Published in final edited form as:

Psychooncology. 2019 April ; 28(4): 750–758. doi:10.1002/pon.5015.

Use of antidepressants after colon cancer diagnosis and risk of recurrence.

Gaia Pocobelli¹, Onchee Yu¹, Rebecca A. Ziebell¹, Erin J. Aiello Bowles¹, Monica M. Fujii¹, Andrew T. Sterrett², Jennifer M. Boggs², Lu Chen¹, Denise M. Boudreau^{1,3,4}, Debra P. Ritzwoller², Rebecca A. Hubbard⁵, and Jessica Chubak^{1,3}

¹Kaiser Permanente Washington Health Research Institute, Seattle, Washington

²Kaiser Permanente Colorado Institute for Health Research, Denver, Colorado

³Department of Epidemiology, School of Public Health, University of Washington, Seattle, Washington

⁴School of Pharmacy, University of Washington, Seattle, Washington

⁵Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Abstract

Objectives—Prior research examining the association between use of antidepressants after colon cancer diagnosis and risk of recurrence is scant. We evaluated this association among colon cancer patients diagnosed at two integrated health care delivery systems in the United States.

Methods—We conducted a cohort study of stage I-IIIa colon cancer patients diagnosed at 18 years of age at Kaiser Permanente Colorado and Kaiser Permanente Washington during 1995–2014. We used pharmacy records to identify dispensings for antidepressants, and tumor registry records and patients' medical charts to identify cancer recurrences. Using Cox proportional hazards models, we estimated the adjusted hazard ratio (HR) of colon cancer recurrence comparing patients who used antidepressants after diagnosis to those who did not. We also evaluated the risk associated with use of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) separately.

Results—Among the 1,923 eligible colon cancer patients, 807 (42%) used an antidepressant after diagnosis and 139 had a colon cancer recurrence during an average 5.6 years of follow-up. Use of antidepressants after colon cancer diagnosis was not associated with risk of recurrence (HR: 1.14, 95% confidence interval [CI]: 0.69–1.87). The HR for use of SSRIs was 1.22 (95% CI: 0.64–2.30) and for TCAs it was 1.18 (95% CI: 0.68–2.07).

Conclusions—Our findings suggest that use of antidepressants after colon cancer diagnosis was common and not associated with risk of recurrence. Future larger studies with greater power to examine risk associated with individual antidepressants would be valuable additions to the evidence base.

Keywords

colon cancer; oncology; recurrence; antidepressants; cohort study; serotonin reuptake inhibitors; tricyclic antidepressants

Background

Depression is estimated to be 2–3 times more common among cancer patients than the general population.^{1–3} In colon cancer patients, the prevalence of depression was reported to be 13%–25% in a systematic review of the literature by Massie.³ Antidepressants have been shown to be an effective treatment for depression among cancer patients,⁴ and selective serotonin reuptake inhibitors (SSRIs) are currently the most common class prescribed.⁵ Given the high prevalence of depression among colon cancer patients, it is important to understand whether use of antidepressants may influence risk of recurrence.

Evidence from laboratory studies examining effects of antidepressants on tumor formation and growth is conflicting.⁶ For example, in some studies in rodents, SSRIs decreased cell proliferation and reduced tumor volume,⁷ whereas in others, they stimulated tumor growth.⁸ Epidemiologic studies have tended to show that use of antidepressants was either not associated with risk of developing colon cancer, or was associated with a decrease in risk.^{9,10} Therefore, we hypothesized that use of antidepressants after colon cancer diagnosis would be associated with a decreased risk of recurrence.

To our knowledge, no prior study has evaluated the association between use of antidepressants after colon cancer diagnosis and risk of recurrence. Two studies have addressed related questions. In one, an increased risk of all-cause mortality was observed in relation to use of antidepressants after colorectal cancer diagnosis (hazard ratio [HR]: 1.37, 95% confidence interval [CI] 1.21–1.54).¹¹ However, the authors of this cohort study did not have information on stage at diagnosis, an important potential confounder.^{11,12} In the other, a case-control study, the authors addressed a broader question. They evaluated risk of cancer recurrence in patients with breast cancer, colon cancer or melanoma (all patients combined) in relation to use of antidepressants or antihistamines (grouped together), and found no association (odds ratio [OR] 0.97; 95% CI 0.52–1.78).¹³

Using data from a cohort of colon cancer patients diagnosed at two integrated health care delivery systems in the United States during 1995–2014, we evaluated whether use of antidepressants after colon cancer diagnosis was associated with risk of recurrence.

