Title

Proton Pump Inhibitor Use and Obesity-Associated Cancer in the Womens Health Initiative.

Journal

Nutrition and Cancer: an international journal, 75(1)

Authors

Ballinger, Tarah
Djuric, Zora
Sardesai, Sagar
et al.

Publication Date

2023

DOI

10.1080/01635581.2022.2108467

Peer reviewed

HHS Public Access

Author manuscript

Nutr Cancer. Author manuscript; available in PMC 2024 January 01.

Published in final edited form as:

Nutr Cancer. 2023 ; 75(1): 265–275. doi:10.1080/01635581.2022.2108467.

Proton pump inhibitor use and obesity-associated cancer in the Women's Health Initiative

Tarah J. Ballinger[a,*], **Zora Djuric**[b], **Sagar Sardesai**[c], **Kathleen M. Hovey**[d], **Chris A. Andrews**[d], **Theodore M. Brasky**[c], **Jian Ting Zhang**[e], **Thomas E Rohan**[f], **Nazmus Saquib**[g], **Aladdin H. Shadyab**[h], **Michael Simon**[i], **Jean Wactawski-Wende**[e], **Robert Wallace**[j], **Ikuko Kato**[i,k]

[a]Department of Medicine, Indiana University School of Medicine, Indianapolis, IN

[b]Departments of Family Medicine and Nutritional Sciences, University of Michigan, Ann Arbor, MI

[c]Division of Medical Oncology, Department of Internal Medicine, The Ohio State University College of Medicine, Columbus, OH

[d]Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, The State University of New York, Buffalo, NY

[e]Department of Cell and Cancer Biology, University of Toledo College of Medicine and Life Sciences, Toledo, OH

[f]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY

[g]College of Medicine, Sulaiman AlRajhi University, Saudi Arabia

[h]Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, La Jolla, CA

[i]Department of Oncology, Karmanos Cancer Institute at Wayne State University School of Medicine, Detroit, MI

[j]Department of Epidemiology, Iowa College of Public Health, Iowa City, IA

[k]Department of Pathology, Wayne State University School of Medicine, Detroit

Abstract

Proton pump inhibitors (PPIs) have off-target activity on fatty acid synthase (FASN), a critical enzyme in energy balance and cancer growth. We evaluated risk of common obesity-related cancers: breast, colorectal (CRC), and endometrial, with use of PPI and histamine-2 receptor antagonists (H2RA) in 124,931 postmenopausal women enrolled in the Women's Health Initiative. Incident cancer cases were physician-adjudicated. Cox proportional hazards models were used to

[*]Corresponding author: Tarah Ballinger, 535 Barnhill Dr. RT 473, Indianapolis, IN 46202, 317-944-3553, Tarahb@iu.edu.

Author Contributions

TB, ZD, SS and IK were involved in the conception of the study. IK was the primary investigator responsible for the data analysis plan and data selection for presentation. KH carried out the statistical analysis and prepared tables and figures. TB and IK prepared the initial manuscript and ZD, SS, CAA, KH, TMB, JTZ, TER, NS, AHS, MS, JWW and RW participated in critical revisions of the manuscript and analyses. All authors read and approved the submitted manuscript.

Disclosure of interest

The authors report there are no competing interests to declare.

estimate multivariable hazard ratios (HR) and 95% confidence intervals (CI) for cancer incidence after year 3. There were 7956 PPI ever users and 9398 H2RA only users. Ever use of either PPI or H2RA was not associated with risk of breast cancer (n=9186) nor risk of endometrial cancer (n=1231). The risk of CRC (n=2280) was significantly lower in PPI users (HR=0.75, 95% CI=0.61–0.92), but not in H2RA users (HR=1.13, 95% CI=0.97–1.31). The association of PPI use with CRC was apparent regardless of BMI or NSAID use, and was stronger with longer PPI duration (p=0.006) and potency (p=0.005). The findings that PPI use, but not H2RA use, demonstrate an inverse dose-response relationship with risk of CRC is consistent with preclinical data showing FASN inhibition prevents colon cancer progression and supports a role of PPI in CRC prevention.

Keywords

Adiposity; Colorectal cancer; Obesity; Endometrial cancer; Cancer risk; Breast Cancer

Introduction

Obesity is highly prevalent among women in the United States and represents a major modifiable risk factor for the development of cancer[1]. In particular, obesity has been linked to increased risk of postmenopausal breast, colon, and endometrial cancers, and to worse outcomes in patients with breast and colon cancers[2–6].

Human fatty acid synthase (FASN) plays a critical role in lipogenesis as the sole cytosolic enzyme responsible for de novo synthesis of palmitate via the condensation of acetyl-CoA and malonyl-CoA[7]. Expression of FASN is regulated by energy balance. Exercise and caloric restriction downregulate FASN, while FASN is upregulated in obesity and functions to store excess glucose as lipids in adipose depots[8–10]. The typical Western diet contains sufficient free fatty acids such that FASN is not required for normal cell function; therefore, its expression is very low in normal cells with the exception of lactating breast, cycling endometrium, and adipose tissue[11]. In contrast, cancer cells require de novo fatty acid synthesis for survival[12]. Conversely, inhibition of FASN induces apoptosis selectively in cancer cells *in vitro* and *in vivo*, with minimal effect on non-malignant cells[13, 14]. Thus, it is an ideal potential target for prevention of cancer development, and it is hypothesized that inhibitors of FASN may have chemopreventive effects[15].

FASN is overexpressed in breast, colon, and endometrial cancers and is related to clinicopathologic features of the disease. In women diagnosed with breast cancer, those with tumors exhibiting higher levels of FASN are more likely to be postmenopausal and to have a higher BMI[16]. In addition, tumors with FASN overexpression are significantly more likely to recur after initial therapy[17–19]. In colon cancer, FASN overexpression has been associated with improved survival outcomes; however, in an analysis done within the Nurses' Health Study and the Health Professionals Follow-Up Study, the effect of FASN on colon cancer outcomes was modified by BMI[20]. In normal weight patients, FASN overexpression was associated with improved survival; however, in overweight and obese patients, FASN overexpression was associated with increased mortality, consistent with what

is seen in breast cancer. Similarly, FASN tumor overexpression is associated with increased risk of endometrial cancer recurrence[21].

In preclinical studies, proton pump inhibitors (PPI) effectively downregulate FASN enzymatic activity and reduce carcinogensis[22, 23]. PPIs are currently FDA approved for the treatment of a variety of acid- related disease of the digestive system and are well-tolerated with minimal adverse effects. To date, studies examining the association of acid suppression with risk of several malignancies have had mixed results[24, 25,26]. Here, we sought to specifically evaluate PPIs and the risk of obesity-associated cancers given the relationships between FASN, energy balance, and cancer pathogenesis. There is a critical need to determine whether commonly used, generally safe medications can be repurposed as chemopreventive agents. The Women's Health Initiative study of postmenopausal U.S. women was therefore utilized to investigate the hypothesis that PPI use is associated with decreased risk of the most common obesity-related cancers in women, including postmenopausal breast cancer, colon cancer, and endometrial cancer.

