46,926 (10.2)	45,436 (96.8)	1,490 (3.2)	42,524 (90.6)	4,402 (9.4)
Alcohol Intake					
Never	36,062 (7.9)	35,106 (97.4)	956 (2.7)	32,801 (91.0)	3,261 (9.0)
Special occasions only	52,258 (11.4)	51,098 (97.8)	1,160 (2.2)	48,076 (92.0)	4,182 (8.0)
One to three times a month	51,295 (11.2)	50,270 (98.0)	1,025 (2.0)	48,211 (94.0)	3,084 (6.0)
Once to four times a week	225,740 (49.2)	221,805 (98.3)	3,935 (1.7)	214,145 (94.9)	11,595 (5.1)
Daily or almost daily	93,849 (20.4)	92,081 (98.1)	1,768 (1.9)	89,012 (94.9)	4,837 (5.2)
Physical Activity					
None	47,582 (10.4)	46,344 (97.4)	1,238 (2.6)	43,644 (91.7)	3,938 (8.3)
Any moderate	105,533 (23.0)	103,267 (97.9)	2,266 (2.2)	98,288 (93.1)	7,245 (6.9)
Any vigorous	275,171 (59.9)	270,728 (98.4)	4,443 (1.6)	262,179 (95.3)	12,992 (4.7)
Missing	30,918 (6.7)	30,021 (97.1)	897 (2.9)	28,134 (91.0)	2,784 (9.0)
Diabetes					
No	435,598 (94.9)	427,504 (98.1)	8,094 (1.9)	411,276 (94.4)	24,322 (5.6)
Yes	23,606 (5.1)	22,856 (96.8)	750 (3.2)	20,969 (88.8)	2,637 (11.2)
Colorectal Cancer Specific					