Methods

We conducted a cohort study of colon cancer patients at Kaiser Permanente Washington and Kaiser Permanente Colorado (**R**ecurrence of **C**olon cancer in **R**elation to **D**rug use [RECORD]).¹⁴ Kaiser Permanente Washington's institutional review board (IRB) approved all study procedures at both sites (#529395). In accordance with states' and federal regulations, we requested, and were granted, a waiver of consent to access patient information from medical records and electronic data files.

Data Sources

Both Kaiser Permanente Washington and Kaiser Permanente Colorado store electronic health data in a Virtual Data Warehouse (VDW) according to specifications established by the Health Care Systems Research Network.¹⁵ These data include: patient enrollment information; diagnosis and procedure codes from health care encounters; routinely collected clinical information such as height and weight; and outpatient prescription medication dispensings. The VDW also stores tumor registry records on incident cancers at both sites, and on cancer recurrence at Kaiser Permanente Colorado. The source of the tumor registry records at Kaiser Permanente Washington was the Seattle-Puget Sound Surveillance, Epidemiology and End Results (SEER) program, and at Kaiser Permanente Colorado it was the health system's own cancer registry. At both registries, information was collected by trained cancer registrars who review pathology reports and patients' medical charts.

Study Population

To identify our cohort, we first ascertained potentially eligible colon cancer patients using the VDW. We identified patients who were 18 years of age when diagnosed with stage I-IIIa (American Joint Commission on Cancer 6th edition) malignant adenocarcinoma of the colon or rectosigmoid junction during 1995–2014 (the "index colon cancer") (n = 3,326; Figure 1). Using the VDW, we applied several exclusion criteria. We required that patients be enrolled from at least 12 months before diagnosis through 3 months afterward and not have a previous colorectal cancer or a concurrent additional one.

Medical chart abstractors then reviewed clinical information from the remaining 2,695 patients' medical charts to 1) confirm eligibility, and 2) ascertain treatment, risk factor, and outcome information for eligible patients. Abstractions occurred from June 2014 through August 2016. Abstractors received extensive training and regularly participated in inter- and intra-rater reliability assessments.

Based on medical chart review, patients were excluded if they had evidence of cancer within 90 days after the end of their colon cancer treatment. A 90-day time frame was selected based on the assumption that patients would receive imaging within 90 days following treatment to determine whether the cancer was still present. If cancer was present, the patient would not be at risk of a recurrence. We also excluded patients with incomplete or unavailable medical records, or indeterminate imaging results during the 90 days after the end of their colon cancer treatment.

Finally, we excluded 116 patients with an index colon cancer diagnosis before January 1, 1999 at Kaiser Permanente Colorado because diagnosis code data, needed to ascertain comorbidities in the year prior to diagnosis, were not available at Kaiser Permanente Colorado until 1998. A total of 1,923 patients remained for analyses. We outline the complete list of VDW- and chart-based exclusions in Figure 1.

Exposure

We ascertained exposure to antidepressants using pharmacy data on prescription medication dispensings. Colon cancer patients were classified as exposed to antidepressants in a time-

varying manner. Patients were classified as unexposed until their first dispensing of an antidepressant on or after their index colon cancer diagnosis date. Once a patient was classified as exposed, they remained so for the duration of their follow-up. Patients were classified as exposed to a specific class of antidepressants once they had a dispensing for that class. We ascertained exposure to selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs); all remaining antidepressants were classified into a single group.

Outcomes

Our primary outcome was colon cancer recurrence. It was defined as a clinical diagnosis of recurrence of the index colon cancer occurring more than 90 days after the patient completed their index colon cancer treatment. Treatment was considered completed on the final day of chemotherapy, radiation therapy, or the date of surgery, whichever occurred last. A clinical diagnosis of colon cancer recurrence was ascertained from the tumor registry and medical chart review (e.g. clinical notes, imaging and pathology reports) at Kaiser Permanente Colorado and medical chart review exclusively at Kaiser Permanente Washington.