Materials and Methods

Study population

Details concerning the WHI study design have been published elsewhere[27]. Briefly, the WHI included an observational study (OS; N = 93,676) and four overlapping clinical trials (CT; n = 68,132), which included hormone therapy (estrogen alone and estrogen plus progestin) , dietary modification, and calcium and vitamin D supplementation trials. Women were recruited between October 1, 1993, and December 31, 1998 at 40 clinical centers in the United States. Participants were eligible if aged 50 to 79 years, postmenopausal, planned to remain in the area where they lived at recruitment, and had an estimated survival of at least 3 years. All protocols were approved by institutional review boards at participating institutions. WHI participants attended baseline screening visits during which they completed self-administered questionnaires regarding demographics, medical and reproductive histories, family history of cancer, physical activity, and other risk factors. Height (cm), weight (kg), waist and hip circumferences and diastolic and systolic blood pressures were measured by clinic staff, and current prescription and over the counter (OTC) medication use was recorded. A significant portion of this information was updated at year 3 of follow-up in both the OS and CT cohorts.

PPI is a relatively new class of medications, and use was limited during the time of initial cohort enrollment; therefore, the present analyses considered cancer incidence that occurred at year 3 or later as endpoints. A total of 36,877 cohort members were excluded from this study due to one or more of the following criteria: (1) did not complete medication inventory at baseline or year 3 (n=21,420); (2) had prior diagnosis of breast, colorectal or endometrial cancer before year 3 (n=11,679); (3) did not have follow-up after year 3 (n=971); or (4) had missing body mass index (BMI, body weight (kg)/ height $(m)^2$), a major covariate in the study, at year 3 (n=4,978). After exclusions, 124,931 women were available for analysis of breast and colorectal cancers. After further exclusion of women reporting hysterectomy prior to year 3 (n=51,918, this includes all women in the estrogen alone arm

of the hormone replacement CT), 73,013 women were available for analysis of endometrial cancer (Supplemental Figure 1).

Exposure assessment

A computer- driven medication- inventory system was developed to capture current medication use[28]. All women were asked to provide medication data at baseline and year 3. Participants were asked to bring prescription and OTC medications used regularly (≥ 2 times/week) over the previous 2 weeks to their clinic visit to facilitate completion of a computer- assisted interview about current medication use. The duration of use and strength of each medication were recorded. We focused specifically on users of acid suppressive medications. We evaluated both PPI and histamine 2 receptor antagonists (H2RA) in order to isolate potential associations of FASN inhibition with cancer risk, rather than of acid suppression. Drugs in the PPI class included: esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole. Drugs in the H2RA class included: cimetidine, famotidine, nizatidine, and ranitidine. Women who reported use at either baseline or year 3 were considered ever users. Durations of use reported at each visit for each class of medications were integrated to calculate cumulative duration. Potency of PPI was considered as “high” if the strength of PPI was higher than 20 mg, and we classified women based on the highest potency reported. Participants using both PPI and H2RA were classified as PPI users. Women who did not use acid suppressive medication were considered the reference population in regression models. Based on our prior phase II trial in breast cancer patients[29] that showed omeprazole biological activity after only 4–7 days of treatment, we did not incorporate a lag in exposure in the statistical analyses.

Potential covariates

Information on all covariates was obtained by self- report and measurements obtained at either the baseline or year 3 visit. Baseline visit information was used for demographics, reproductive history (including pregnancy, hormone replacement therapy, age at menarche, and contraceptive use), family history of cancer, habitual diet and alcohol intake, and waist circumstance, while year 3 information was used for smoking, other medication use, medical and cancer screening histories (prior hysterectomy, mammography screening, and sigmoidoscopy/colonoscopy), body weight and height, and physical activity measured as metabolic equivalent tasks (METs hours/week). The Healthy Eating Index (HEI 2015) was calculated from the food frequency questionnaire[30].

Outcome ascertainment

Incident invasive and *in situ* cancer cases were reported by questionnaire annually in OS and semi-annually in CT. Medical records were obtained and reviewed, and cancer diagnoses were confirmed by physician adjudicators. Only confirmed cancer diagnoses occurring after year 3 were considered as cases. Breast cancer cases were further characterized by sex steroid hormone receptor status (positive, negative, or undetermined) as noted in the medical record and confirmed by adjudicators. The vital status of all participants was confirmed using National Death Index linkages at 2- to 3-year intervals. Women were followed through February 28, 2020.

Statistical analyses

The number of person-years at risk was calculated from the date of the year 3 time point of the WHI cohort to the date of each cancer diagnosis, death or last follow-up, whichever occurred first. Cox proportional hazards regression models were used to estimate multivariable- adjusted hazard ratios (HR) and 95% confidence intervals (CI) for associations between acid suppressive medication use (PPI and/or H2RA) and cancer risk for the three cancer types. Two models were fitted for each cancer type to examine potential confounding. Model 1 adjusted for age, BMI, randomization assignment for hormone therapy trials, and an indicator for OS versus CT cohorts. Model 2 further adjusted for variables specifically predictive of each cancer type based on a review of the literature. Because additional covariates differed by cancer site, the number of women included in the analytic cohort varied for each outcome (N=121,615 for breast cancer, N=122,117 for colorectal cancer, and N=71,931 for endometrial cancer analyses).

Women with missing values on selected covariates ≤ 2% were excluded from the fully-adjusted multivariable model; otherwise, women remained in the analysis with unknown/missing indicator variables for covariates with missing values of more than 2% (physical activity, alcohol intake, age at menopause, and family history of breast, colorectal and endometrial cancer). First, we calculated HRs among PPI users or H2RA users versus non-users of either medication. Second, we calculated HRs and 95% CIs according to two measures of PPI exposure: cumulative duration of use (<1 year, 1 to 3 years, or >3 years) and maximum strength used (low vs high), using non-PPI users as the reference. Linear trend in cancer risk was tested using median duration of each category for duration of use and using ordinal values for potency. We hypothesized *a priori* that associations between PPI use and cancer risk would be modified by obesity[20] and non-steroidal anti-inflammatory drug (NSAIDs) /aspirin (ASA) use[31, 32]. Therefore, we calculated HR according to duration of PPI use stratified by dichotomized BMI (≥30 vs. <30 kg/m^2) and NSAIDs/ASA use status (yes vs. no) and tested the interaction (P interaction) using a cross-product term between median duration of the three categories of PPI use and dichotomized BMI or NSAIDs/ASA use in regression models. NSAIDs/ASA use at year 3 was used for this stratified analysis, instead of continuous use at both baseline and year 3, because a preclinical study indicated that intermittent dosing of combinations did not alter inhibitory effects of PPI[33]. The proportional hazards assumption was checked with a time- dependent main explanatory variable in the model as well as graphically. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). All statistical tests were two-sided.

Results

Of the 124,931 women included in this study, 107,577 reported no use of either acid suppressive medication, while 7,956 were PPI users and 9,398 were sole H2RA users (Table 1). There was no appreciable difference in age at enrollment, race, smoking history, or total calorie intake across these groups. Both types of medication users had lower educational attainment, family income and alcohol intake, earlier menarche, later menopause, higher frequency of use of hormone therapy, higher use of other medications to treat chronic conditions, higher incidence of cancer screening tests, and were more obese and physically

inactive relative to non-users. PPI users were more likely to be enrolled in the southern region of the United States, compared with the other groups (Supplemental Table 1).

