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Antidepressant Use and Risk of Colorectal Cancer in The Women's Health Initative

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ANTIDEPRESSANT USE AND RISK OF COLORECTAL CANCER IN THE WOMEN'S HEALTH INITIATIVE

A Thesis Presented

by

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Love is not only something you feel it's something you do

So I guess you can say you've done a thing or two

And I know I'm not great at rhyming

But there really is no better timing

To thank you for cooking my meals

And driving your wheels

No matter how far

And how many miles you put on your car

Thanks for lending an ear

And always being such a dear

For making me smile

And reminding me to rest every once in while

But mostly thanks for showing me how much you care

And reminding me not to pull out my hair

Without you this all would have been for not

Thanks for always being my rock

-xoxo always and forever

ABSTRACT

ANTIDEPRESSANT USE AND RISK OF COLORECTAL CANCER IN THE WOMEN'S HEALTH INITIATIVE

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Colorectal cancer is the third most common cancer among U.S. women; 63,610 new cases were estimated to have occurred in 2015. Prior studies found a reduced risk of colorectal cancer among antidepressant (AD) users, however, none adjusted for depression, which is itself linked to increased colorectal cancer risk and could confound this relationship. We assessed associations between ADs and AD drug classes with the risk of colorectal cancer in a prospective cohort of 145,190 women ages 50-79 without a previous history of cancer at enrollment. Current AD use was assessed at baseline. Over an average follow-up of 14 years, 5,280 cases of colorectal cancer cases were diagnosed and 6.9% of women were AD users. Cox proportional hazard ratios, adjusted for colorectal cancer risk factors including depressive symptoms, were used to model the associations. Of all AD users, 51.1% used selective serotonin reuptake inhibitors (SSRIs), 40.7% used tricyclic antidepressants (TCAs), and 15.1% used other ADs. No association was seen between total AD use, SSRI use, and/or other ADs and risk of colorectal cancer. We observed a reduced risk of colorectal cancer among TCA users, which was significant for colon cancer specifically (HR 0.68, 95% CI: 0.48-0.96). Although a reduced risk of colon cancer was observed for individuals who used TCAs for less than two years (HR

0.42, 95% CI: 0.22-0.81), no association was observed for individuals who used for two or more years (HR 0.97, 95%CI: 0.69-1.37). Our data suggests a protective association between TCA use and risk of colorectal cancer, however more research is needed to verify these findings. These results show no negative effects of AD in relation to colorectal cancer.

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CHAPTER 1

INTRODUCTION

Colorectal cancer is the third most common cancer among U.S women, 63,610 new cases were estimated to have occurred in 2015.[1] Older women, ages 50-70, have a considerably higher risk of developing colorectal cancer as compared to younger women.[1] Antidepressant (AD) use is also common among older women, with 23% of women ages 40-59 and 18.6% of women ages 60 and over taking ADs according to the National Health and Nutrition Examination Survey (2008).[2] Among those treated with ADs, selective serotonin reuptake inhibitors (SSRIs) are the most common, whereas tricyclic antidepressants (TCAs) and other antidepressants have become less common, since 1995.[3] Roughly 78% of ADs are prescribed for depression, however other uses of ADs include mood disorders, anxiety, and chronic pain.[4, 5] Compared to healthy individuals, women with depression have high levels of inflammatory markers, which may lead to a 40% increased risk of colorectal cancer.[6,7] Furthermore, women with depression are more likely to have risk factors of colorectal cancer such as higher body mass index (BMI), poor diet (i.e. high fat, low fiber diets), smoking, drinking, and physical inactivity.[6, 7] This is important as depression is highly related to AD use and studies suggest that depression may lead to inflammatory and behavioral risk factors for colorectal cancer; thus, to determine the true effects of AD use on risk of colorectal cancer we must consider the effects of depression.

