Research Article

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Antidepressant Use and Risk of Colorectal Cancer in the Women's Health Initiative

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Abstract

Background: Some prior studies have reported reduced colorectal cancer risk among individuals using antidepressant medications, especially selective serotonin reuptake inhibitors (SSRIs). Yet most studies have not considered the potential role of depression or other confounders in their analyses.

Methods: We utilized prospectively collected data from 145,190 participants in the Women's Health Initiative, among whom 2,580 incident colorectal cancer cases were diagnosed. Antidepressant use and depressive symptoms were assessed at baseline and follow-up study visits. Cox proportional hazards regression models with adjustment for depressive symptoms and other covariates were utilized to estimate HRs and 95% confidence intervals (CIs) for associations between antidepressant use and colorectal cancer.

Results: Antidepressant use was reported by 6.9% of participants at baseline, with SSRIs the most common class of antidepressant used. In multivariable analyses, including adjustment for depressive symptomology, we observed no statistically significant association between antidepressant use overall (HR = 0.90; 95% CI, 0.75–1.09) or with SSRIs specifically (HR = 1.08; 95% CI, 0.85–1.37) and colorectal cancer risk. A borderline significant reduction in colorectal cancer risk was observed for use of tricyclic antidepressants (HR = 0.76; 95% CI, 0.56–1.04). Severe depressive symptoms were independently associated with a 20% increased risk of colorectal cancer (HR = 1.21; 95% CI, 1.09–1.48). Results were similar for separate evaluations of colon and rectal cancer.

Conclusions: We observed no evidence of an association between antidepressant use, overall or by therapeutic class, and colorectal cancer risk.

Impact: These results suggest that antidepressants may not be useful as chemopreventive agents for colorectal cancer. *Cancer Epidemiol Biomarkers Prev; 27(8); 892–8. ©2018 AACR.*

Introduction

Inflammation plays a key role in promoting colorectal cancer; for example, individuals with inflammatory conditions such as inflammatory bowel disease or Crohn disease have a higher colorectal cancer risk (1). Conversely, use of nonsteroidal anti-inflammatory drugs (NSAIDs) is related to lower colorectal cancer risk (2). Antidepressant medications also have documented anti-inflammatory actions (3, 4).

Serotonin may promote angiogenesis of colon cancer cells, which requires cellular uptake of serotonin (5). Selective serotonin reuptake inhibitors (SSRIs) reduce colorectal tumor cell growth in both mouse xenograft models (6–9) and in *in vitro* studies (6, 10), perhaps through preventing angiogenesis and promoting apoptosis. Laboratory data suggest tricyclic antidepressants (TCAs) also increase apoptosis of colorectal cancer cells (11, 12), although some animal studies report that TCAs increase colorectal cancer cell growth (13, 14). Because of their potential anti-inflammatory and serotonergic reuptake inhibitory actions, antidepressants, especially SSRIs, have been hypothesized to be associated with reduced colorectal cancer risk.

Antidepressant use is increasingly common: 24.4% of U.S. women ages ≥60 reported using antidepressants in the past month (15). Antidepressants are primarily used to treat depression, although some additional indications exist (e.g., treatment of menopausal vasomotor symptoms). SSRIs are the most commonly used antidepressant class, followed by TCAs. Several studies report decreased colorectal cancer risk among regular antidepressant users compared with nonusers (16–18), with especially strong risk reductions associated with SSRI use, specifically (17, 18). For example, a case–control study reported a significant 45% reduction in colorectal cancer risk among regular SSRI users (OR = 0.55; 95% CI, 0.35–0.88) compared with nonusers (17). TCA use was not significantly associated with colorectal cancer risk (17, 18). In addition, two recent record-linkage studies reported no association of antidepressant use overall or by class with colorectal cancer risk (19, 20). Given the high prevalence of antidepressant use in the population, it is critical to clarify the relationship, if any, between antidepressant use and risk of colorectal cancer.

An important limitation of prior studies is the lack of consideration of depression. Depression is itself an inflammatory condition and has been associated with an increased risk of colorectal cancer (21). Because the vast majority of antidepressants are prescribed to treat depression, failure to adjust for depression or depressive symptoms may result in important confounding or interaction effects, obscuring the true association between antidepressants and colorectal cancer. Additional limitations of prior work include use of historical cohorts

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based on record linkages from large databases that lack information on additional relevant confounders. Although reports of significant decreases in colorectal cancer risk associated with antidepressant use are provocative, findings are not consistent across studies and the true effects of antidepressant on colorectal cancer risk remain unclear.