Variables					
History of Bowel Screening					
No	313,090 (68.2)	307,872 (98.3)	5,218 (1.7)	299,213 (95.6)	13,877 (4.4)
Yes	138,810 (30.2)	135,364 (97.5)	3,446 (2.5)	126,299 (91.0)	12,511 (9.0)
Missing	7,304 (1.6)	7,124 (97.5)	180 (2.5)	6,733 (92.2)	571 (7.8)
Aspirin Use					
No	395,051 (86.0)	388,012 (98.2)	7,039 (1.8)	374,490 (94.8)	20,561 (5.2)
Yes	64,153 (14.0)	62,348 (97.2)	1,805 (2.8)	57,755 (90.0)	6,398 (10.0)
Non-aspirin NSAID Use					
No	390,072 (84.9)	383,143 (98.2)	6,929 (1.8)	366,583 (94.0)	23,489 (6.0)
Yes	69,132 (15.1)	67,217 (97.2)	1,915 (2.8)	65,662 (95.0)	3,470 (5.0)
Menopause Status/PMH Use^d					
Pre-menopausal	61,631 (24.8)	60,754 (98.6)	877 (1.4)	59,892 (97.2)	1,739 (2.8)
Post-menopausal w/o PMH Use	83,861 (33.8)	82,561 (98.5)	1,300 (1.6)	79,588 (94.9)	4,273 (5.1)
Post-menopausal w/ PMH Use	88,001 (35.4)	85,678 (97.4)	2,323 (2.6)	79,485 (90.3)	8,516 (9.7)
Missing	14,845 (6.0)	14,547 (98.0)	298 (2.0)	14,023 (94.5)	822 (5.5)
Fruit Intake (servings per day)^e					
0-<2	149,508 (32.6)	146,253 (97.8)	3,255 (2.2)	140,877 (94.2)	8,631 (5.8)
2-<3	115,243 (25.1)	113,210 (98.2)	2,033 (1.8)	108,889 (94.5)	6,354 (5.5)
3-<4	87,999 (19.2)	86,408 (98.2)	1,591 (1.8)	82,781 (94.1)	5,218 (5.9)
≥4	100,630 (21.9)	98,819 (98.2)	1,811 (1.8)	94,335 (93.7)	6,295 (6.3)
Missing	5,824 (1.3)	5,670 (97.4)	154 (2.6)	5,636 (92.1)	461 (7.9)
Vegetable Intake (servings per day)^f					
0-<2	156,197 (34.0)	152,981 (97.9)	3,216 (2.1)	146,839 (94.0)	9,358 (6.0)
2-<3	152,665 (33.2)	149,870 (98.2)	2,795 (1.8)	144,019 (94.3)	8,646 (5.7)
3-<4	80,189 (17.5)	78,720 (98.2)	1,469 (1.8)	75,509 (94.2)	4,680 (5.8)
≥4	61,858 (13.5)	60,702 (98.1)	1,156 (1.9)	58,247 (94.2)	3,611 (5.8)
Missing	8,295 (1.8)	8,087 (97.5)	208 (2.5)	7,631 (92.0)	664 (8.0)
Processed Meat (times/wk)^g					
Never	42,544 (9.3)	41,861 (98.4)	683 (1.6)	40,286 (94.7)	2,258 (5.3)
<1	139,495 (30.4)	136,980 (98.2)	2,515 (1.8)	131,200 (94.1)	8,295 (5.9)
1	133,837 (29.1)	131,209 (98.0)	2,628 (2.0)	125,956 (94.1)	7,881 (5.9)
≥2	142,441 (21.0)	139,448 (97.9)	2,993 (2.1)	133,999 (94.1)	8,442 (5.9)
Missing	887 (0.2)	862 (97.2)	25 (2.8)	804 (90.6)	83 (9.4)
Red Meat Intake (times/wk)^h					
0 - <1	46,115 (10.0)	45,377 (98.4)	738 (1.6)	43,869 (95.1)	2,246 (4.9)
1-<2	179,492 (39.1)	176,275 (98.2)	3,217 (1.8)	169,224 (94.3)	10,268 (5.7)
2-<3	127,684 (27.8)	125,254 (98.1)	2,430 (1.9)	120,166 (94.1)	7,518 (5.9)
≥3	101,040 (22.0)	98,715 (97.7)	2,325 (2.3)	94,487 (93.5)	6,553 (6.5)
Missing	4,873 (1.1)	4,739 (97.3)	134 (2.8)	4,499 (92.3)	374 (7.7)
Lung Cancer-Specific Variables					
Any pre-existing lung disease					
No	451,397 (98.3)	442,882 (98.1)	8,515 (1.9)	425,568 (94.3)	25,829 (5.7)
Yes	7,807 (1.7)	7,478 (95.8)	329 (4.2)	6,677 (85.5)	1,130 (14.5)
Breast Cancer Specific Variables^d					
History of Screening/mammogram					
No	52,450 (21.1)	51,646 (98.5)	804 (1.5)	50,854 (97.0)	1,596 (3.0)

