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Colorectal cancer risk in relation to antidepressant medication use

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Abstract

Laboratory studies suggest that antidepressants affect the risk of some cancers, including colorectal cancer. To investigate whether selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) are associated with colorectal cancer risk, we conducted a case-control study among enrollees of an integrated healthcare delivery system in Washington State. Cases were first diagnosed with invasive colorectal cancer between 2000-2003; controls were randomly selected from Group Health enrollees and matched to cases on age, sex, and length of enrollment before diagnosis/reference date. We used logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) for colorectal cancer in relation to use of any antidepressant, SSRIs only, or TCAs only among 649 cases and 656 controls. Use of any antidepressant was associated with a reduced risk of colorectal cancer (OR=0.7, 95%CI=0.5-0.9). Associations were similar for persons who used SSRIs exclusively (OR=0.7, 95%CI=0.4-1.1) and TCAs exclusively (OR=0.7, 95%CI=0.5-1.2); however, this reduction in risk appeared limited to persons without a prior cancer at another site. Our data support findings from previous epidemiologic and animal studies that suggest antidepressants may reduce the risk of colorectal cancer. Future studies with larger sample sizes should further examine individual drugs, as well as dose, duration, and recency of use.

Keywords

colorectal cancer; antidepressant medications; pharmacoepidemiology

INTRODUCTION

Antidepressant use is on the rise in the United States,1 and it is important to determine what role, if any, these medications might play in altering the risk of diseases such as cancer. There have been several reports of null associations between use of antidepressants and the risk of breast 2, 3 and ovarian 4-6 cancers. However, there is a lack of research on these relatively commonly used medications in relation to other major causes of cancer mortality, including colorectal cancer. A large epidemiologic study reported that serotonin reuptake

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inhibitors (SSRI) use reduced risk of colorectal cancer, but observed no association with use of tricyclic antidepressants (TCA).7 Another large study observed an increased risk of colon cancer with >4 years use of non-SSRI antidepressants.8 A recent study noted a reduced risk of colorectal cancer associated with SSRI use and a non-significant reduction with TCA use.9

Laboratory evidence suggests a decreased risk of colorectal cancer associated with SSRI use. In mice xenografted with human colorectal carcinomas, administration of anti-serotoninergic agents, including the SSRIs fluoxetine and citalopram,10 reduced colorectal tumor growth, as measured by tumor volume, compared to controls.10-12 In rats, the mitotic rate of chemically induced colonic tumors was lower in those subsequently treated with anti-serotoninergic agents compared to controls injected with saline.10, 13 These studies, along with *in vitro* studies of human colorectal cancer cell lines treated with SSRIs,14, 15 suggest that SSRIs may impede growth of colorectal tumors.

Evidence linking TCA use to colorectal cancer risk is less clear. *In vitro* studies of human colorectal carcinoma cell lines report that the TCAs desipramine, imipramine, and amitriptyline induced apoptosis;16, 17 however, desipramine has been shown to increase colon tumor incidence in rats18 and proliferation of mouse intestinal cell lines.19 Thus, there is evidence to support that TCAs may increase or decrease the risk of colorectal cancer.

The goal of the current study was to investigate the potential associations between SSRIs and TCAs and colorectal cancer risk.

MATERIALS AND METHODS

Study setting and population

To investigate the relationship between antidepressant use and colorectal cancer risk, we conducted a population-based case-control study at Group Health, an integrated healthcare delivery system that provides comprehensive healthcare to approximately 550,000 members in western Washington State. Using the western Washington Surveillance Epidemiology and End Results (SEER) cancer registry, we identified cases of first primary colorectal cancer among Group Health members, diagnosed between January 1, 2000 and December 31, 2003.20, 21 Internal audits show that the registry has nearly complete ascertainment of Group Health cancer cases.22 For comparison, we randomly selected controls from the Group Health enrollment file. Controls were matched 1:1 to cases on age, gender, and duration of Group Health enrollment prior to the case's diagnosis date; controls were assigned a reference date (month/year) corresponding to the case's diagnosis date.

We excluded patients who were enrolled in Group Health for <2 years before their reference date, had a prior diagnosis of colorectal cancer at any time, or were diagnosed with inflammatory bowel disease. We restricted analyses to patients 40+ years of age at their reference date. Analyses were conducted on 649 cases and 656 controls. Study methods were approved by Group Health's Institutional Review Board.