During an average follow-up period of 14.1 years after the year 3 survey, 9186 newly diagnosed breast, 2280 newly diagnosed colorectal, and 1231 newly diagnosed endometrial cancer cases were ascertained. The risk of breast cancer did not differ by overall use of PPI or H2RA (Table 2). There were 1688 ductal carcinoma in situ cases (DCIS) among the total 9186 breast cancer cases; however, exclusion of the DCIS cases did not change these associations. Further, combining both invasive and in situ cases, we carried out analyses stratified by hormone receptor status (Supplemental Table 2). There were 7102 hormone receptor positive, 1077 hormone receptor negative, and 1007 hormone receptor status unclassifiable cases. PPI use was not associated with the risk of any hormone receptor subtype, while a decreased risk in H2RA ever users was seen for hormone receptor status unclassifiable breast cancer (HR 0.73, 95% CI 0.56–0.96).

The risk of colorectal cancer among PPI users was significantly reduced in both models (HR 0.71, 95% CI 0.58–0.86 with model 1 and HR 0.75, 95% CI 0.61–0.92 with model 2). This association did not change when we adjusted for consistent NSAID/ASA use at baseline and year 3 as done in a previous WHI study[34], instead of year 3 use, in model 2 (HR=0.75 95% CI 0,62–0.92) (Table 2). The risk of endometrial cancer was decreased in PPI users but did not reach statistical significance. H2RA use was not associated with risk of either colorectal or endometrial cancer (Table 2).

Further analysis according to level of PPI exposure, based on either cumulative duration or maximum potency, did not reveal any dose response trends for breast cancer. We observed decreased risk of colorectal cancer with increasing PPI both in duration of use and in potency. The p-values for linear trend with the fully adjusted model were 0.006 and 0.005, respectively. For endometrial cancer, an inverse-dose-response trend was found with potency only (p=0.048 for the fully adjusted model) and the risk of endometrial cancer in high potency users was significantly reduced (HR 0.50, 95% CI 0.26–0.96 with model 1 and HR 0.51, 95% CI 0.26–0.98 with model 2) (Table 3). We did not find any dose-response-trend with duration of H2RA use for any of the three cancers (Supplemental Table 3).

Analyses stratified by obesity (yes/no) and NSAID/ASA use (yes/no) with fully adjusted models did not reveal any significant interactions with duration of PPI use for breast or colorectal cancer. Decreased risk of colorectal cancer with duration of PPI use was similarly observed in both strata of BMI and NSAID/ASA use. However, there was an indication that reduced risk of endometrial cancer associated with prolonged PPI use was more pronounced in NSAID/ASA users (p-trend = 0.032), while the p-value for the interaction remained marginal (0.06) with small sample size (Table 4). Further testing of interaction based on potency did not provide any additional information (Supplemental Table 4) for breast or colorectal cancer. This interaction test was not done for endometrial cancer due to small sample size.

Discussion

The present study is one of the largest prospective cohort studies of PPI and cancer risk, with the exception of record linkage studies based on administrative databases[25, 35]. The majority of earlier studies were focused on digestive tract cancers because of the primary pharmacological action of PPI in gastric acid suppression. In contrast, our study was the first to investigate the association of PPI use with risk of several types of obesity- associated cancers, given its auxiliary effects on FASN suppression, the role of FASN in cancer development [15, 36], and robust preclinical data[23, 31, 37]. PPIs also enhance cancer cell apoptosis via off-target inhibition of V-ATPase, which may induce apoptosis in malignant cells [38, 39]. Our study of postmenopausal women participating in the WHI did not show an association between PPI use and breast cancer risk, but did show an inverse association between PPI ever use and colorectal cancer risk with a dose- responsive trend. H2RA use was examined as well to explore whether the association between PPI use and cancer risk may be to acid suppression; no association was observed for H2RA use and colorectal cancer. The association of PPI use with endometrial cancer was inconclusive, although there was some suggestion of a protective effect with high potency PPI or concurrent NSAID use. Partly due to prior hysterectomy being an eligibility criterion in one of the WHI hormone therapy trials, the number of incident endometrial cancer cases was limited.

To our knowledge, this is the first prospective cohort study to evaluate PPI use and breast cancer risk. Several record linkage studies showed inconsistent results. A population-based case-control record linkage study from Iceland did not show any association (odds ratio (OR) 1.03, 95% CI: 0.92–1.16)[24]. In contrast, a case-control study from Taiwan based on claims data reported that PPI use was associated with lower risk of breast cancer (OR 0.75, 95% CI 0.72–0.78) [40]. In addition, a cohort study of gastric ulcer patients in Taiwan revealed a markedly reduced risk of breast cancer in association with PPI use (HR 0.32, 95% CI 0.20–0.49) [41]. This alternate result may be secondary to different ethnicity, differing etiologies of breast cancer, and varied competing risks between Asian and US populations. Prior work has discovered FASN is essential to breast cancer cell survival and is implicated in chemotherapeutic resistance[14, 42]. Our prior phase II trial of high potency omeprazole in patients with triple negative breast cancer[29] showed downregulation of FASN expression and enzymatic activity in triple negative tumor tissue after only 4–7 days of PPI exposure. In addition, the pathologic complete response rate to the combination of PPI with standard neoadjuvant chemotherapy was 72.4% (95% CI 52.8–87.3), significantly higher than historical rates. Based on these findings and the known association between energy balance and postmenopausal breast cancer, we hypothesized that perhaps PPI may have chemopreventive properties through FASN inhibition, particularly for obese patients or those at risk for triple negative tumors. In this prospective cohort study within the WHI with adjustment for many confounding variables, we found no association between PPI use and any subtype of breast cancer, regardless of BMI, PPI duration, or PPI potency. Although these results did not support our hypothesis, continued investigation of FASN in obesity-related breast cancer pathogenesis is warranted, as it is possible that other effects of PPI use that could not be measured in this cohort study may have attenuated the impact of FASN inhibition, such as alteration of the gut microbiome[43, 44].

Concerns have been raised about potential adverse effects of long- term PPI use on colorectal cancer risk due to suppression of gastric acid leading to higher levels of systemic gastrin, inducing colon epithelial proliferation[45]. Studies investigating this question have been inconsistent; those that have found a non- significant increase in colorectal cancer risk with PPI use have been primarily in non- North American populations[35]. A recent meta-analysis of 10 studies investigating PPI use and risk of colorectal cancers did not exclude protective or adverse effects of PPI on colorectal cancer risk (RR 1.24, 95% CI 0.93–1.66); however, risk did decrease with longer duration of PPI use in that analysis[35]. Prior work has primarily been limited to studies based on administrative databases or medical records with lack of adjustment for important confounders such as BMI, NSAID use, prior colonoscopy, and family history. A prospective study of PPI and H2RA and colorectal cancer risk in the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS) that included these adjustments found that PPI current use in women was significantly associated with lower risk of colorectal cancer (HR 0.80, 95% CI 0.65–0.98), similar to the point estimate seen in the present study[46]. Lack of association with H2RA in our study also indicates that the observed association with PPI was unlikely due to alteration of the gut microbiome caused by acid suppression. Alternatively, although we included prior colonoscopy in the multivariable analysis, we cannot completely rule out a possibility that PPI users, who suffered from gastrointestinal conditions and needed more potent medication than H2RA, underwent colonoscopy screening and polyp resection more often during the follow-up period, which may explain the association with lower cancer risk in our study.