Whether AD use influences colorectal cancer remains unclear. Several studies have reported decreased risk of colorectal cancer among regular AD users compared to non-users.[8-12] When SSRIs and TCAs were examined separately, three out of five studies observed strong inverse associations between SSRIs and risk of colorectal cancer.[8,9,12] A significant reduction in risk of colorectal cancer was observed among SSRI users taking a high cumulative dose (>0.01

mol) within the five years before diagnosis (OR 0.69, 95% CI: 0.50-0.96)[12] and among regular users of SSRIs (taking SSRIs consecutively for three months) (OR 0.55, 95% CI: 0.35-0.88) when compared with non-users.[9] Another study observed a non-statistically significant reduced risk among SSRI users, specifically among those using SSRIs for less than 2 years.[8] Conversely, two studies found no association between SSRIs and risk of colorectal cancer when considering different intensities and durations of use.[10,11]

Studies which examined the effects of TCA use on risk of colorectal cancer were similarly unclear. A non-significant reduction of colorectal cancer was observed among regular TCA users (OR 0.77, 95% CI: 0.52-1.16), [9] regardless of duration of use.[8, 9] Conversely, a record linkage study that looked at non-SSRI use, much of which is likely TCAs, found a non-significant increased risk of colon cancer within the highest category (1460 mg average maintenance dose per day) as compared to users within the lowest category (RR 2.19, 95% CI: 0.85-5.66 and RR 2.03, 95% CI: 0.83-4.96 respectively).[11] Furthermore, a separate case-control study found no association between TCAs and colorectal cancer when considering various intensities and duration of use.[10]

Laboratory studies support a possible protective effect of SSRIs on colorectal cancer. Elevated levels of serotonin have been hypothesized to play a role in colorectal cancer, promoting cell division of adenocarcinomas of the large intestine. SSRIs act as an antagonist, inhibiting the reuptake of serotonin, reducing the mitotic rate of tumor cells within the colon.[12, 13] Laboratory studies examining the effects of TCAs on colorectal cancer have been less clear, as *in vitro* studies of the effects of TCAs on human carcinoma cell lines have shown evidence to support both an increase and decrease in the risk of colorectal cancer.[8]

Prior epidemiologic studies of colorectal cancer have not considered depression and AD use together, despite the high concordance between these exposures. As mentioned previously, 78% of AD users take ADs for depression. Additionally, depression may lead to the increased appearance of behavioral and inflammatory risk factors for colorectal cancer, confounding the relationship between AD use and risk of colorectal cancer.[7, 14- 17] Additionally, prior studies have relied on either prescription records or self-report to assess AD use.[8-12] While prescription records provide information on dosage and duration, they might not reflect compliance and actual use. Within the Women's Health Initiative (WHI) information on current medication use was assessed at baseline via an in-person interview to which participants brought their current pill bottle, aiding in verification of AD exposure. Information on duration of use was also available through self-report. Additionally, the WHI has extensive information available on potential confounders including depressive symptoms. Therefore, we examined the influence of AD use on risk of colorectal cancer in the WHI cohort. We hypothesized that AD use, particularly SSRI use, would be associated with a reduced risk of colorectal cancer.

CHAPTER 2

METHODS

2.1 Study Population

The WHI began with the enrollment of 161,808 postmenopausal women aged 50-79 between 1993 and 1998. Briefly, recruitment of participants took place at 40 clinical centers in 24 states, including the District of Columbia and nationally at the National Institute of Health's Clinical Coordination Center.[18]

The WHI is divided into two study arms, a randomized clinical trial (CT) and an observational study (OS). Women could not participate in both the observational and clinical trial arm. The randomized clinical trial (N=68,132)[18] focused on prevention strategies and consisted of three components: 1) hormone therapy trials, 2) a dietary modification trial, and 3) a calcium and vitamin D trial. Women eligible for the clinical trial arm were randomized into one, two, or all three components. Women who were not eligible[18] for the clinical trial were invited to join the observational study. The observational study (N=93,676)[18] examined the relationship between lifestyles, health and risk factors, and specific disease outcomes. The medical history and health habits of the women in this arm were followed through 2005.

Eligibility criteria that was the same for both arms of the WHI was defined as being between the ages of 50-79, postmenopausal, and planning to reside within the study area for at least three years after enrollment. If participants had a pre-existing medical condition that was predictive of a survival time less than three years, a condition that could interfere with consistency or adherence, or if they were currently participating in another randomized control trial they were excluded from both the CT and OS.[18] Exclusion criteria for this analysis included missing information on AD use (n=2), and/or missing information on follow-up time (n=691).

No participants had missing information on diagnosis of colorectal, colon, or rectal cancers. Further, participants were excluded from our analysis if they had a previous history of any cancer (n=15,925), with the exception of those with non-melanoma skin cancer. Primary analysis consisted of 145,190 women with an average length of follow up time of 14.3 years.