Medication use

Electronic pharmacy records were the primary source of information on prescription medication use. Since 1976, the Group Health pharmacy database has included a record for each prescription medication dispensed to Group Health enrollees. Each record includes a patient identifier, drug name, strength, date dispensed, quantity dispensed, instructions for use, and form. We ascertained medication use in the 10 years before the reference date. To reduce the likelihood that the medication was being taken for symptoms resulting from

undetected colorectal cancer, we did not count antidepressant use that occurred in the year before the reference date. We defined use of SSRIs, TCAs, or miscellaneous antidepressants as ≥2 prescription fills for any drug in that class within a 6-month period to give some assurance that the medication was actually being taken. For each prescription filled, we estimated the date when the prescription should have run out (run-out date) based on quantity dispensed and instructions for use. A new run-out date was set with each successive dispensing. A 60-day lag period between the run-out date of one dispensing and fill date of the successive dispensing was used to define continuous use. Periods of continuous use were summed for total duration of use.23 We classified persons as either non-users of any antidepressant or users of any antidepressants as well as exclusive users of SSRIs, TCAs, or miscellaneous antidepressants. In a secondary analysis, we estimated risk associated with use of genotoxic (n=61) vs. non-genotoxic (n=41) TCAs, based on whether they have been observed to cause somatic mutations in *Drosophila*. 7, 24-26

Covariates

Trained chart abstractors used a standardized data collection instrument to collect data beginning 10 years before the reference date. Medical records (paper and electronic) were abstracted for potential covariates including: weight; race; any prescription or evidence in the medical record of over-the-counter use of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin and Cox-2 inhibitors; peptic ulcer disease; smoking status; and diabetes (defined by ≥2 dispensings for a medication used to treat diabetes; fasting glucose >125 mg/dL confirmed by a second out-of-range test within 1 year; random glucose >200 mg/dL confirmed by a second test within 1 year; hospital discharge of diabetes; or 2 outpatient diagnosis of diabetes). Data on any use of hormone therapy in the 10-years prior to reference was also obtained using electronic pharmacy records.

Statistical Analyses

All analyses were conducted in Stata 9.2 and 10.1. (Stata Corporation, College Station, TX). We compared colorectal cancer cases and controls with respect to demographic and health characteristics. Non-users of any antidepressants served as the reference group for all analyses. We estimated odds ratios (OR) and two-sided 95% confidence intervals (CI) using logistic regression, adjusting for matching factors: age, gender, and length of enrollment at Group Health before the reference date. We also adjusted for potential confounders that were identified *a priori*: smoking status, NSAID/aspirin use, and diabetes. We also investigated whether previous hormone therapy use, body mass index (BMI), race, or a previous diagnosis of cancer at another site confounded the relationship between antidepressant use and colorectal cancer risk in univariate analyses, changing the OR by ≥10%. In exploratory analyses, we stratified results by previous diagnosis of cancer at another site and NSAID use, and examined duration and recency of antidepressant use. Due to small numbers of long-term users whose last use was many years before the reference date, we were only able to stratify by recency of use for short-term users.

RESULTS

On average, subjects were 70 years old and had been enrolled at Group Health for 19 years before their reference date. Females comprised 51% of the sample. Compared to controls, cases were more likely to have diabetes, a previous diagnosis of cancer at another site, and a history of smoking, and less likely to have used hormone therapy (Table 1).

While cases were less likely than controls to have ever used any antidepressants (19.7% and 24.2%, respectively) (Table 2); duration of use of any antidepressant use was longer among cases than controls (mean 2.9 vs. 2.1 years, p=0.01). The distribution of stage of disease was

similar among antidepressant users and non-users (results not shown). Overall, any antidepressant use was associated with a reduced risk of colorectal cancer (adjusted OR=0.7, 95% CI=0.5-0.9). The risk of colorectal cancer was similar among participants who exclusively used SSRIs or TCAs, although the results for these antidepressant classes did not achieve statistical significance (Table 2). The OR for exclusive use of other antidepressants in relation to colorectal cancer risk was significant.