Prior preclinical work has shown anticancer properties of PPI on colon cancer cells *in vitro* and *in vivo. In vivo* work in an azoxymethane-induced colorectal cancer rat model found dietary omeprazole significantly reduced aberrant crypt foci formation in a dose-response fashion[31]. In addition to prevention of early cancer initiation, omeprazole has also been shown to reduce progression to adenocarcinoma from the adenoma stage[31]. Madka et al showed later use of omeprazole in an azoxymethane-induced colorectal cancer rat model suppressed progression of adenoma to adenocarcinoma in a dose dependent manner, including a significant reduction in tumor multiplicity[23]. Transcriptomic analysis showed a significant increase in inhibitory gene expression and downregulation of adenocarcinoma progression genes with omeprazole compared to controls[47]. Our clinical findings show a clear inverse association between PPI use and colorectal cancer risk but no association for H2RA, which does not inhibit FASN, supporting preclinical data on colon cancer prevention.

Strengths of the present study include the large sample size and the availability of data on a wide range of confounding factors not readily available in investigations based on administrative databases. Because of these strengths, we were able to adjust for baseline differences in numerous health-related factors between PPI/H2RA users and non-users. This analysis is further strengthened by exposure assessment of regular medication use based on direct examination of prescription and non-prescription pill bottle/packages that participants brought at each clinic visit[28] , rather than relying on participants' memory and self-report. Thus, identification and classification of medications were less prone to error.

Several limitations are present in our study. As PPI is a newer class of medications, its usage has been increasing since FDA approval for an OTC version in 2003[48]. Thus, we would expect that some fraction of women who were classified as non-users became users at some points during the follow-up period. To assess the extent of this exposure misclassification, we examined partial cohort data at years 6 and 9, which covered 42% and 9% of the study subjects included in this analysis, respectively. At both time points, approximately 70% of PPI ever users in this study remained users, while 94% and 89% of never user remained non-users at year 6 and 9, respectively. Thus, PPI users in our study were considered relatively stable over time. Overall, these data indicate that extent of misclassification was relatively small and that misclassification may have led to an underestimate of the association. In addition, because the number and frequency of pills taken were not collected in WHI, our ability to perform more detailed analyses beyond duration and potency was limited. Self- selection bias should also be considered. Our study subjects were volunteers in long- term clinical trials and a cohort study and were relatively well educated, thus caution needs to be exercised in generalizing the results of this study to postmenopausal women in the general population. Indications for taking medications are not available for PPIs and H2RAs in the WHI; however, this is unlikely to impact our results as the indications for these medications are similar. PPIs are used for H. pylori eradication, but for a period of 14 days and thus unlikely to impact results. We also acknowledge that multiple endpoints, subgroups, and exposure measurements were tested in this study, involving multiple comparisons. Thus, conventional p-values should be interpreted very cautiously, taking potential biological mechanisms and clinical significance into consideration. Finally, for colorectal and endometrial cancers, we had limited statistical power to test interactions between PPI and co-factors that may potentiate the effect of PPI.

In conclusion, we found that PPI use was associated with lower risk of colorectal cancer in postmenopausal women. Given that H2RA use did not show any association, the results suggest that other off- target effects of PPI could explain the association with reduced risk, such as the inhibition of FASN or VTPase that are not seen with H2RAs. There is growing interest in FASN inhibitors for cancer treatment and data are emerging for cancer prevention[49], warranting further evaluation. There is an intriguing possibility that PPI might be utilized together with NSAIDs to minimize the gastro-intestinal toxicities and maximize tumor suppressive effects in colorectal cancer prevention[50]. Continued work to repurpose PPIs and other clinically approved drugs with known history, mechanism, and side effect profile will advance cancer prevention efforts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Authors thank the following:

Dean Brenner, M.D., for helpful discussions.

Program Office: (National Heart, Lung, and Blood Institute, Bethesda, Maryland) Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller.

Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA) Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg.

Investigators and Academic Centers: (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Robert Wallace; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker.

Women's Health Initiative Memory Study: (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker.

Financial support

The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health (NIH), U.S. Department of Health and Human Services through contracts N01WH22110, 24152, 32100–2, 32105–6, 32108–9, 32111–13, 32115, 32118–32119, 32122, 42107–26, 42129–32, and 44221, and by the National Cancer Institute, NIH through the Cancer Center Support Grants P30CA022453, P30CA082709 and P30CA046592. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Abbreviation List:

PPI	proton pump inhibitor
FASN	fatty acid synthase
WHI	Women's Health Initiative
H2RA	histamine 2 receptor antagonist
HR	hazards ration
CI	confidence interval
BMI	body mass index
NSAID	non-steroidal anti-inflammatory drug
OS	observational study
CT	clinical trials
OTC	over the counter
MET	metabolic equivalent task
HEI	healthy eating index
ASA	aspirin
DCIS	ductal carcinoma in situ
OR	odds ratio
RR	relative risk