2.2 Exposure Assessment - Antidepressant use

AD use was assessed at baseline. Women were asked to bring in all current prescription medications to in-person interviews. Information on AD medication name and duration of use was documented[19] by clinical interviewers into a database, using Medi-Span software (First Databank inc., San Bruno, CA), which assigned Therapeutic Class Codes (TCCODE) to medications used regularly (for at least two weeks). Duration of use was self-reported.[20] For our analysis, women were categorized as AD users or non-AD users at baseline. Additionally, we considered AD use by drug class (SSRIs, TCAs, and other ADs) and evaluated the impact of duration of AD use (e.g., use for up to two years, or use for greater than two years). Duration was dichotomized by median years of use for ADs. For comparison purposes median cuts for ADs were applied across all AD subgroups (SSRI, TCA, and other AD).[8-10]

2.3 Outcome Assessment- Colorectal cancer

Our outcome was the occurrence of colorectal, colon, rectal, and/or recto-sigmoid cancer through follow-up (2005). Details of outcome assessment, including adjudication procedures in the WHI, have been described elsewhere.[21] In short, colorectal, colon, rectal and recto- sigmoid cancers were self-reported on a semiannual basis for CT participants and annually for OS participants through 2005. Medical records were collected for physician adjudication according to standardized criteria. Primary colorectal cancer diagnosis was confirmed through review of pathology reports, and additional information by trained coders at the WHI clinical coordinating

center. Tumor registry coders determined grade and stage of the tumor and assigned appropriate codes. Only colorectal, colon, rectal, recto sigmoid cases confirmed by adjudication were included in these analyses. Rectal cancer cases consisted of both rectal and recto-sigmoid cancers.[22-23]

2.4 Covariate Assessment

Covariates were selected based on inclusion in prior literature and known risk factors for colorectal cancer and AD use (Table 1).[8-12] Age, race and ethnic subgroup (White (not Hispanic, Asian Pacific Islander, Black, Hispanic/ Latino), smoking status (never, <5 pack-years, 5-20 pack-years, >20 pack-years, don't know duration of smoking), diabetes, diverticulitis, hypertension, primary care provider, hormone replacement therapy (HRT) use (never, past estrogen-alone, past estrogen and progesterone, current estrogen, current estrogen and progesterone), involvement in hormone therapy study arm of WHI, physical activity (MET-hours/week (quartiles)), family history of colorectal cancer, early screening for colorectal cancer, and polyp removal were obtained through self-administered forms at baseline. Drinking habits were abstracted from a food frequency questionnaire and categorized as (none, past <1 drink per month, <1 drink per week, 1-7 drinks per week, 7+ drinks per week). Current use or non-use of non-steroidal- anti-inflammatory drugs (NSAIDs) was collected during an in-person interview at a baseline and recorded in a database. For this analysis, duration of NSAID use was categorized as <1 year, 1-3 years, 3-8 years, and 8-20 years. BMI was calculated from height and weight measurements during a screening visit (Underweight (<18.5 kg/m^2), Normal (18.5-24.9 kg/m^2), Overweight (24.9-<30 kg/m^2), Obese I (30-34.9 kg/m^2), Obese II (35.0-39.9 kg/m^2), Extreme Obese (40kg/m^2)). The healthy eating index score (HEI2005 (quartiles)) was used as a measure of diet quality and was calculated via food frequency questionnaires.

Information on depressive symptoms was self-reported at baseline using the Burnam eight item scale, [24] which contained six items from the Center for Epidemiologic Studies Depression Scale (CES-D) and two items from the National Institute of Mental Health's Diagnostic Interview Schedule. The six items from the CES-D assessed the frequency of depressive symptoms within the last week, while the two items from the National Institute of Mental Health assessed depressive symptoms within the last year or two.[25] Consistent with prior studies in the WHI, [26, 27] the Burnam score was categorized into two groups (< 0.06 and ≥ 0.06), to classify women as experiencing depressive symptoms consistent with women with clinical depression. The Burnam scale was found to have 74% sensitivity and 87% specificity when compared to clinical diagnosis of depression.[25]

2.5 Statistical Analysis

Participants were categorized by AD use (AD user, non-AD user) at baseline to examine the distribution of covariates between participants (Table 1). Additionally we examined the distribution of AD drug class (Table 2) and colorectal cancers (Table 3) by AD use. To examine the distribution of drug class, covariates, and colorectal cancers by AD use, we used chi square tests and t-tests as appropriate.