Our secondary outcome included colon cancer recurrence (our primary outcome) plus second primary colorectal cancer. This allowed us to more broadly evaluate colon cancer risk associated with use of antidepressants after colon cancer diagnosis. Second primary colorectal cancer was ascertained from the tumor registries at both sites, supplemented with information from review of patients' medical charts by study abstractors.

To minimize missed outcomes, after we completed our data collection, we re-reviewed the medical charts of patients who died of colon cancer but did not have evidence of a recurrence or second primary colon cancer. We discovered that these patients often had a cancer of unknown type diagnosed shortly before death (for example, a lung lesion found on imaging that was never biopsied to determine the primary site). In a sensitivity analysis, we added these events to our definition of colon cancer recurrence.

Covariates

Patient demographics, including age, sex, and race were ascertained from the VDW, along with information on the index colon cancer, including year of diagnosis, stage and treatment. VDW treatment data were supplemented with information from medical chart review. The presence of various medical conditions in the year prior to the index colon cancer was ascertained from procedure and diagnosis codes and used to compute patients' Charlson comorbidity index.¹⁶ We also ascertained depression in the year prior to diagnosis and during follow-up using diagnosis codes. Height and weight at diagnosis was ascertained from the VDW and supplemented with information from medical chart review. Smoking history at and after diagnosis was ascertained from chart review. Aspirin use at and after diagnosis was ascertained from pharmacy data on dispensed medications and supplemented with information from medical chart review.

Statistical Analysis

We compared characteristics of patients who did and did not use antidepressants after their index colon cancer diagnosis. We also computed incidence rates of each outcome per 1,000 person-years and 95% CIs according to antidepressant use status. We used Cox proportional hazards models to estimate the adjusted HR and 95% CI for the association between use of antidepressants after colon cancer diagnosis and risk of each outcome. Use of antidepressants was ascertained beginning on the date of the index colon cancer diagnosis, whereas study follow-up began when the patient became at-risk of a recurrence, which was defined as 90 days after the end of primary treatment for their index colon cancer.¹⁷ For example, a patient who had a dispensing for an antidepressant a few days after colon cancer diagnosis began contributing person-time as an antidepressant user as of the start of follow-up for recurrence, i.e. 90 days after the end of treatment. Once a patient had a dispensing for an antidepressant in a particular class, they continued contributing person-time to that class for the remainder of follow-up.

For the analyses of colon cancer recurrence, patients were censored at the earliest of: a recurrence of non-colorectal cancer; a second primary cancer at any site; disenrollment from the health plan; death; or date of chart abstraction. For the analyses of our secondary outcome, which included second primary colorectal cancer as well as colon cancer recurrence, patients were censored at the earliest of: a recurrence of non-colorectal cancer; a second primary non-colorectal cancer; disenrollment from the health plan; death; or date of chart abstraction.

We estimated parsimoniously-adjusted and fully-adjusted HRs. Adjustment variables were categorized as shown in Table 1 unless otherwise noted. The parsimonious models controlled for age at index colon cancer diagnosis (natural cubic splines with knots at tertiles), year of diagnosis (natural cubic splines with knots at tertiles), stage at diagnosis, sex, and health plan. The fully-adjusted models additionally controlled for race (Black, non-Black, unknown), smoking history at diagnosis and afterward (time-varying: any prior smoking, no prior smoking), body mass index (BMI) at diagnosis, use of antidepressants in the year before diagnosis, Charlson comorbidity score in the year before diagnosis, depression in the year before diagnosis and afterward (time-varying: any prior diagnosis, no prior diagnosis), and use of aspirin at diagnosis and afterward (time-varying: any prior use, no prior use).

For each outcome, we also estimated HRs associated with any use of SSRIs and with any use of TCAs after colon cancer diagnosis. For these class-specific analyses, the comparison group was no use of the specific class of antidepressant, and we adjusted for use of the other classes of antidepressants (e.g. SSRIs or TCAs, and all other antidepressants as a single group). Thus, the model included variables for exposure to SSRIs, TCAs, and other antidepressants. Finally, we evaluated risks associated with exclusive use of SSRIs and exclusive use of TCAs. In these analyses, patients who used other classes of antidepressants after index colon cancer diagnosis but prior to the start of follow-up were excluded. The comparison group was no use of antidepressants, and patients were censored when they had a dispensing for another class of antidepressant.