We sought to clarify whether antidepressants, overall and by class, affect colorectal cancer risk using data from the large, prospective Women's Health Initiative (WHI) cohort.

Materials and Methods

Study population

WHI participants were recruited from 40 clinical centers nationwide between October 1, 1993, and December 21, 1998. Details of WHI recruitment have been reported previously (22). Briefly, the WHI consisted of three clinical trials (CT): postmenopausal hormone therapy (HT; $N = 27{,}347$), dietary modification (DM; $N = 48{,}835$), and calcium/vitamin D supplementation (CaD; $N = 36{,}282$); participants were able to take part in more than one trial. Women who were either not interested or not eligible for the CT were enrolled in an observational study (OS; $N = 93{,}676$). All participants were between the ages of 50 and 79 at the time of enrollment. Participants provided data through annual in-person clinic visits (CT) or through annual mailed questionnaires and in-person clinic visits every 3 years (OS). Participants were followed for up to 10 years within the WHI, and many continue follow-up in the WHI Extension Study.

For the current analysis, we included eligible women enrolled in the CT and the OS. We excluded women missing information on antidepressant use at baseline ($n = 2$), missing information on follow-up time ($n = 691$), or reporting a history of cancer other than nonmelanoma skin cancer at baseline ($n = 15{,}925$). Our primary analysis included 145,190 women with an average length of follow-up time of 14.3 years.

Measurement of antidepressant use and depression

At the enrollment visit and subsequent clinic visits, participants brought in all current prescription medications used regularly, defined as use for at least 2 weeks. Information on antidepressant medication name and duration of use was recorded by clinical interviewers, and Medi-Span software (First Databank Inc.) was used to assign therapeutic class codes to each medication.

We categorized women as antidepressant users or nonusers at baseline and created separate indicator variables for each class of antidepressant used (SSRI, TCA, and other antidepressant). Duration of use was dichotomized at the median (<2 years, ≥2 years). In addition, we incorporated antidepressant use data collected at the year 3 clinic visit, when medication data were available for both OS and CT participants, to evaluate consistency of use (i.e., never antidepressant use, antidepressant use at baseline only, antidepressant use at year 3 only, antidepressant use at baseline and year 3).

Information on depressive symptoms was self-reported at baseline using the Burnam eight-item scale (23). Consistent with prior studies in the WHI (24, 25), Burnam scores at or above 0.06 were used to classify women with severe depressive symptoms. We relied on depressive symptoms at baseline and did not incorporate subsequent measurements of depressive symptoms in the current analysis.

Measurement of colorectal cancer incidence

Participants initially self-reported diagnoses of colorectal cancer on the semiannual (CT) or annual (OS) questionnaires. Self-reports were then centrally adjudicated as described previously (26). Briefly, medical records were collected and colorectal cancer diagnoses confirmed through review of pathology reports. Tumor registry coders determined grade and stage of the tumor. We defined colorectal cancer cases as those confirmed by adjudication in these analyses.

Measurement of covariates

Additional information on potentially important covariates was derived from data provided at the baseline clinic visit. We considered the following covariates, based on prior knowledge of relationships with antidepressant use and/or colorectal cancer: age (continuous), race/ethnicity (Caucasian, Asian Pacific Islander, African American, Hispanic), smoking status (never, <5 pack-years, 5–20 pack-years, >20 pack-years, smokers with unknown pack-years), diabetes (no, yes), diverticulitis (no, yes), hypertension (no, yes), primary care provider (no, yes), HT use at baseline (never, past estrogen-alone, past estrogen and progesterone, current estrogen, current estrogen, and progesterone), WHI HT trial study arm (not in HT trial, estrogen-alone intervention, estrogen-alone control, estrogen + progesterone intervention, estrogen + progesterone control), physical activity [MET-hours/week (quartiles)], family history of colorectal cancer (no, yes), ever had colorectal cancer screening (no, yes), history of colorectal polyp removal (no, yes), alcohol use (none, past <1 drink per month, <1 drink per week, 1–7 drinks per week, 7+ drinks per week), current duration of NSAID use (never, <1 year, 1–3 years, 3–8 years, and 8–20 years), body mass index (BMI; underweight, <18.5 kg/m^2; normal, 18.5–24.9 kg/m^2; overweight, 24.9–<30 kg/m^2; obese, ≥30 kg/m^2), and healthy eating index score (quartiles).