We conducted several exploratory analyses. The risk of colorectal cancer associated with TCA use did not differ on the basis of genotoxicity classification (adjusted OR for non-genotoxic TCAs only=0.8, 95% CI=0.4-1.5; adjusted OR for genotoxic TCAs only=0.7, 95% CI=0.4-1.2). The reduced risk associated with antidepressant use appeared to be restricted to persons without a prior diagnosis of cancer at another site, though the interaction term was not statistically significant (adjusted OR for any antidepressant use among persons without previous cancer=0.6, 95% CI=0.4-0.8; adjusted OR for any antidepressant use among persons with previous cancer=1.1, 95% CI = 0.6-1.9). In another exploratory analysis, the reduced risk of colorectal cancer associated with antidepressant use was restricted to NSAID/aspirin users (adjusted OR for any antidepressant use=0.6, 95% CI 0.5-0.9 in NSAID/aspirin users; adjusted OR for any antidepressant use=0.9, 95% CI 0.6-1.5 in NSAID/aspirin non-users), but the interaction term was not significant (p=0.2).

Adjusting for BMI altered risk estimates by >10%, largely due to the exclusion of almost a third (28%) of study participants due to missing BMI data; however, adjusting for BMI with a separate category for missing BMI did not alter results meaningfully. Given the large amount of missing data, we did not include BMI in our final models. Nevertheless, we examined stratum-specific estimates and observed that the reduced risk associated with any antidepressant use was strongest among persons with BMI ≥30kg/m^2 (adjusted OR=0.4, 95% CI=0.3-0.8), though the interaction terms were not statistically significant.

Despite limited power, we also explored whether risk of colorectal cancer varied by duration of use and time since last use of antidepressants (Table 3). The reduced risk associated with antidepressant use appeared to be limited to short-term use (duration <2 years); for TCAs there was a slight, but not significant, suggestion of an increased risk with duration of use ≥2 years.

DISCUSSION

In this population-based case-control study, we observed a reduced risk of colorectal cancer associated with antidepressant use in the 10 years before diagnosis. Results were similar for exclusive use of SSRIs or TCAs, but not statistically significantly.

Even with this relatively small sample, our findings with respect to SSRIs are similar to those of a larger case-control study of antidepressant use and colorectal cancer risk.7 SSRI use was more common in our study population compared to this Canadian study. In their large study of Saskatchewan residents (3,306 cases, 13,201 controls), Xu et al. observed a decreased risk of colorectal cancer associated with SSRI use (OR =0.84, 95% CI: 0.68-1.03) and in particular among those who had used high doses of SSRIs within five years of the reference date (OR=0.70, 95% CI: 0.50, 0.96).7 A recent hospital-based case-control study also observed a reduced risk of colorectal cancer associated with regular SSRI use (OR=0.55, 95%CI: 0.35-0.88).9 They did not observe differences in risk according to duration of use. A large Finnish cohort study recently reported adjusted relative risks ranging from 0.81 to 1.39 for colorectal cancer in relation to different durations of SSRI use, but none was significant.8 Results from our study and most previous research suggest a reduced risk of colorectal cancer associated with SSRI use. Possible mechanisms might

include reducing cell proliferation 10¯13 or a direct cytotoxic effect on cells that have undergone malignant transformation.14, 15

The relationship between TCA use and colorectal cancer has varied across studies. Our findings with respect to TCAs differed from Xu et al., who did not observe an association between TCA use and colorectal cancer. They suggested that their lack of association with TCAs could be due to confounding by SSRI use; i.e., any increased risk associated with TCA use was nullified by subsequent SSRI use. In our study, we compared exclusive TCA users to non-users of any antidepressants and did not observe an increased risk of colorectal cancer, suggesting that the lack of association between TCA use and colorectal cancer risk in the Xu study was not due to confounding by SSRI use. Our results were similar to the hospital-based case control study, which reported a non-significant reduction in risk associated with regular TCA use (OR=0.77, 95%CI: 0.52-1.16).9 The reduced risk of colorectal cancer that we observed with TCA use is consistent with laboratory results of TCA induced apoptosis in human colon cancer cells lines.16, 17 However, a recent cohort study reported an increased risk of colorectal cancer associated with >4 years of non-SSRI antidepressant use8, which is also consistent with laboratory studies of the TCA desipramine.18, 19 Our finding of an association between exclusive use of other (non-TCA, non-SSRI) antidepressants and colorectal cancer risk should be interpreted cautiously because of small numbers, this group's heterogeneity, and the lack of data from laboratory studies.

An exploratory analysis suggested that the reduced risk associated with antidepressants may be limited to persons without a prior history of cancer at another site. One possible explanation is that the risk of colorectal cancer associated with a prior cancer at a different site is strong enough to outweigh any modest reduction in colorectal cancer risk associated with antidepressant use. Another exploratory analysis suggested that the reduced risk associated with antidepressant use may be limited to NSAID users. While we do not know of laboratory data to support this association as is the case for NSAIDs and statins,27, 28 coadministration of chemopreventive drugs could be synergistic. These findings should be interpreted cautiously because of our sample size and their exploratory nature.