References

1. Sung H; Siegel RL; Torre LA; Pearson-Stuttard J; Islami F; Fedewa SA; Goding Sauer A; Shuval K; Gapstur SM; Jacobs EJ; Giovannucci EL; Jemal A, Global patterns in excess body weight and the associated cancer burden. CA Cancer J Clin 2019, 69 (2), 88–112. [PubMed: 30548482]
2. Calle EE; Rodriguez C; Walker-Thurmond K; Thun MJ, Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003, 348 (17), 1625–38. [PubMed: 12711737]
3. Kwan ML; Chen WY; Kroenke CH; Weltzien EK; Beasley JM; Nechuta SJ; Poole EM; Lu W; Holmes MD; Quesenberry CP Jr.; Pierce JP; Shu XO; Caan BJ, Pre-diagnosis body mass index and survival after breast cancer in the After Breast Cancer Pooling Project. Breast Cancer Res Treat 2012, 132 (2), 729–39. [PubMed: 22187127]
4. Schmitz KH; Neuhouser ML; Agurs-Collins T; Zanetti KA; Cadmus-Bertram L; Dean LT; Drake BF, Impact of obesity on cancer survivorship and the potential relevance of race and ethnicity. J Natl Cancer Inst 2013, 105 (18), 1344–54. [PubMed: 23990667]
5. Prizment AE; Flood A; Anderson KE; Folsom AR, Survival of women with colon cancer in relation to precancer anthropometric characteristics: the Iowa Women's Health Study. Cancer Epidemiol Biomarkers Prev 2010, 19 (9), 2229–37. [PubMed: 20826830]
6. McTiernan A; Friedenreich CM; Katzmarzyk PT; Powell KE; Macko R; Buchner D; Pescatello LS; Bloodgood B; Tennant B; Vaux-Bjerke A; George SM; Troiano RP; Piercy KL; Physical Activity Guidelines Advisory, C., Physical Activity in Cancer Prevention and Survival: A Systematic Review. Med Sci Sports Exerc 2019, 51 (6), 1252–1261. [PubMed: 31095082]
7. Liu H; Liu JY; Wu X; Zhang JT, Biochemistry, molecular biology, and pharmacology of fatty acid synthase, an emerging therapeutic target and diagnosis/prognosis marker. Int J Biochem Mol Biol 2010, 1 (1), 69–89. [PubMed: 20706604]
8. Lenhard JM, Lipogenic enzymes as therapeutic targets for obesity and diabetes. Curr Pharm Des 2011, 17 (4), 325–31. [PubMed: 21375498]
9. Boizard M; Le Liepvre X; Lemarchand P; Foufelle F; Ferre P; Dugail I, Obesity-related overexpression of fatty-acid synthase gene in adipose tissue involves sterol regulatory element-binding protein transcription factors. J Biol Chem 1998, 273 (44), 29164–71. [PubMed: 9786926]
10. Kusunoki J; Kanatani A; Moller DE, Modulation of fatty acid metabolism as a potential approach to the treatment of obesity and the metabolic syndrome. Endocrine 2006, 29 (1), 91–100. [PubMed: 16622296]
11. Kusakabe T; Maeda M; Hoshi N; Sugino T; Watanabe K; Fukuda T; Suzuki T, Fatty acid synthase is expressed mainly in adult hormone-sensitive cells or cells with high lipid metabolism and in proliferating fetal cells. J Histochem Cytochem 2000, 48 (5), 613–22. [PubMed: 10769045]
12. Montesdeoca N; Lopez M; Ariza X; Herrero L; Makowski K, Inhibitors of lipogenic enzymes as a potential therapy against cancer. FASEB J 2020, 34 (9), 11355–11381. [PubMed: 32761847]
13. Chajes V; Cambot M; Moreau K; Lenoir GM; Joulin V, Acetyl-CoA carboxylase alpha is essential to breast cancer cell survival. Cancer Res 2006, 66 (10), 5287–94. [PubMed: 16707454]
14. Liu H; Liu Y; Zhang JT, A new mechanism of drug resistance in breast cancer cells: fatty acid synthase overexpression-mediated palmitate overproduction. Mol Cancer Ther 2008, 7 (2), 263–70. [PubMed: 18281512]
15. Fhu CW; Ali A, Fatty Acid Synthase: An Emerging Target in Cancer. Molecules 2020, 25 (17).
16. Porta R; Blancafort A; Casoliva G; Casas M; Dorca J; Buxo M; Vinas G; Oliveras G; Puig T, Fatty acid synthase expression is strongly related to menopause in early-stage breast cancer patients. Menopause 2014, 21 (2), 188–91. [PubMed: 23982110]
17. Kuhajda FP; Piantadosi S; Pasternack GR, Haptoglobin-related protein (Hpr) epitopes in breast cancer as a predictor of recurrence of the disease. N Engl J Med 1989, 321 (10), 636–41. [PubMed: 2475778]
18. Alo PL; Visca P; Marci A; Mangoni A; Botti C; Di Tondo U, Expression of fatty acid synthase (FAS) as a predictor of recurrence in stage I breast carcinoma patients. Cancer 1996, 77 (3), 474–82. [PubMed: 8630954]

19. Giro-Perafita A; Sarrats A; Perez-Bueno F; Oliveras G; Buxo M; Brunet J; Vinas G; Miquel TP, Fatty acid synthase expression and its association with clinico-histopathological features in triple-negative breast cancer. Oncotarget 2017, 8 (43), 74391–74405. [PubMed: 29088795]
20. Ogino S; Nosho K; Meyerhardt JA; Kirkner GJ; Chan AT; Kawasaki T; Giovannucci EL; Loda M; Fuchs CS, Cohort study of fatty acid synthase expression and patient survival in colon cancer. J Clin Oncol 2008, 26 (35), 5713–20. [PubMed: 18955444]
21. Wysham WZ RD, Han J, Zhang L, Guo H, Gehrig PA, Zhou C, Bae-Jump VL. Effects of Fatty Acid Synthase Inhibition by Orlistat on Proliferation of Endometrial Cancer Cell Lines. Target Oncol 2016 Dec;11(6):763–769. doi: 10.1007/s11523-016-0442-9. [PubMed: 27188391]
22. Fako VE; Wu X; Pflug B; Liu JY; Zhang JT, Repositioning proton pump inhibitors as anticancer drugs by targeting the thioesterase domain of human fatty acid synthase. J Med Chem 2015, 58 (2), 778–84. [PubMed: 25513712]
23. Madka V; Kumar G; Pathuri G; Panneerselvam J; Zhang Y; Ganta V; Lightfoot S; Lubet R; Suen CS; Steele VE; Janakiram NB; Mohammed A; Rao CV, Proton Pump Inhibitor Omeprazole Suppresses Carcinogen-induced Colonic Adenoma Progression to Adenocarcinoma in F344 Rat. Cancer Prev Res (Phila) 2021.
24. Halfdanarson OO; Fall K; Ogmundsdottir MH; Lund SH; Steingrimsson E; Ogmundsdottir HM; Zoega H, Proton pump inhibitor use and risk of breast cancer, prostate cancer, and malignant melanoma: An Icelandic population-based case-control study. Pharmacoepidemiol Drug Saf 2019, 28 (4), 471–478. [PubMed: 30565786]
25. Song HJ; Jeon N; Squires P, The association between acid-suppressive agent use and the risk of cancer: a systematic review and meta-analysis. Eur J Clin Pharmacol 2020, 76 (10), 1437–1456. [PubMed: 32548678]
26. Hwang IC; Chang J; Park SM, Emerging hazard effects of proton pump inhibitor on the risk of colorectal cancer in low-risk populations: A Korean nationwide prospective cohort study. PLoS One 2017, 12 (12), e0189114. [PubMed: 29216279]
27. Group TW s. H. I. S., Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. Control Clin Trials 1998, 19 (1), 61–109. [PubMed: 9492970]
28. Anderson GL; Manson J; Wallace R; Lund B; Hall D; Davis S; Shumaker S; Wang CY; Stein E; Prentice RL, Implementation of the Women's Health Initiative study design. Ann Epidemiol 2003, 13 (9 Suppl), S5–17. [PubMed: 14575938]
29. Sardesai SD; Thomas A; Gallagher C; Lynce F; Ottaviano YL; Ballinger TJ; Schneider BP; Storniolo AM; Bauchle A; Althouse SK; Perkins SM; Masters AR; Stratford RE Jr.; Dong Z; Liu JY; Zhang JT; Miller KD, Inhibiting Fatty Acid Synthase with Omeprazole to Improve Efficacy of Neoadjuvant Chemotherapy in Patients with Operable TNBC. Clin Cancer Res 2021, 27 (21), 5810–5817. [PubMed: 34400413]
30. Vargas AJ; Neuhouser ML; George SM; Thomson CA; Ho GY; Rohan TE; Kato I; Nassir R; Hou L; Manson JE, Diet Quality and Colorectal Cancer Risk in the Women's Health Initiative Observational Study. Am J Epidemiol 2016, 184 (1), 23–32. [PubMed: 27267948]
31. Patlolla JM; Zhang Y; Li Q; Steele VE; Rao CV, Anti-carcinogenic properties of omeprazole against human colon cancer cells and azoxymethane-induced colonic aberrant crypt foci formation in rats. Int J Oncol 2012, 40 (1), 170–5. [PubMed: 21956158]
32. Janakiram NB; Mohammed A; Patlolla JMR; Zhang Y; Biddick L; Madka V; Qian L; Lightfoot S; Dunn B; Lubet R; Suen CS; Steele VE; Rao CV, Abstract 5260: NGS Transcriptome analysis of colon adenocarcinomas treated with individual and combination of aspirin and omeprazole. Cancer Research 2017, 77 (13 Supplement), 5260–5260.
33. Altaf Mohammed JMRP, Zhang Yuting, Biddick Laura, Madka Venkateshwar, Li Qian, Lightfoot Stan, Lubet Ronald, Suen Chen S., Steele Vernon E., Rao Chinthalapally V.. Omeprazole alone, or in combination with Aspirin inhibits azoxymethane-induced colon adenoma progression to adenocarcinoma and carcinoma invasion in F344 rat model. [abstract]. In: Proceedings of the 106th Annual Meeting of the American Association for Cancer Research; 2015 Apr 18–22; Philadelphia, PA. Philadelphia (PA): AACR; Cancer Res 2015;75(15 Suppl):Abstract nr 2820. doi:10.1158/1538-7445.AM2015-2820.