Statistical analysis

We evaluated the distribution of covariates between antidepressant users and nonusers using t tests or χ^2 tests as appropriate.

We used multivariable Cox proportional hazards regression to estimate HRs and 95% confidence intervals (CI) of the association between antidepressant use and time to colorectal cancer diagnosis while adjusting for potential confounders. Our initial multivariable model included all variables with $P < 0.25$ in univariate analyses, and backward selection was used based on likelihood ratio tests to generate a parsimonious model including all variables with $P < 0.05$; age, WHI study arm, and BMI were included in the final model regardless of statistical significance. Women contributed person-time to the analysis until diagnosis of colorectal cancer, death, loss to follow-up, or September 30, 2015, whichever happened first. We also evaluated associations between antidepressant class (SSRI, TCA, other antidepressant) and colorectal cancer, and also by the duration of antidepressant use. In secondary analyses, we separately examined the risk of colon and rectal cancers. In addition, we examined the joint distribution of antidepressant use and depression by testing for the significance of an interaction term between antidepressant use and depression as well as modeling the effect of a jointly defined exposure variable: no antidepressant use/no depression, antidepressant use only, depression only, antidepressant use and depression.

We incorporated antidepressant use information from the year 3 clinical visit to evaluate associations between groups defined by

consistency of antidepressant use at baseline and year 3 (never, antidepressant use at baseline only, antidepressant use at year 3 only, and antidepressant use at both baseline and year 3) on colorectal cancer risk. For these analyses, we restricted our sample to women alive and at risk for incident colorectal cancer at their year 3 visit. Follow-up time began on the date of the year 3 visit and continued until a censoring event as defined above.

Two sided P values ($P \leq 0.05$) were considered statistically significant. All analyses were performed with STATA version 14.0 (Stata Corporation).

Results

At baseline, 6.9% of the study population reported current antidepressant use. Antidepressant users were more likely to be obese, smokers, diabetic, hypertensive, and depressed (Table 1), and they also were more likely to have a primary care provider and to have had colorectal cancer screening and a history of colorectal polyp removal. Current use of postmenopausal HT and NSAIDs was higher among women using antidepressants compared with nonusers, whereas physical activity levels were lower among antidepressant users (Table 1). Of the 7% of participants who used antidepressants, SSRIs were the most common, with 51.1% of antidepressant users taking SSRIs, followed by 40.7% taking TCAs and 15.1% using others. In addition, some women reported concurrent use of multiple antidepressant classes (303 TCAs and SSRIs; 312 SSRIs and other antidepressant; 81 TCAs and other antidepressant; 7 all three classes). At baseline, the majority of women using SSRIs (56.3%) reported durations of use <2 years, whereas the majority of TCA users (62.1%) had used these medications for ≥2 years.

The median length of follow-up was 16.9 years (range, 0.003–21.7 years). During the follow-up period, 2,580 women were diagnosed with colorectal cancer, including 2,150 colon cancers and 490 rectal cancers; 60 women had cancer in both the colon and rectal regions. We included participants with complete data on needed covariates in our multivariable analysis, including 2,197 cases of colorectal cancer. Among the colorectal cancer cases, 123 cases were diagnosed among women reporting antidepressant use. In multivariable analyses (Table 2), we observed no statistically significant association between any antidepressant use at baseline and colorectal cancer risk (HR = 0.90; 95% CI, 0.75–1.09). When examining by class, we found no association with SSRI use specifically (HR = 1.08; 95% CI, 0.85–1.37), although we did observe a borderline significant reduced risk associated with TCA use (HR = 0.76; 95% CI, 0.56–1.04), which was stronger and statistically significant among women using TCAs for <2 years (HR = 0.42; 95% CI, 0.22–0.81). We likewise observed borderline significant inverse associations with use of other antidepressants and colorectal cancer (HR = 0.63; 95% CI, 0.36–1.11), although the number of colorectal cancer cases among users of other antidepressants was very small ($n = 12$ cases).

Overall, similar patterns were observed for colon cancer when examined separately in multivariable analyses. Of note, we observed a statistically significant inverse association between TCA use and colon cancer ($n = 32$ cases; HR = 0.68; 95% CI, 0.48–0.96), which was statistically significant among women using these drugs for <2 years ($n = 7$ cases; HR = 0.39; 95% CI, 0.19–0.82) but not among those using them for ≥2 years ($n = 25$ cases; HR = 0.85; 95% CI, 0.57–1.26). There were too few rectal cancer cases to provide reliable estimates in multivariable analyses.