Yes	195,535 (78.7)	191,546 (98.0)	3,989 (2.0)	181,793 (93.0)	13,742 (7.0)
Missing	353 (0.1)	348 (98.6)	5 (1.4)	341 (96.6)	12 (3.4)
Age at Menarcheⁱ					
< 11	11,095 (4.5)	10,827 (97.6)	268 (2.4)	10,235 (92.3)	860 (7.8)
11-12	82,482 (33.2)	80,799 (98.0)	1,683 (2.0)	77,035 (93.4)	5,447 (6.6)
13-15	133,214 (53.6)	130,782 (98.2)	2,432 (1.8)	125,456 (94.2)	7,758 (5.8)
≥16	14,191 (5.7)	13,888 (97.9)	303 (2.1)	13,299 (93.7)	892 (6.3)
Missing	7,356 (3.0)	7,244 (98.5)	112 (1.5)	6,963 (94.7)	393 (5.3)
Parity^j					
0	46,480 (18.7)	45,590 (98.1)	890 (1.9)	44,077 (94.8)	2,403 (5.2)
1-2	141,812 (57.1)	139,165 (98.1)	2,647 (1.9)	133,211 (93.9)	8,601 (6.1)
≥3	59,839 (24.1)	58,586 (97.9)	1,253 (2.1)	55,509 (92.8)	4,330 (7.2)
Missing	207 (0.1)	199 (96.1)	8 (3.9)	191 (92.3)	16 (7.7)
Menopause Status/PMH Use^d					
Pre-menopausal	61,631 (24.8)	60,754 (98.6)	877 (1.4)	59,892 (97.2)	1,739 (2.8)
Post-menopausal w/o PMH Use	83,861 (33.8)	82,561 (98.5)	1,300 (1.6)	79,588 (94.9)	4,273 (5.1)
Post-menopausal w/ PMH Use	88,001 (35.4)	85,678 (97.4)	2,323 (2.6)	79,485 (90.3)	8,516 (9.7)
Missing	14,845 (6.0)	14,547 (98.0)	298 (2.0)	14,023 (94.5)	822 (5.5)
Prostate Cancer Specific Variables^k					
Prostate Specific Antigen Screening					
No	141,259 (67.0)	138,677 (98.2)	2,582 (1.8)	134,810 (95.4)	6,449 (4.6)
Yes	58,721 (27.8)	57,518 (98.0)	1,203 (2.1)	54,432 (92.7)	4,289 (7.3)
Missing	10,886 (5.2)	10,625 (97.6)	261 (2.4)	10,015 (92.0)	871 (8.0)
Liver Cancer Specific Variables					
Any pre-existing liver disease					
No	456,962 (99.5)	448,167 (98.1)	8,795 (1.9)	430,218 (94.2)	26,744 (5.9)
Yes	2,242 (0.5)	2,193 (97.8)	49 (2.2)	2,027 (90.4)	215 (9.6)
Kidney Cancer Specific Variables					
Non-aspirin NSAID Use					
No	390,072 (84.9)	383,143 (98.2)	6,929 (1.8)	366,583 (94.0)	23,489 (6.0)
Yes	69,132 (15.1)	67,217 (97.2)	1,915 (2.8)	65,662 (95.0)	3,470 (5.0)
Hypertension					
No	334,793 (72.9)	329,212 (98.3)	5,581 (1.7)	319,177 (95.3)	15,616 (4.7)
Yes - unmedicated	34,822 (7.6)	34,054 (97.8)	768 (2.2)	32,591 (93.6)	2,231 (6.4)
Yes - medicated	89,589 (19.5)	87,094 (97.2)	2,495 (2.8)	80,477 (89.8)	9,112 (10.2)
Ovarian Cancer Specific Variables^d					
Oral Contraceptive Use					
No	45,787 (18.4)	44,822 (97.9)	965 (2.1)	42,268 (92.3)	3,519 (7.7)
Yes	201,901 (81.3)	198,092 (98.1)	3,809 (1.9)	190,122 (94.2)	11,779 (5.8)
Missing	650 (0.3)	626 (96.3)	24 (3.7)	598 (92.0)	52 (8.0)
History of tubal ligation					
No	228,634 (92.1)	224,344 (98.1)	4,290 (1.9)	215,059 (94.1)	13,575 (5.9)
Yes	19,704 (7.9)	19,196 (97.4)	508 (2.6)	17,929 (91.0)	1,775 (9.0)
History of Hysterectomy					
No	203,591 (82.0)	200,088 (98.3)	3,503 (1.7)	192,971 (94.8)	10,620 (5.2)
Yes	44,747 (18.0)	43,452 (97.1)	1,295 (2.9)	40,017 (89.4)	4,730 (10.6)
Parity^j					
0	46,480 (18.7)	45,590 (98.1)	890 (1.9)	44,077 (94.8)	2,403 (5.2)
1-2	141,812 (57.1)	139,165 (98.1)	2,647 (1.9)	133,211 (93.9)	8,601 (6.1)

≥3	59,839 (24.1)	58,586 (97.9)	1,253 (2.1)	55,509 (92.8)	4,330 (7.2)
Missing	207 (0.1)	199 (96.1)	8 (3.9)	191 (92.3)	16 (7.7)
Menopause Status/PMH Use ^d					
Pre-menopausal	61,631 (24.8)	60,754 (98.6)	877 (1.4)	59,892 (97.2)	1,739 (2.8)
Post-menopausal w/o PMH Use	83,861 (33.8)	82,561 (98.5)	1,300 (1.6)	79,588 (94.9)	4,273 (5.1)
Post-menopausal w/ PMH Use	88,001 (35.4)	85,678 (97.4)	2,323 (2.6)	79,485 (90.3)	8,516 (9.7)
Missing	14,845 (6.0)	14,547 (98.0)	298 (2.0)	14,023 (94.5)	822 (5.5)