34. Brasky TM; Liu J; White E; Peters U; Potter JD; Walter RB; Baik CS; Lane DS; Manson JE; Vitolins MZ; Allison MA; Tang JY; Wactawski-Wende J, Non-steroidal anti-inflammatory drugs and cancer risk in women: results from the Women's Health Initiative. Int J Cancer 2014, 135 (8), 1869–83. [PubMed: 24599876]
35. Zeng R; Cheng Y; Luo D; Wang J; Yang J; Jiang L; Zhuo Z; Guo K; Wu H; Leung FW; Sha W; Chen H, Comprehensive analysis of proton pump inhibitors and risk of digestive tract cancers. Eur J Cancer 2021, 156, 190–201. [PubMed: 34481369]
36. Singh S; Karthikeyan C; Moorthy N, Recent Advances in the Development of Fatty Acid Synthase Inhibitors as Anticancer Agents. Mini Rev Med Chem 2020, 20 (18), 1820–1837. [PubMed: 32781957]
37. Jin UH; Lee SO; Pfent C; Safe S, The aryl hydrocarbon receptor ligand omeprazole inhibits breast cancer cell invasion and metastasis. BMC Cancer 2014, 14, 498. [PubMed: 25011475]
38. He J; Shi XY; Li ZM; Pan XH; Li ZL; Chen Y; Yan SJ; Xiao L, Proton pump inhibitors can reverse the YAP mediated paclitaxel resistance in epithelial ovarian cancer. BMC Mol Cell Biol 2019, 20 (1), 49. [PubMed: 31718559]
39. Song T; Jeon HK; Hong JE; Choi JJ; Kim TJ; Choi CH; Bae DS; Kim BG; Lee JW, Proton Pump Inhibition Enhances the Cytotoxicity of Paclitaxel in Cervical Cancer. Cancer Res Treat 2017, 49 (3), 595–606. [PubMed: 27669706]
40. Chen CH; Lee CZ; Lin YC; Kao LT; Lin HC, Negative Association of Proton Pump Inhibitors With Subsequent Development of Breast Cancer: A Nationwide Population-Based Study. J Clin Pharmacol 2019, 59 (3), 350–355. [PubMed: 30329162]
41. Ding DC; Sung FC; Chen W; Wang JH; Lin SZ, Proton pump inhibitors reduce breast cancer risk in gastric ulcer patients: A population-based cohort study. Breast J 2020, 26 (3), 474–478. [PubMed: 31478297]
42. Wang CJ; Li D; Danielson JA; Zhang EH; Dong Z; Miller KD; Li L; Zhang JT; Liu JY, Proton pump inhibitors suppress DNA damage repair and sensitize treatment resistance in breast cancer by targeting fatty acid synthase. Cancer Lett 2021, 509, 1–12. [PubMed: 33813001]
43. Goedert JJ; Jones G; Hua X; Xu X; Yu G; Flores R; Falk RT; Gail MH; Shi J; Ravel J; Feigelson HS, Investigation of the association between the fecal microbiota and breast cancer in postmenopausal women: a population-based case-control pilot study. J Natl Cancer Inst 2015, 107 (8).
44. Soto-Pantoja DR; Gaber M; Arnone AA; Bronson SM; Cruz-Diaz N; Wilson AS; Clear KYJ; Ramirez MU; Kucera GL; Levine EA; Lelievre SA; Chaboub L; Chiba A; Yadav H; Vidi PA; Cook KL, Diet Alters Entero-Mammary Signaling to Regulate the Breast Microbiome and Tumorigenesis. Cancer Res 2021, 81 (14), 3890–3904. [PubMed: 34083249]
45. Dacha S; Razvi M; Massaad J; Cai Q; Wehbi M, Hypergastrinemia. Gastroenterology Report 2015, 3 (3), 201–208. [PubMed: 25698559]
46. Babic A; Zhang X; Morales-Oyarvide V; Yuan C; Khalaf N; Khalili H; Lochhead P; Chan AT; Ogino S; Wolpin BM; Wu K; Fuchs CS; Giovannucci EL; Stampfer MJ; Ng K, Acid-suppressive medications and risk of colorectal cancer: results from three large prospective cohort studies. Br J Cancer 2020, 123 (5), 844–851. [PubMed: 32541871]
47. Zuo Y; Jing Z; Bie M; Xu C; Hao X; Wang B, Association between Helicobacter pylori infection and the risk of colorectal cancer: A systematic review and meta-analysis. Medicine (Baltimore) 2020, 99 (37), e21832. [PubMed: 32925719]
48. Kantor ED; Rehm CD; Haas JS; Chan AT; Giovannucci EL, Trends in Prescription Drug Use Among Adults in the United States From 1999–2012. JAMA 2015, 314 (17), 1818–31. [PubMed: 26529160]
49. Menendez JA; Lupu R, Fatty acid synthase (FASN) as a therapeutic target in breast cancer. Expert Opin Ther Targets 2017, 21 (11), 1001–1016. [PubMed: 28922023]
50. Cuzick J; Thorat MA; Bosetti C; Brown PH; Burn J; Cook NR; Ford LG; Jacobs EJ; Jankowski JA; La Vecchia C; Law M; Meyskens F; Rothwell PM; Senn HJ; Umar A, Estimates of benefits and harms of prophylactic use of aspirin in the general population. Ann Oncol 2015, 26 (1), 47–57. [PubMed: 25096604]

Table 1.

Characteristics of participants by acid suppressive medication (as N and % unless noted).