In our multivariable models, we consistently observed a statistically significant approximate 20% increased risk of colorectal cancer associated with severe depressive symptoms (e.g., HR = 1.21; 95% CI, 1.09–1.48 in the model for antidepressant use). Because of the high concordance between antidepressant use and depression, we jointly evaluated their effect on colorectal cancer risk; we observed no statistically significant interaction between depressive symptoms and any of the antidepressant use variables (all $P > 0.3$).

At year 3, 4.4% of participants continued to use an antidepressant, 4.4% started using an antidepressant, 2.3% stopped using an antidepressant, and 88.9% continued to be non-antidepressant users. We further evaluated whether consistency of antidepressant use between baseline and year 3 affected colorectal cancer risk (Table 3). We observed slight, nonstatistically significant, inverse associations among users of any antidepressants or specific classes of antidepressants at both baseline and year 3 and among users at year 3 only.

Discussion

In this large prospective study of postmenopausal women, including 2,197 incident cases, we found no evidence of an association between total antidepressant use and SSRI use specifically on the risk of colorectal cancer. Colorectal cancer risk was 58% lower among short-term TCA users (<2 years) but not among longer term users; however, this result was not consistent with prior work and also was based on only nine cases. In addition, antidepressant use did not affect colorectal cancer risk even among women using these medications at both baseline and a follow-up visit 3 years later. Women with severe depressive symptoms had a 20% increase in colorectal cancer risk compared with those without, although no effect modification by antidepressant use was apparent. Although two record-linkage studies included more cases (19, 20), our study is the largest, prospective epidemiologic cohort study to include participant-provided data on important potential confounders, including depression. Furthermore, the careful and thorough collection of current medication use and the adjudication of colorectal cancer cases are important strengths and provide confidence in our results. In addition, prior studies included both males and females, without a separate examination of associations in these groups. Our study population included only women, which may contribute to differences between our findings and those of prior work.

Prior evidence of the relationship between TCAs and colorectal cancer is contradictory. Although some studies observed no association (17–20), another reported a nonsignificant 30% reduced colorectal cancer risk among TCA users (16). Interestingly, only short-term use of TCAs was associated with statistically significant reductions in colorectal cancer risk in our study. The failure to observe a decrease with longer duration of use may indicate acute effects in reducing risk that are not maintained. Alternatively, our findings could be related to the method of exposure assessment used in the WHI. In our study, participants self-reported duration of use of each current medication only; thus, antidepressant use prior to the baseline visit or taken after baseline but discontinued before the year 3 visit was not captured. Given the episodic nature of depression as well as the tendency for patients to need to switch between and within classes of