We conducted a sensitivity analysis to assess whether our results varied if we required patients to have at least two prescriptions for an antidepressant before they could begin contributing person-time to the exposed group (instead of only one prescription). In this analysis we censored patients once they switched to a new type of antidepressant (i.e. SSRIs, TCAs or other).

We evaluated the proportional hazards assumption by including an interaction term between time and antidepressant exposure status, and by examining Schoenfeld residuals. The assumption was not violated in any models.

All statistical tests were 2-sided and a p-value <0.05 was considered statistically significant. Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

A total of 1,923 patients diagnosed with incident colon cancer met our eligibility criteria. Patients were followed for colon cancer recurrence for a median 4.7 years (interquartile range: 2.2–8.4 years; mean = 5.6 years). By the end of follow-up, 807 patients (42%) had one or more dispensings for an antidepressant after their diagnosis. SSRIs were used by 25% of patients, TCAs by 15%, and the remaining antidepressants by 24% (percentages are not mutually exclusive). These remaining antidepressants were trazodone (used by 14% of patients), mirtazapine (6%), bupropion (4%), venlafaxine (3%), duloxetine (<1%), and nefazodone (<1%).

Patients who used antidepressants after their index colon cancer diagnosis were more likely than those who did not to be female, white, obese, and diagnosed in earlier study years (Table 1). They were also more likely in the year prior to their colon cancer diagnosis to have a higher comorbidity score, depression diagnosis, antidepressant usage, and aspirin usage.

A total of 139 colon cancer patients had a colon cancer recurrence during 10,831 person-years of follow-up, a recurrence rate of 12.8 per 1,000 person-years (95% CI: 10.8–15.2). Risk of colon cancer recurrence was similar among patients who used antidepressants after their diagnosis compared to those who did not (HR: 1.14, 95% CI: 0.69–1.87, Table 2). Recurrence risk was also not associated with use of SSRIs (HR: 1.22, 95% CI: 0.64–2.30) or TCAs (HR: 1.18, 95% CI: 0.68–2.07) after diagnosis. Our findings were similar when we evaluated exclusive use of SSRIs and TCAs after diagnosis (Table 2).

In a secondary analysis, we included second primary colorectal cancers in our outcome definition (n=36), yielding a total of 175 events (Table 3). Our findings were similar to those from our primary analysis. The HR for any use of antidepressants after colon cancer diagnosis was 1.32 (95% CI: 0.86–2.02). Risk was also not associated with use of SSRIs or TCAs (Table 3).

In a sensitivity analysis, we expanded our definition of colon cancer recurrence to include patients who did not have documentation of a recurrence in their medical chart, but did have a diagnosis of an unknown cancer shortly before their death (n = 14), yielding a total of 153

events. Our findings were consistent with our primary analysis. The HR for any antidepressant use after diagnosis was 1.17 (95% CI: 0.74–1.88). The HRs associated with use of SSRIs and TCAs, whether exclusive or not, were also relatively unchanged (data not shown).

In another sensitivity analysis, we required patients have at least two prescriptions for an antidepressant before they could start contributing person-time to the exposed group. Again, our results were relatively unchanged from our primary analysis. The HR for any antidepressant use after diagnosis was 1.23 (95% CI: 0.72–2.12).

To minimize any influence of pre-diagnosis use of antidepressants on our risk estimates, we conducted an analysis restricted to patients who had not used antidepressants in the year before their colon cancer diagnosis (n=1,569 patients; n=113 recurrences). All HRs were again relatively unchanged from our primary analysis (data not shown), for example, the HR for any antidepressant use after diagnosis was 1.20 (95% CI: 0.68–2.11).

Conclusions

In this cohort study of colon cancer patients, risk of colon cancer recurrence was similar in patients who used antidepressants after diagnosis compared to those who did not (HR: 1.14, 95% CI: 0.69–1.87). Risk did not differ by use of SSRIs or TCAs after diagnosis. Our finding of no association between use of antidepressants after colon cancer diagnosis and risk of recurrence was consistent across the secondary and sensitivity analyses.