	Numbers of women with acid suppressive medication use[1]			
	Overall	**Never**	**PPI ever**	**H2RA ever**
	124,931	**107,577**	**7,956**	**9,398**
Age, in years, Mean (SD)	66.1 (7.1)	66.0 (7.1)	67.2 (6.9)	66.8 (7.0)
Ethnicity				
Not Hispanic/Latino	119,167 (95.4)	102,556 (95.3)	7,610 (95.7)	9,001 (95.8)
Hispanic/Latino	5,064 (4.1)	4,395 (4.1)	314 (3.9)	355 (3.8)
Unknown/Not reported	700 (0.6)	626 (0.6)	32 (0.4)	42 (0.4)
Race				
American Indian/Alaska Native	358 (0.3)	302 (0.3)	24 (0.3)	32 (0.3)
Asian	3,296 (2.6)	3,097 (2.9)	95 (1.2)	104 (1.1)
Native Hawaiian/Other PI	112 (0.1)	108 (0.1)	1 (0.0)	3 (0.0)
Black	9,955 (8.0)	8,455 (7.9)	651 (8.2)	849 (9.0)
White	107,916 (86.4)	92,787 (86.3)	6,969 (87.6)	8,160 (86.8)
More than one race	1,516 (1.2)	1,299 (1.2)	116 (1.5)	101 (1.1)
Unknown/Not reported	1,778 (1.4)	1,529 (1.4)	100 (1.3)	149 (1.6)
Observation Study assignment				
No	56,356 (45.1)	48,925 (45.5)	3,233 (40.6)	4,198 (44.7)
Yes	68,575 (54.9)	58,652 (54.5)	4,723 (59.4)	5,200 (55.3)
Hormone Therapy (HT) trial assignment				
Randomized to HT	22,957 (18.4)	20,061 (18.6)	1,251 (15.7)	1,645 (17.5)
Healthy Eating Index 2015				
Mean (SD)	65.3 (10.4)	65.6 (10.3)	64.1 (10.5)	63.9 (10.3)
Physical Activity[2] MET hours/week, Mean (SD)	12.9 (14.1)	13.4 (14.3)	10.2 (12.3)	10.2 (12.2)
BMI (kg/m^2)[2]				
<25	42,541 (34.1)	38,639 (35.9)	1,640 (20.6)	2,262 (24.1)
25 to <30	43,874 (35.1)	37,613 (35.0)	2,894 (36.4)	3,367 (35.8)
≥30	38,516 (30.8)	31,325 (29.1)	3,422 (43.0)	3,769 (40.1)
Aspirin use[2]				
No	91,434 (73.2)	79,283 (73.7)	5,600 (70.4)	6,551 (69.7)
Yes	33,497 (26.8)	28,294 (26.3)	2,356 (29.6)	2,847 (30.3)
Non-steroidal anti-inflammatory (NSAID) medication use[2]				
No	101,925 (81.6)	89,391 (83.1)	5,715 (71.8)	6,819 (72.6)
Yes	23,006 (18.4)	18,186 (16.9)	2,241 (28.2)	2,579 (27.4)
Diabetes medication use[2]				
No	118,948 (95.2)	102,739 (95.5)	7,391 (92.9)	8,818 (93.8)
Yes	5,983 (4.8)	4,838 (4.5)	565 (7.1)	580 (6.2)
Lipid lowering medication use[2]				

	Numbers of women with acid suppressive medication use[1]			
	Overall	**Never**	**PPI ever**	**H2RA ever**
	124,931	**107,577**	**7,956**	**9,398**
No	105,652 (84.6)	92,332 (85.8)	5,866 (73.7)	7,454 (79.3)
Yes	19,279 (15.4)	15,245 (14.2)	2,090 (26.3)	1,944 (20.7)
Antacids use[2]				
No	120,278 (96.3)	104,116 (96.8)	7,523 (94.6)	8,639 (91.9)
Yes	4,653 (3.7)	3,461 (3.2)	433 (5.4)	759 (8.1)

[1]Variables were updated at year 3 after enrollment.

[2]Acid suppressive medication use definitions: Never – not using PPI or H2RA at either time point; PPI ever – using PPI at baseline or year 3 (could also have used H2RA); H2RA ever – using H2RA at baseline or year 3 but never used PPI. Abbreviations: PPI - Proton pump inhibitors, H2RA - histamine-2 receptor antagonists.

Table 2.

Hazard ratios (HR) and 95% CI for breast, colorectal and endometrial cancers according to ever, past and current acid suppressive medication (ASM) use at year 3.

		Model 1[1]	Model 2[2]
	N (%)[3]	HR (95% CI)	HR (95% CI)
Breast cancer			
Never ASM	7,969 (0.54)	Reference	Reference
PPI use	572 (0.56)	1.01 (0.93–1.10)	1.01 (0.93–1.10)
H2RA use	645 (0.53)	0.95 (0.88–1.03)	0.95 (0.87–1.03)
Colorectal cancer			
Never ASM	1,985 (0.13)	Reference	Reference
PPI use	106 (0.10)	0.71 (0.58–0.86)	0.75 (0.61–0.92)
H2RA use	189 (0.15)	1.07 (0.92–1.25)	1.13 (0.97–1.31)
Endometrial cancer[4]			
Never ASM	1,086 (0.12)	Reference	Reference
PPI use	54 (0.11)	0.80 (0.61–1.05)	0.81 (0.61–1.07)
H2RA use	91 (0.15)	1.11 (0.90–1.38)	1.13 (0.91–1.40)

[1] Model 1 was adjusted for age and BMI (n breast cancer events=9,186, colorectal cancers n=2,280, endometrial cancer models n events=1,231). All Models were stratified by observational study/clinical trial status and hormone therapy (HT) trial arm assignment.

[2] Model 2 was adjusted for variables in model 1 plus additional variable specific for each cancer type:

Breast cancer models include region, race and ethnicity, education, Total MET hours/week, alcohol consumption, age at menarche, age at menopause, hormone replacement therapy use, number of months breastfed, oral contraceptive use, number of term pregnancies, family history of breast cancer, mammogram history, lipid lowering medications and antacid use (n events=8,970).

Colorectal cancer models include region, race and ethnicity, education, Total MET hours/week physical activity, alcohol consumption, HEI 2015, smoking status, family history of colorectal cancer, hormone replacement therapy use, oral contraceptive use, lipid lowering medications, diabetes medication, calcium supplement, NSAIDs or ASA use, sigmoidoscopy, or colonoscopy and antacid use (n events=2,220).

Endometrial cancer models include region, race and ethnicity, education, family history of endometrial cancer, hormone replacement therapy use, oral contraceptive use, age at menarche, age at menopause, number of term pregnancies, Lipid lowering medication, diabetes medication use, and antacid use (n events = 1,217).

[3] N (%) – number of cancer events and annualized percent

[4] Those with hysterectomy were excluded from the endometrial cancer models

Table 3.

Hazard ratios (HR) and 95%CI for breast, colorectal and endometrial cancers according to cumulative duration and maximum potency of proton pump inhibitor (PPI) medications used.