Table 1. Baseline characteristics of study population, by antidepressant use

Characteristics	No AD use $n = 135,154$	Current AD use $n = 10,036$
Age; mean (SD)	63.1 (7.2)	62.0 (7.2)
Race/ethnicity; *n* (%)		
Asian or Pacific Islander	3,812 (2.8)	77 (0.8)
Black or African American	12,756 (9.5)	538 (5.4)
Hispanic/Latino	5,548 (4.1)	339 (3.4)
White (not Hispanic origin)	110,560 (82.0)	8,913 (89.0)
Other	2,150 (1.6)	144 (1.4)
BMI, kg/m^2; *n* (%)		
Underweight (<18.5)	1,155 (0.9)	75 (0.8)
Normal (18.5–<24.9)	46,425 (34.6)	2,771 (27.9)
Overweight (25.0–<30)	46,658 (34.8)	3,414 (34.3)
Obese (≥30)	39,766 (29.7)	3,683 (37.0)
Healthy eating index score; *n* (%)		
<60.05	33,666 (25.0)	2,762 (27.6)
60.05–68.63	33,868 (25.1)	2,493 (24.9)
68.63–75.66	33,759 (25.0)	2,468 (24.6)
≥75.66	33,609 (24.9)	2,296 (22.9)
Physical activity, MET-hours/week; *n* (%)		
<2.25	31,853 (24.8)	3,143 (32.7)
2.25–<8.34	32,220 (25.1)	2,465 (25.6)
8.34–<17.76	31,905 (24.9)	2,168 (22.6)
≥17.76	32,422 (25.3)	1,838 (19.1)
Alcohol consumption; *n* (%)		
None	14,956 (11.2)	963 (9.7)
Past	24,022 (17.9)	2,622 (26.3)
<1 drink/month	16,732 (12.5)	1,276 (12.8)
<1 drink/week	27,638 (20.6)	2,004 (20.1)
1 to <7 drinks/week	34,965 (26.1)	2,158 (21.7)
>7 drinks/week	15,821 (11.8)	939 (9.4)
Smoking, pack-years; *n* (%)		
Never	69,069 (51.8)	4,477 (45.3)
<5	18,872 (14.1)	1,406 (14.2)
5–20	18,766 (14.1)	1,369 (13.8)
>20	23,628 (17.7)	2,418 (24.4)
Do not know	3,087 (2.3)	222 (2.2)
Has a primary care provider; *n* (%)	124,894 (93.3)	9,739 (97.8)
Has had a medical visit within the past year; *n* (%)	105,461 (80.8)	8,958 (91.5)
History of diabetes; *n* (%)	7,515 (5.6)	854 (8.5)
History of diverticulitis; *n* (%)	9,982 (7.9)	1,119 (11.8)
History of hypertension; *n* (%)	44,181 (32.7)	4,047 (40.3)
Colorectal cancer screening (colonoscopy, sigmoidoscopy, or flexible sigmoidoscopy); *n* (%)		
Never	64,091 (50.1)	3,627 (37.9)
<5 years ago	39,614 (31.0)	3,935 (41.1)
>5 years ago	23,940 (18.7)	1,995 (20.8)
Yes, unsure of date	235 (0.2)	19 (0.2)
History of colon polyp removal; *n* (%)[a]	10,623 (15.0)	1,117 (17.4)
Depressive symptoms; *n* (%)		
Not depressed	119,126 (90.6)	6,882 (70.9)
Depressed	12,389 (9.4)	2,832 (29.2)
Postmenopausal HT history; *n* (%)		
Never	60,307 (44.6)	2,807 (28.0)
Past, estrogen-alone	12,682 (9.4)	988 (9.8)
Past, estrogen and progesterone	8,002 (5.9)	669 (6.7)
Current estrogen alone	29,541 (21.9)	3,318 (33.1)
Current estrogen and progesterone	24,621 (18.2)	2,254 (22.5)
NSAID use; *n* (%)		
Never	80,716 (59.7)	4,653 (46.4)
Use for up to 1 year	16,962 (12.6)	1,618 (16.1)
1–3 years	12,377 (9.2)	1,193 (11.9)
3–8 years	11,652 (8.6)	1,235 (12.3)
8–20 years	9,578 (7.1)	1,020 (10.2)
>20 years	3,869 (2.9)	317 (3.2)
First-degree relative with colorectal cancer; *n* (%)	20,267 (15.7)	1,453 (15.2)

(Continued on the following page)

Table 1. Baseline characteristics of study population, by antidepressant use (Cont'd)

Characteristics	No AD use $n = 135,154$	Current AD use $n = 10,036$
HT study arm; *n* (%)		
Not randomized to HT	110,223 (81.6)	8,586 (85.6)
Estrogen alone intervention	4,719 (3.5)	328 (3.3)
Estrogen alone control	4,771 (3.5)	330 (3.3)
Estrogen and progesterone intervention	7,916 (5.9)	396 (4.0)
Estrogen and progesterone control	7,525 (5.6)	396 (4.0)

Abbreviation: AD, antidepressant.
[a]Among participants with a history of colonoscopy or flexible sigmoidoscopy.

antidepressant to try to find the most effective treatment for their depression (27), we may have substantial misclassification in duration of use. Such misclassification of exposure could explain our nonsignificant results, especially for longer term use of specific classes that would require use of the exact same medication for an extended period of time (at least 2 years). Furthermore, we were not able to incorporate antidepressant use beyond year 3, which also might induce misclassification and attenuate our results. Although our findings are suggestive of reduced colorectal cancer risk associated with TCA use, further prospective studies would need to confirm this finding, especially given the small numbers of cases contributing to the TCA use duration analyses.