To our knowledge, this study is the first to evaluate risk of colon cancer recurrence in relation to use of antidepressants after diagnosis. Two prior studies examined related questions. Walker et al. found that colorectal cancer patients who used TCAs after diagnosis had a 37% increased hazard of all-cause mortality compared to colon cancer patients who did not use TCAs (HR: 1.37, 95% CI: 1.21–1.54).¹¹ However, the authors did not control for stage at diagnosis which is associated with an increased risk of death.¹² In a separate study, Weiss et al. evaluated the association between use of antidepressants or antihistamines and risk of recurrence in patients with breast cancer, colorectal cancer, or melanoma. The authors did not observe an association (OR: 0.97, 95% CI: 0.52–1.78), but these analyses were not limited to antidepressants as the exposure or colon cancer patients as the population.

Our study has several strengths. Cancer recurrence information is not routinely collected by US cancer registries;¹⁸ however, using data collected from a health system registry and patients' medical charts, we were able to ascertain this outcome in our population-based study. In addition, risk estimates were adjusted for several potentially important confounders including race, comorbidity at diagnosis, body mass index at diagnosis, stage at diagnosis, and smoking history. Further, use of antidepressants was ascertained from prospectively recorded pharmacy data on medication dispensings. Finally, all Kaiser Permanente Washington and Kaiser Permanente Colorado patients meeting eligibility criteria were included and therefore participation bias was not a concern.

Study Limitations

Limitations of our study include the possibility of residual confounding. Although we had detailed information on many study variables, some information, such as aspirin use, may have been underascertained in our data sources. Confounding by unmeasured factors is also a possibility as we did not have information on diet and exercise. However, the degree to which these factors may be related to recurrence of colon cancer is unclear.^{19,20} If recurrence risk factors were more common in antidepressant users, then our risk estimates would be falsely high (that is, the true HRs may be closer to the null or less than one). We also had limited power which resulted in a lack of precision to some degree in our HRs, especially those associated with individual classes of antidepressants.

Clinical Implications

Findings from our study of 1,923 colon cancer patients do not have direct clinical implications. However, our study has many strengths and therefore it is an important addition to the limited evidence to date on the relation between use of antidepressants after colon cancer diagnosis and risk of recurrence.

In conclusion, we did not observe an association between use of antidepressants after a colon cancer diagnosis and risk of recurrence. Our findings also suggest that risk does not vary according to use of SSRIs or TCAs. Given limited prior data on this question, and somewhat wide confidence intervals in the present study, additional studies that are larger and evaluate risk in relation to use of specific antidepressants would be valuable additions to the evidence base.

Acknowledgements

Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under Award Numbers R01CA172073 (Chubak) and R50CA211115 (Bowles). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The collection of cancer incidence data used in this study was supported by the Cancer Surveillance System of the Fred Hutchinson Cancer Research Center, which is funded by Contract No. N01-CN-67009 and N01-PC-35142 from the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute with additional support from the Fred Hutchinson Cancer Research Center and the State of Washington. Funders did not participate in the design, data collection, manuscript drafting, or decision to submit the manuscript for publication.

Conflict of interest statement:

Gaia Pocobelli reports receiving funding from a research grant awarded to Kaiser Permanente Washington Health Research Institute from Jazz Pharmaceuticals. Onchee Yu reports receiving funding from a research grant awarded to the Kaiser Permanente Washington Health Research Institute from Bayer. Monica Fujii reports receiving funding from research contracts awarded to Kaiser Permanente Washington Health Research Institute from Allergan, BioDelivery Sciences, Collegium, Daiichi Sankyo, Depomed, Egalet, Endo, Janssen, Mallinckrodt, Pernix, Pfizer, Purdue, and West-Ward. Denise Boudreau reports receiving funding from research contracts awarded to Kaiser Permanente Washington Health Research Institute from Allergan, BioDelivery Sciences, Collegium, Daiichi Sankyo, Depomed, Egalet, Endo, Janssen, Mallinckrodt, Pernix, Pfizer, Purdue, and West-Ward.