Cancer	PPI exposure		N (%)[3]	Model 1[1] HR (95% CI)	Model 2[2] HR (95% CI)
Breast	Duration	0 YR	8,614 (0.54)	Reference	Reference
		<1	203 (0.56)	1.02 (0.89–1.17)	1.02 (0.89–1.17)
		1-<3	202 (0.51)	0.92 (0.80–1.05)	0.91 (0.79–1.05)
		3+	167 (0.66)	1.17 (1.00–1.36)	1.16 (1.00–1.36)
		Trend[4]		P=0.329	P=0.353
	Potency[5]	Never	8,614 (0.54)	1 (Reference)	1 (Reference)
		Low	423 (0.57)	1.03 (0.93–1.13)	1.03 (0.93–1.14)
		High	149 (0.55)	0.99 (0.84–1.16)	0.98 (0.83–1.16)
		Trend[6]		P=0.815	P=0.888
Colorectal	Duration	0 YR	2,174 (0.13)	Reference	Reference
		<1	42 (0.11)	0.80 (0.59–1.09)	0.84 (0.62–1.15)
		1-<3	39 (0.09)	0.67 (0.48–0.91)	0.68 (0.49–0.95)
		3+	25 (0.09)	0.64 (0.43–0.94)	0.69 (0.47–1.03)
		Trend[4]		P=0.001	P=0.006
	Potency[5]	Never	2,174 (0.13)	1 (Reference)	1 (Reference)
		Low	79 (0.10)	0.71 (0.57–0.89)	0.75 (0.59–0.94)
		High	27 (0.10)	0.69 (0.47–1.01)	0.73 (0.49–1.07)
		Trend[6]		p<0.001	P=0.005
Endometrial[7]	Duration	0 YR	1,177 (0.12)	Reference	Reference
		<1	20 (0.11)	0.86 (0.55–1.34)	0.88 (0.57–1.38)
		1-<3	20 (0.10)	0.73 (0.47–1.14)	0.73 (0.47–1.14)
		3+	14 (0.12)	0.80 (0.47–1.35)	0.80 (0.47–1.36)
		Trend[4]		P=0.143	P=0.147
	Potency[5]	Never	1,177 (0.12)	1 (Reference)	1 (Reference)
		Low	45 (0.12)	0.90 (0.67–1.21)	0.91 (0.67–1.22)
		High	9 (0.07)	0.50 (0.26–0.96)	0.51 (0.26–0.98)
		Trend[6]		P=0.041	P=0.048

[1]Model 1 adjusted for age and BMI (n breast cancer events=9,186, colorectal cancers n=2,280, endometrial cancer models n events=1,231). All models were stratified by OS/CT status and HT trial arm

[2]Multivariable models for each cancer include the same covariates listed for Model 2 in Table 2.

[3]N (%) – number of cancer events and annualized percent.

[4]Test for trend assigning median value to each category of duration.

[5]Potency of ≦ 20 mg/day was classified as “low” and > 20 mg/d was classified as “high” potency.

[6]Test for trend assigning values, 0, 1 ,2 for never, low and high potencies.

[7]Those with hysterectomy are excluded from the endometrial cancer models.

Table 4.

Multivariable Hazard ratios (HR) and 95% CI for breast, colorectal and endometrial cancers according to duration of PPI use stratified by body mass index (BMI) and use of non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin.

	BMI <30		BMI >=30		Interaction-P-value[3]
PPI duration (yrs)	**N (%)[1]**	**HR[2] (95% CI)**	**N (%)[1]**	**HR[2] (95% CI)**	
Breast cancer					
0	5,678 (0.51)	1 (Reference)	2,732 (0.60)	1 (Reference)	0.496
<1	114 (0.53)	1.02 (0.85–1.23)	84 (0.61)	1.01 (0.81–1.26)	
1-<3	97 (0.44)	0.84 (0.69–1.03)	99 (0.60)	0.98 (0.80–1.20)	
3+	79 (0.60)	1.13 (0.91–1.42)	87 (0.74)	1.19 (0.96–1.48)	
P-trend[4]		0.988		0.206	
Colorectal cancer					
0	1,412 (0.12)	1 (Reference)	705 (0.15)	1 (Reference)	0.774
<1	23 (0.10)	0.82 (0.54–1.24)	18 (0.12)	0.86 (0.54–1.38)	
1-<3	21 (0.09)	0.72 (0.47–1.11)	16 (0.09)	0.64 (0.39–1.05)	
3+	11 (0.08)	0.61 (0.34–1.11)	14 (0.11)	0.76 (0.45–1.30)	
P-trend[4]		0.029		0.077	
Endometrial cancer					
0	658 (0.09)	1 (Reference)	505 (0.19)	1 (Reference)	0.321
<1	11 (0.10)	1.02 (0.56–1.86)	9 (0.14)	0.76 (0.39–1.47)	
1-<3	8 (0.07)	0.67 (0.33–1.35)	12 (0.15)	0.76 (0.43–1.35)	
3+	7 (0.12)	1.11 (0.53–2.34)	7 (0.12)	0.63 (0.30–1.33)	
P-trend[4]		0.666		0.128	
	No NSAID/Aspirin		**NSAID/Aspirin use**		
Breast cancer					
0	5,056 (0.53)	1 (Reference)	3,354 (0.55)	1 (Reference)	0.578
<1	109 (0.57)	1.04 (0.86–1.25)	89 (0.55)	1.00 (0.81–1.24)	
1-<3	100 (0.52)	0.93 (0.76–1.13)	96 (0.50)	0.90 (0.73–1.10)	
3+	74 (0.62)	1.08 (0.85–1.36)	92 (0.72)	1.26 (1.02–1.55)	
P-trend[4]		0.893		0.215	
Colorectal cancer					
0	1,311 (0.13)	1 (Reference)	806 (0.13)	1 (Reference)	0.626
<1	25 (0.13)	0.91 (0.61–1.35)	16 (0.10)	0.75 (0.46–1.23)	
1-<3	12 (0.06)	0.42 (0.24–0.75)	25 (0.12)	0.96 (0.65–1.44)	
3+	15 (0.12)	0.82 (0.49–1.36)	10 (0.07)	0.57 (0.30–1.06)	
P-trend[4]		0.022		0.106	
Endometrial cancer					
0	660 (0.11)	1 (Reference)	503 (0.14)	1 (Reference)	0.060
<1	14 (0.14)	1.22 (0.72–2.07)	6 (0.08)	0.53 (0.24–1.18)	

	BMI <30		BMI >=30		Interaction-P-value[3]
PPI duration (yrs)	**N (%)[1]**	**HR[2] (95% CI)**	**N (%)[1]**	**HR[2] (95% CI)**	
1-<3	14 (0.14)	1.13 (0.66–1.92)	6 (0.06)	0.39 (0.18–0.88)	
3+	7 (0.12)	0.99 (0.47–2.09)	7 (0.11)	0.67 (0.32–1.42)	
P-trend[4]		0.793		0.032	

[1] N (%) – number of cancer events and annualized percent

[2] Multivariable models for each cancer include the same covariates listed for Model 2 in Tables 2 but exclude BMI and NSAID/ASA from the respective stratified analysis. All models were stratified by observational study/clinical trial status and hormone therapy trial arm.

[3] Interaction was tested in a separate model including the interaction term between median duration in trend analysis and a dichotomized stratification variable and their main effects in addition to the covariates included in stratified analyses.

[4] P-trend – test for trend assigning median value to each category of duration