We observed no association between SSRI use and colorectal cancer, in contrast to some prior studies reporting reduced colorectal cancer risk among SSRI users (16–18). One case–control study of SSRIs and colorectal cancer risk reported a significant 45% decreased risk among SSRI users (17), whereas another reported a 30% decreased risk among SSRI users taking a high daily dose within the previous 5 years (18). Another nested case–control study reported a 30% reduced colorectal cancer risk with any antidepressant use, which was similar but not statistically significant when restricting to SSRI users only (16). However, our results are in agreement with two studies, one of which was prospective, that reported no association between SSRI use and colorectal cancer (17, 20).

When we jointly evaluated antidepressant use and depression, we observed that women with depressive symptoms but without current antidepressant use had a significant increase in colorectal cancer risk compared with women with neither antidepressant use nor depression. Compared with healthy individuals, those with depression have higher levels of inflammatory markers, such as C-reactive protein, proinflammatory cytokines, and raised serum levels of IL6, IL1β, and TNFα (28, 29), which may be involved in the development of colorectal cancer (30). Our findings are consistent with those reported in the Nurses' Health Study, in which depressive symptomatology was associated with an increased risk of colorectal cancer (21). Similarly, our measure of depression only included depressive symptoms as opposed to a clinical diagnosis, but it has acceptable validity in identifying individuals with severe depressive symptoms (31).

Our results must be interpreted in the context of some limitations. Antidepressant use was fairly low (7%) within our population, and small numbers of colorectal cancer cases were observed in some antidepressant use categories. Second, SSRIs were new to the market at the time of WHI baseline. SSRI prescriptions quickly outpaced TCAs following their introduction in 1987, but long-term use of SSRIs was not common at WHI baseline in 1993 to 1997. Third, antidepressant use was assessed by visual inspection of pill bottles participants brought with them to clinic visits; therefore, prior use of antidepressant medications within the same class or in a different class was not captured, possibly causing nondifferential misclassification and attenuating results. Our ability to estimate cumulative, long-term usage of antidepressants is limited as a result. However, this approach to assessing medication use has the advantage of capturing actual, current

Table 2. Age- and multivariable-adjusted HRs and 95% CIs of baseline antidepressant use and colorectal cancer risk[a]

AD use category at baseline	Cases $N = 2,197$	Person-years	Crude incidence rate (per 100,000 person-years)	Age-adjusted HR (95% CI)	Multivariable-adjusted[b] HR (95% CI)
No AD use	2,074	1,646,416.70	125.97	—	—
Any AD use	123	117,083.73	105.05	0.90 (0.75–1.08)	0.90 (0.75–1.09)
<2 years of use	56	56,058.89	99.89	0.87 (0.66–1.13)	0.85 (0.65–1.11)
≥2 years of use	67	61,024.85	109.79	0.93 (0.73–1.19)	0.96 (0.75–1.22)
No SSRI use	2,124	1,702,963.30	124.72	—	—
SSRI use	73	60,537.14	120.59	1.10 (0.87–1.38)	1.08 (0.85–1.37)
<2 years of use	44	33,691.94	130.60	1.18 (0.87–1.59)	1.14 (0.85–1.55)
≥2 years of use	29	26,845.20	108.03	0.99 (0.69–1.43)	0.99 (0.68–1.43)
No TCA use	2,154	1,716,517.90	125.49	—	—
TCA use	43	46,982.57	91.52	0.74 (0.55–1.00)	0.76 (0.56–1.04)
<2 years of use	9	17,955.97	50.12	0.41 (0.21–0.79)	0.42 (0.22–0.81)
≥2 years of use	34	29,026.60	117.14	0.94 (0.67–1.31)	0.97 (0.69–1.37)
No other AD use	2,185	1,746,072.80	125.14	—	—
Other AD use	12	17,427.66	68.86	0.62 (0.35–1.10)	0.63 (0.36–1.11)
<2 years of use	5	9,253.94	54.03	0.50 (0.21–1.20)	0.47 (0.19–1.13)
≥2 years of use	7	8,173.72	85.64	0.76 (0.36–1.59)	0.82 (0.39–1.73)

Abbreviation: AD, antidepressant.
[a]All HRs are reported versus no use within the specific antidepressant category.
[b]Adjusted for age, WHI study arm, BMI, healthy eating index, physical activity, pack-years of smoking, diabetes, history of colonoscopy/flexible sigmoidoscopy, history of colorectal polyp removal, depressive symptoms, NSAID use, family history of colorectal cancer, diverticulitis, and HT use.