References

1. Caruso R, Nanni MG, Riba M, et al. Depressive spectrum disorders in cancer: prevalence, risk factors and screening for depression: a critical review. *Acta Oncol* 2017; 56(2): 146–55. [PubMed: 28140731]

2. Pirl WF. Evidence report on the occurrence, assessment, and treatment of depression in cancer patients. *J Natl Cancer Inst Monogr* 2004; (32): 32–9. [PubMed: 15263039]
3. Massie MJ. Prevalence of depression in patients with cancer. *J Natl Cancer Inst Monogr* 2004; (32): 57–71. [PubMed: 15263042]
4. Grassi L, Nanni MG, Rodin G, Li M, Caruso R. The use of antidepressants in oncology: a review and practical tips for oncologists. *Ann Oncol* 2018; 29(1): 101–11. [PubMed: 29272358]
5. Sanjida S, Janda M, Kissane D, et al. A systematic review and meta-analysis of prescribing practices of antidepressants in cancer patients. *Psychooncology* 2016; 25(9): 1002–16. [PubMed: 26775715]
6. Sternbach H Are antidepressants carcinogenic? A review of preclinical and clinical studies. *J Clin Psychiatry* 2003; 64(10): 1153–62. [PubMed: 14658962]
7. Tutton PJ, Barkla DH. Influence of inhibitors of serotonin uptake on intestinal epithelium and colorectal carcinomas. *British journal of cancer* 1982; 46(2): 260–5. [PubMed: 6983886]
8. Brandes LJ, Arron RJ, Bogdanovic RP, et al. Stimulation of malignant growth in rodents by antidepressant drugs at clinically relevant doses. *Cancer Res* 1992; 52(13): 3796–800. [PubMed: 1617649]
9. Lee HK, Eom CS, Kwon YM, Ahn JS, Kim S, Park SM. Meta-analysis: selective serotonin reuptake inhibitors and colon cancer. *Eur J Gastroenterol Hepatol* 2012; 24(10): 1153–7. [PubMed: 22735609]
10. Kiridly-Calderbank JF, Sturgeon SR, Kroenke CH, Reeves KW. Antidepressant Use and Risk of Colorectal Cancer in the Women's Health Initiative. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2018; 27(8): 892–8.
11. Walker AJ, Grainge M, Bates TE, Card TR. Survival of glioma and colorectal cancer patients using tricyclic antidepressants post-diagnosis. *Cancer causes & control : CCC* 2012; 23(12): 1959–64. [PubMed: 23065071]
12. SEER Cancer Stat Facts: Colorectal Cancer National Cancer Institute Bethesda, MD, <https://seer.cancer.gov/statfacts/html/colorect.html>.
13. Weiss SR, McFarland BH, Burkhart GA, Ho PT. Cancer recurrences and secondary primary cancers after use of antihistamines or antidepressants. *Clin Pharmacol Ther* 1998; 63(5): 594–9. [PubMed: 9630832]
14. Chubak J, Yu O, Ziebell RA, et al. Risk of colon cancer recurrence in relation to diabetes. *Cancer causes & control : CCC* 2018.
15. Ross TR, Ng D, Brown JS, et al. The HMO Research Network Virtual Data Warehouse: A Public Data Model to Support Collaboration. *EGEMS (Wash DC)* 2014; 2(1): 1049. [PubMed: 25848584]
16. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *Journal of clinical epidemiology* 1992; 45(6): 613–9. [PubMed: 1607900]
17. Chubak J, Bowles EJ, Yu O, Buist DS, Fujii M, Boudreau DM. Breast cancer recurrence in relation to antidepressant use. *Cancer causes & control : CCC* 2016; 27(1): 125–36. [PubMed: 26518198]
18. Warren JL, Yabroff KR. Challenges and opportunities in measuring cancer recurrence in the United States. *Journal of the National Cancer Institute* 2015; 107(8).
19. Meyerhardt JA, Mangu PB, Flynn PJ, et al. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2013; 31(35): 4465–70. [PubMed: 24220554]
20. van Zutphen M, Kampman E, Giovannucci EL, van Duijnhoven FJB Lifestyle after Colorectal Cancer Diagnosis in Relation to Survival and Recurrence: A Review of the Literature. *Curr Colorectal Cancer Rep* 2017; 13(5): 370–401. [PubMed: 29104517]

Figure. 1.