Strengths of our study included unbiased ascertainment of exposure from electronic records of medications dispensed in a population-based setting. Approximately 97% of patients in this setting fill most or all of their prescriptions at Group Health pharmacies,29 underscoring the completeness of these records for research purposes, particularly for medications like antidepressants that are not available over-the-counter. An additional study strength was our ability to adjust for a number of potential confounding factors such as smoking, diabetes, and NSAID use as reported in the medical record and electronic pharmacy file; however, our ability to adjust for BMI was limited by missing data.

The main limitation of this study is its relatively small sample size and modest statistical power to examine risk associated with individual antidepressants, dose, duration, and recency of use. If antidepressants have a cytotoxic effect on cancerous colorectal cells, we would expect high doses and recent use to be associated reduced risk, as was noted by Xu et al.7 and supported by laboratory studies that used very high concentrations of antidepressants.15 It is not clear why, in our study, the reduced risk associated with antidepressant use was only present for short-term use or why there may be an increased risk associated with longer term TCA use. Given our limited power to look at duration and recency, these findings should not be over-interpreted – they could be due to chance; however, they do provide some evidence against an argument of true protection by antidepressant use. It is also unclear why the associations appeared strongest in obese

persons; results from this secondary analysis with small numbers in each stratum should also be interpreted cautiously since they could be due to chance alone.

A second study limitation is that exposure ascertainment was restricted to the 10-year period before the reference date. Given the potentially long natural history of colorectal cancer, it is possible that the etiologically relevant period for exposure is >10 years before diagnosis. However, other medication exposures, such as hormone therapy, may act in more recent exposure intervals.30

Additionally, at least three sources of confounding are possible. If depression were associated with increased risk of colorectal cancer, then antidepressants might appear to increase the risk of colorectal cancer. However, given that antidepressant use was associated with a reduced risk, confounding by indication is unlikely to explain our results. History of colorectal cancer screening and family history of colorectal cancer are other potential confounders for which we did not have data. If antidepressant users were more likely to undergo colorectal cancer screening and therefore have a premalignant condition treated, screening history could confound the analysis. Adjusting for screening history is problematic if one is not able to accurately distinguish screening from diagnostic testing.31 NSAID use could also confound the association between antidepressants and colorectal cancer risk: if NSAID use is more common among antidepressant users, then antidepressants could appear to reduce the risk of colorectal cancer even if no true association exists. We adjusted for and stratified by NSAID use ascertained by chart review and automated data, but if NSAIDs are commonly purchased over-the-counter and not noted in the medical record, there could be residual confounding. We used both medical records and automated pharmacy data to capture NSAID use; however, the potential for misclassification remains since most use is over-the-counter.

Antidepressants are commonly prescribed medications and it is reassuring that we did not observe an increased risk of colorectal cancer among users of these medications. Additional observational studies on this topic are warranted, particularly those that have power to examine individual antidepressants, different doses, duration, and recency of use, as well as detailed information on important confounders.

Key points

- In our study, antidepressant use was associated with a reduced risk of colorectal cancer
- The reduction in colorectal cancer risk risk was similar, but not significant, for exclusive users of SSRIs and TCAs

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Abbreviations use

BMI	body mass index
CI	confidence intervals
NSAIDs	non-steroidal anti-inflammatory drugs

OR	odds ratios
TCAs	tricyclic antidepressants
SSRIs	serotonin reuptake inhibitors
SEER	Surveillance Epidemiology and End Results