ABBREVIATIONS: BMI (Body mass index); PMH (Post-menopausal hormone)

^a Percentages in these columns reflect row percentages (for example, 2.7% of adults ages 70+ year of age report use of ranitidine, as compared to 1.6% of adults <50 years of age)

^b Age range for <50: 38 - 49; age range for ≥70: 70-73

^c BMI range for <25: 12.1 - 24.9; BMI range for ≥35: 35-74.7

^d Tertile 1 (0.05 - 12.5); Tertile 2 (>12.5- 26.3); Tertile 3 (>26.3- 301.0)

^e Descriptive statistics calculated only in women

^f Fruit intake category ≥4: 4-65

^g Vegetable intake category ≥4: 4-50

^h Processed meat category ≥2: 2/week- ≥1/day

ⁱ Red meat category ≥3: 3-21

^j Age menarche range <11: 5-10; ≥16: 16-25

^k Parity range ≥3: 3-22

^l Descriptive statistics calculated only in men

Supplemental Table 2. Time-Stratified Analyses

	First 5 Years of Follow-up ^a			Latter Follow-up ^b		
	Cohort N (%)	Case N (%)	Multivariable- Adjusted ^a HR (95% CI)	Cohort N (%)	Case N (%)	Multivariable- Adjusted ^a HR (95% CI)
Overall Cancer^c						
Regular Ranitidine Use						
No	450,360 (98.1)	18,179 (97.7)	Reference	428,647 (98.1)	7,486 (98.1)	Reference
Yes	8,844 (1.9)	422 (2.3)	1.07 (0.97, 1.18)	8,314 (1.9)	143 (1.9)	0.86 (0.73, 1.01)
Ranitidine vs Omeprazole						
Regular Omeprazole Use	26,139 (76.5)	1,374 (78.3)	Reference	24,401 (73.4)	533 (80.6)	Reference
Regular Ranitidine Use	8,024 (23.5)	381 (21.7)	0.99 (0.88, 1.11)	7,553 (23.6)	128 (19.4)	0.86 (0.73, 1.01)

^a Defined by the first 5 years of each participant's follow-up (such that all participants censored at 5 years of follow-up)

^b Includes the follow-up beyond the first 5 years of each participant's follow-up, such that all participants with more than 5 years of follow-up are entered into the models at 5 years and followed for the remainder of their follow-up

Supplemental Methods

Minimally-adjusted models were adjusted for age, sex, and race, with multivariable models further adjusted for income, body mass index (BMI), smoking status, pack-years smoked, alcohol intake, physical activity, and diabetes (detailed in table footnotes). Covariates were assessed at baseline, at the time of exposure assessment. We have largely used a complete case approach, whereby analyses only include participants with complete data (ie, those missing covariate data are excluded). However, for those variables for whom data are missing for >5% of the study population (household income and physical activity), we have alternatively used a missing indicator. This hybrid approach avoids the issue of non-convergence due to small cells (resulting from small numbers missing for most covariates), but also avoids dropping large groups due to missing data for a particular covariate. Models of each cancer site were adapted to additionally include covariates specific to that site; thus, sample size differs slightly across analyses.

Sensitivity analyses were conducted with regard to covariate selection in site-specific analyses. As information on family history of cancer was only available for certain cancer sites (colorectum, lung, breast, prostate), we conducted sensitivity analyses of these sites adjusting for site-specific family history. Results were unchanged, thus family history variables were not included in final models. For breast cancer, sensitivity analyses were conducted additionally adjusting for age at menopause (as determined at baseline); as effect estimates did not materially change, we have not included this covariate in the analyses. Lastly, in models of kidney cancer, we were unable to adjust for pre-existing kidney disease (indicated by renal/kidney failure, polycystic kidney disease, or transplant), given the small number of persons with these conditions; thus, we conducted a sensitivity analysis excluding these persons from analyses. Results did not differ from the main model, and thus persons with these conditions were not excluded