Identification of the study cohort of stage I–IIIA incident colon cancer adenocarcinoma cases at Kaiser Permanente Washington and Colorado, 1995–2014. AJCC = American Joint Committee on Cancer; EOT = end of treatment; KPCO = Kaiser Permanente Colorado; RECORD = Recurrence of Colon cancer in Relation to Drug use; VDW = Virtual Data Warehouse (electronic health data stored according to specifications established by the Health Care Systems Research Network)

Table 1.

Characteristics of colon cancer patients according to use of antidepressants after diagnosis.

Characteristic	All colon cancer patients N = 1,923		Use of antidepressants after colon cancer diagnosis			
			No N = 1,116		Yes N = 807	
	n	(%)	n	(%)	n	(%)
Study site						
Kaiser Permanente Washington	1,064	(55.3)	598	(53.6)	466	(57.7)
Kaiser Permanente Colorado	859	(44.7)	518	(46.4)	341	(42.3)
Year of colon cancer diagnosis (years)						
1995–1999	294	(15.3)	151	(13.5)	143	(17.7)
2000–2004	569	(29.6)	311	(27.9)	258	(32.0)
2005–2009	579	(30.1)	344	(30.8)	235	(29.1)
2010–2014	481	(25.0)	310	(27.8)	171	(21.2)
Age at colon cancer diagnosis (years)						
<50	88	(4.6)	52	(4.7)	36	(4.5)
50–59	282	(14.7)	183	(16.4)	99	(12.3)
60–69	488	(25.4)	312	(28.0)	176	(21.8)
70–79	631	(32.8)	343	(30.7)	288	(35.7)
80	434	(22.6)	226	(20.3)	208	(25.8)
Sex						
Female	1,008	(52.4)	500	(44.8)	508	(62.9)
Male	915	(47.6)	616	(55.2)	299	(37.1)
Race						
White	1,521	(79.1)	841	(75.4)	680	(84.3)
Black	68	(3.5)	49	(4.4)	19	(2.4)
Asian	65	(3.4)	49	(4.4)	16	(2.0)
American Indian/Alaska Native	9	(0.5)	3	(0.3)	6	(0.7)
Hawaiian/Pacific Islander	5	(0.3)	5	(0.4)	0	(0)
Multiple Race	19	(1.0)	8	(0.7)	11	(1.4)
Other/Unknown	236	(12.3)	161	(14.4)	75	(9.3)
Smoking before diagnosis [†]						
No	871	(45.4)	508	(45.6)	363	(45.1)
Yes	1,047	(54.6)	606	(54.4)	441	(54.9)
Unknown	5		2		3	
Body mass index at diagnosis (kg/m ²) [‡]						
<25.0	619	(33.6)	352	(32.8)	267	(34.6)
25.0–<30.0	665	(36.1)	421	(39.3)	244	(31.6)
30.0	560	(30.4)	299	(27.9)	261	(33.8)
Unknown	79		44		35	

Characteristic	All colon cancer patients N = 1,923		Use of antidepressants after colon cancer diagnosis			
			No N = 1,116		Yes N = 807	
	n	(%)	n	(%)	n	(%)
Comorbidity and medication use						
Charlson score in the year prior to diagnosis						
0	1,085	(56.4)	680	(60.9)	405	(50.2)
1	429	(22.3)	228	(20.4)	201	(24.9)
2	409	(21.3)	208	(18.6)	201	(24.9)
Depression in year prior to diagnosis	228	(11.9)	33	(3.0)	195	(24.2)
Antidepressant use in year prior to diagnosis	354	(18.4)	42	(3.8)	312	(38.7)
Aspirin use in year prior to diagnosis [†]	671	(35.5)	363	(33.2)	308	(38.7)
Characteristics and treatment of index colon cancer						
Stage at diagnosis						
I	860	(44.7)	503	(45.1)	357	(44.2)
IIA	884	(46)	512	(45.9)	372	(46.1)
IIB	109	(5.7)	67	(6.0)	42	(5.2)
IIIA	70	(3.6)	34	(3.0)	36	(4.5)
Chemotherapy	257	(13.4)	153	(13.7)	104	(12.9)
Radiation	28	(1.5)	18	(1.6)	10	(1.2)

[†]Patients with unknown values for smoking at diagnosis, body mass index, and aspirin use were excluded from the denominator of the percentages. A total of 32 patients were missing information on aspirin use (21 patients did not use antidepressants after diagnosis, and 11 did).