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Table 1

Characteristics of colorectal cancer cases and controls, Group Health, 2000-2003

	Cases (N=649)	Controls (N=656)
Sex		
Female	336 (51.8)	337 (51.4)
Male	313 (48.2)	319 (48.6)
Mean age, years (SD)	70 (12)	70 (12)
Mean enrollment at Group Health, years (SD)	19 (11)	19 (11)
Body Mass Index (BMI), kg/m^2 [1]	28.6 (7.0)	27.3 (5.9)
Missing	185	180
Race		
White	581 (89.5)	501 (76.4)
African American	27 (4.2)	23 (3.5)
Asian/Pacific Islander	40 (6.2)	31 (4.7)
Other/unknown	1 (0.2)	101 (15.4)
Diabetes mellitus[2,3]		
No	491 (75.7)	540 (82.3)
Yes	158 (24.3)	116 (17.7)
Previous cancer diagnosis[2]		
No	487 (75.0)	536 (81.7)
Yes	162 (25.0)	120 (18.3)
Ever smoker[4]		
No	271 (41.8)	333 (50.8)
Yes	378 (58.2)	323 (49.2)
Hormone therapy use[2] (among women only, N=673)		
No	208 (61.9)	172 (51.0)
Yes	128 (38.1)	165 (49.0)
NSAID/Aspirin use (dispensed from Group Health pharmacy or use noted in medical record)[2]		
No	255 (39.3)	238 (36.3)
Yes	394 (60.7)	418 (63.7)

SD = standard deviation

[1] Based on weight 12-36 months before reference date

[2] In the 10 years before reference date

[3] Diabetes defined as one or more of the following: 2+ dispensings for a medication used to treat diabetes; fasting glucose >125 mg/dL confirmed by a second out-of-range test within 1 year; random glucose >200 mg/dL confirmed by a second test within 1 year; hospital discharge of diabetes; or 2 outpatient diagnosis of diabetes (ICD-9=250, 250.0, 250.1, 250.2, 250.3, 250.4, 250.5, 250.6, 250.7, 250.8, 250.9)

[4] At least 12 months before reference date

Table 2

Association between use of antidepressant medications and colorectal cancer risk, Group Health, 2000-2003

	Cases (N=649)	Controls (N=656)	Minimally adjusted odds ratio (95% CI)[1]	Fully adjusted odds ratio (95% CI)[1,2]
	n (%)	n (%)		
No antidepressant use	521 (80.3)	497 (75.8)	*Reference*	*Reference*
Any antidepressant use	128 (19.7)	159 (24.2)	0.8 (0.6, 1.0)	0.7 (0.5, 0.9)
SSRI use exclusively	29 (4.5)	40 (6.1)	0.7 (0.4, 1.1)	0.7 (0.4, 1.1)
TCA use exclusively	47 (7.2)	55 (8.4)	0.8 (0.5, 1.2)	0.7 (0.5, 1.1)
Other antidepressant use exclusively	6 (0.9)	16 (2.4)	0.4 (0.1, 0.9)	0.3 (0.1, 0.9)

SSRI = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants; CI = confidence interval

[1] Adjusted for matching factors: sex, age, and length of enrollment at Group Health prior to reference date

[2] Also adjusted for smoking status, NSAID/aspirin dispensed from Group Health pharmacy or use noted in medical record, and history of diabetes mellitus

Table 3

Association between use of antidepressant medications and colorectal cancer risk, according to duration and recency of use, Group Health, 2000-2003

	Cases (N=649)	Controls (N=656)	Minimally adjusted odds ratio (95% CI)[1]	Fully adjusted odds ratio (95% CI)[1,2]
	n (%)	n (%)		
Non-users	521 (80.3)	497 (75.8)	*Reference*	*Reference*
Any antidepressant use				
Duration of use <2 years, & current use or last use <2 years before reference	38 (5.9)	59 (9.0)	0.6 (0.4, 0.9)	0.5 (0.3, 0.8)
Duration of use <2 years, & last use ≥2 years before reference	29 (4.5)	45 (6.9)	0.6 (0.4, 1.0)	0.6 (0.4, 1.0)
Duration ≥2 years	61 (9.4)	55 (8.4)	1.1 (0.7, 1.6)	1.0 (0.7, 1.5)
SSRI use exclusively				
Duration of use <2 years	20 (3.1)	31 (4.7)	0.6 (0.3, 1.1)	0.6 (0.3, 1.1)
Duration of use ≥2 years	9 (1.4)	9 (1.4)	1.0 (0.4, 2.4)	1.0 (0.4, 2.8)
TCA use exclusively				
Duration of use <2 years	29 (4.5)	42 (6.4)	0.6 (0.4, 1.0)	0.6 (0.3, 1.0)
Duration of use ≥2 years	18 (2.8)	13 (2.0)	1.3 (0.6, 2.7)	1.3 (0.6, 2.7)

SSRI = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants; CI = confidence interval

[1] Adjusted for matching factors: sex, age, and length of enrollment at Group Health prior to reference date

[2] Also adjusted for smoking status, NSAID/aspirin dispensed from Group Health pharmacy or use noted in medical record, and history of diabetes mellitus