Table 3. Age- and multivariable-adjusted HRs and 95% CIs of antidepressant use status between baseline and year 3 with colorectal cancer risk

AD use at baseline and year 3	Cases $N = 1{,}544$	Person-years	Crude incidence rate (per 100,000 person-years)	Age-adjusted HR (95% CI)	Multivariable-adjusted[a] HR (95% CI)
Any AD					
Non-AD users	1,407	1,110,703.9	126.68	1.00 (—)	1.00 (—)
Baseline AD use only	32	26,611.296	120.25	0.87 (0.73–1.47)	1.02 (0.72–1.46)
Year 3 AD use only	51	50,771.707	100.45	0.84 (0.63–1.11)	0.84 (0.63–1.12)
Baseline and year 3 AD use	54	53,275.781	101.36	0.87 (0.67–1.15)	0.89 (0.67–1.17)
SSRI					
Non-SSRI users	1,461	1,167,200.3	125.17	1.00 (—)	1.00 (—)
Baseline SSRI use only	25	15,843.157	157.80	1.46 (0.98–2.16)	1.43 (0.96–2.13)
Year 3 SSRI use only	32	33,121.128	96.62	0.84 (0.59–1.19)	0.84 (0.59–1.20)
Baseline and year 3 SSRI use	26	25,198.174	103.18	0.94 (0.63–1.38)	0.93 (0.63–1.38)
TCA					
Non-TCA users	1,496	1,193,388	125.36	1.00 (—)	1.00 (—)
Baseline TCA use only	13	14,668.704	88.62	0.73 (0.42–1.26)	0.74 (0.43–1.28)
Year 3 TCA use only	17	15,741.12	108.00	0.85 (0.53–1.37)	0.85 (0.53–1.37)
Baseline and year 3 TCA use	18	17,564.942	102.48	0.82 (0.52–1.31)	0.87 (0.55–1.39)

Abbreviation: AD, antidepressant.

[a]Adjusted for age, WHI study arm, BMI, healthy eating index, physical activity, pack-years of smoking, diabetes, history of colonoscopy/flexible sigmoidoscopy, history of colorectal polyp removal, depressive symptoms, NSAID use, family history of colorectal cancer, diverticulitis, and HT use.

usage, as opposed to relying on pharmacy databases that identify filled prescriptions but offer no insight on whether the medications were actually taken. In addition, current antidepressant use was assessed only at baseline and year 3; therefore, we were unable to evaluate effects of cumulative duration of antidepressant use on our outcomes.

Previous studies evaluating relationships between antidepressant use and colorectal cancer are mainly derived from record linkages within large health insurance systems or population databases. Although such studies are important and have many advantages, they typically lack the ability to fully adjust for potential confounders (e.g., diet, physical activity). Furthermore, the reliance on database information on antidepressant use may capture prescriptions written and/or filled, yet may overestimate actual usage if the medications were not taken. The differences in approach to classifying antidepressant use may account for the different results observed across studies. Given these limitations and the inconsistent findings of prior studies, we sought to evaluate whether antidepressants were associated with colorectal cancer risk in a large, population-based cohort. Particular strengths of our study are its prospective design, large sample size, and comprehensive data on potential confounders, including depressive symptoms, utilization of colorectal cancer screening, history of colorectal polyp removal, family history of colorectal cancer, diet, and BMI. Importantly, all medication use was verified by a research nurse examining participants' pill bottles, and all colorectal cancer cases included in the analysis were adjudicated, incident cancers.

In summary, we did not find compelling evidence that antidepressants reduced risk of colorectal cancer. Importantly, we observed no increase in colorectal cancer risk associated with use of any class of antidepressant. Our findings agree with those of two large registry-based studies; the consistency of these findings indicates that there is likely no significant association between antidepressant use and later risk of colorectal cancer. Although it does not appear that antidepressants, especially SSRIs, would be useful as chemopreventive agents for colorectal cancer, it is reassuring that the use of antidepressants, which can effectively treat depression in most individuals, does not result in elevated risk of colorectal cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: K.W. Reeves

Development of methodology: K.W. Reeves

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K.W. Reeves

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.F. Kiridly-Calderbank, S.R. Sturgeon, C.H. Kroenke, K.W. Reeves

Writing, review, and/or revision of the manuscript: J.F. Kiridly-Calderbank, S. R. Sturgeon, C.H. Kroenke, K.W. Reeves

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.F. Kiridly-Calderbank

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