Table 2.

Incidence rates and hazard ratios for colon cancer recurrence in relation to use of antidepressants after colon cancer diagnosis.

	Follow-up time (person-years)	Number of events	Incidence per 1,000 person-years (95% CI)	Hazard ratio (95% confidence interval)	
				Parsimoniously adjusted [†]	Fully adjusted [‡]
Overall	10,831	139	12.8 (10.8–15.2)	N/A	N/A
Any use of antidepressants					
No	7,314	97	13.3 (10.8–16.2)	1.00 (Reference)	1.00 (Reference)
Yes	3,517	42	11.9 (8.6–16.1)	1.22 (0.84–1.76)	1.14 (0.69–1.87)
Exclusive use of SSRIs	1,003	14	14.0 (7.6–23.4)	1.31 (0.74–2.31)	1.22 (0.52–2.85)
Exclusive use of TCAs	724	9	12.4 (5.7–23.6)	1.35 (0.68–2.69)	1.13 (0.53–2.38)
Any use of SSRIs					
No	8,832	115	13.0 (10.7–15.6)	1.00 (Reference)	1.00 (Reference)
Yes	1,998	24	12.0 (7.7–17.9)	1.20 (0.75–1.92)	1.22 (0.64–2.30)
Any use of TCAs					
No	9,475	122	12.9 (10.7–15.4)	1.00 (Reference)	1.00 (Reference)
Yes	1,356	17	12.5 (7.3–20.1)	1.30 (0.77–2.19)	1.18 (0.68–2.07)

[†] Adjusted for age at index colon cancer diagnosis, year of diagnosis, stage at diagnosis, sex, and health plan.

[‡] Adjusted for age at index colon cancer diagnosis, year of diagnosis, stage at diagnosis, sex, health plan, race, smoking history at diagnosis and afterward (time-varying), body mass index at diagnosis, use of antidepressants in the year before diagnosis, Charlson comorbidity score in the year before diagnosis, depression in the year before diagnosis and afterward (time-varying), and use of aspirin at diagnosis and afterward (time-varying).

Table 3.

Incidence rates and hazard ratios for colon cancer recurrence or second primary colorectal cancer in relation to use of antidepressants after colon cancer diagnosis.

	Follow-up time (person-years)	Number of events	Incidence per 1,000 person-years (95% CI)	Hazard ratio (95% confidence interval)	
				Parsimoniously adjusted [†]	Fully adjusted [‡]
Overall	10,831	175	16.2 (13.9–18.7)	N/A	N/A
Any use of antidepressants					
No	7,314	115	15.7 (13.0–18.9)	1.00 (Reference)	1.00 (Reference)
Yes	3,517	60	17.1 (13.0–22.0)	1.39 (1.01–1.92)	1.32 (0.86–2.02)
Exclusive use of SSRIs	1,003	19	18.9 (11.4–29.6)	1.42 (0.87–2.34)	1.20 (0.57–2.51)
Exclusive use of TCAs	724	13	18.0 (9.6–30.7)	1.56 (0.87–2.79)	1.30 (0.69–2.45)
Any use of SSRIs					
No	8,832	141	16.0 (13.4–18.8)	1.00 (Reference)	1.00 (Reference)
Yes	1,998	34	17.0 (11.8–23.8)	1.25 (0.83–1.87)	1.16 (0.68–1.99)
Any use of TCAs					
No	9,475	152	16.0 (13.6–18.8)	1.00 (Reference)	1.00 (Reference)
Yes	1,356	23	17.0 (10.8–25.5)	1.28 (0.81–2.02)	1.24 (0.77–2.00)

[†] Adjusted for age at index colon cancer diagnosis, year of diagnosis, stage at diagnosis, sex, and health plan.

[‡] Adjusted for age at index colon cancer diagnosis, year of diagnosis, stage at diagnosis, sex, health plan, race, smoking history at diagnosis and afterward (time-varying), body mass index at diagnosis, use of antidepressants in the year before diagnosis, Charlson comorbidity score in the year before diagnosis, depression in the year before diagnosis and afterward (time-varying), and use of aspirin at diagnosis and afterward (time-varying).