We used multivariable Cox proportional hazards regression to estimate hazard ratios (HR) and 95% confidence intervals (CI) of the association between AD use and time to colorectal cancer diagnosis while adjusting for potential confounders. In these analyses, women were followed from enrollment through 2005, contributing person-time to the analysis until diagnosis of colorectal, colon, or rectal cancers, death, loss-to follow-up, or the end of the study/ administrative censor date defined as the participants last available date, whichever happened first. We separately examined the relationship between AD use and the risks of colon cancer and

rectal cancer, and evaluated the associations between subgroups of ADs most commonly used in this cohort (SSRIs, TCAs, and other ADs) and colorectal cancer. We additionally examined the effects of duration of AD use, including duration of SSRIs, TCAs, and other ADs.

To further evaluate the effects of depression on the relationship of AD use and risk of colorectal cancer, we examined the joint distribution of AD use and depression within our multivariable model, estimating HR and 95% confidence intervals. Our primary variable for the model was broken into those with no depressive symptoms and no AD use, no depressive symptoms and AD use, depressive symptoms and no AD use, and depressive symptoms and AD use. Additionally, we conducted a stratified analysis to evaluate whether the relationship of AD use and risk of colorectal cancer varied by strata of depression (depressive symptoms vs no depressive symptoms). To test the overall significance of the interaction, we included an interaction term in our multivariable model and used the likelihood ratio test to compare the full and reduced models.

Variables were selected for our preliminary model based on univariate analyses and prior literature; [8-12] variables with a log rank ratio test p-value ≤ 0.25 were included in our initial multivariable model. In our final model, likelihood ratio tests were completed for all remaining variables; selected covariates were chosen based on p-values ($p \leq 0.05$). Our final model was adjusted for age, smoking status, diabetes, HRT use, physical activity (MET-hours/week (quartiles)), family history of colorectal cancer, early screening for colorectal cancer, polyp removal, NSAID use, HRT study arm, depression, and BMI, as described above. Due to the fact that BMI [28], age [28], and HRT arm [29] are known to have associations with colorectal cancer, they remained in the model regardless of p-value. To further examine the independent relationships

of age, BMI and depression, we created three separate models; age adjusted, age and BMI adjusted, and age, BMI, and depression adjusted.

Two sided p-values ($p \leq 0.05$) were considered statistically significant. This analysis was performed with STATA version 14.0 (Stata Corporation, College Station, TX).

CHAPTER 3

RESULTS

After all exclusions, 145,190 participants of the Women's Health Initiative were included in our analyses, of which 135,154 (93.1%) women were non-users of antidepressant (AD) at baseline while 10,036 (6.9%) women were current AD users at baseline.

Distribution of baseline covariates by AD use are presented in Table 1. At baseline, 29.2% of women who were current AD users and 9.4% of non-users were experiencing depressive symptoms. Overall, current AD users tended to be younger at enrollment, obese, be current smokers, have a poor diet, and be physically inactive as compared to non-users. Also, a greater percentage of AD users self-reported health complications such as diabetes (8.5% vs. 5.6%), diverticulitis (11.8% vs. 7.9%), and hypertension (40.3% vs. 32.7%). Women who were current AD users were more likely to have a health care provider who they had visited within the last year as compared to non-users (91.5% vs 80.8%). Furthermore, AD users were more likely to have had a recent colonoscopy within the last five years (41.1% vs 31.0%) and, among those who had a colonoscopy, to have had a polyp removed (18.8% vs 16.7%). Concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) or postmenopausal hormonal therapy was higher among AD users versus non-users.

Among AD users, the most common treatment was SSRIs (51.1%), followed by TCAs (40.7%), and other antidepressants (15.1%) (Table 2). Additionally, some women reported use of more than one AD, with 303 taking TCAs and SSRIs, 312 taking SSRIs and some other AD, 81 taking TCAs and some other AD, and 7 women taking all three (data not shown).

During the study follow-up period, 2,580 women were diagnosed with colorectal cancer (Table 3) including 2,150 cases of colon cancer, 149 cases of recto-sigmoid cancer, and 341 cases of rectal cancer; 60 women had more than one type of colorectal cancer (data not shown).

Results from age adjusted and multivariable adjusted Cox proportional hazard regression models are presented in Table 4. In our multivariable-adjusted model, we observed a borderline significant reduced colorectal cancer risk associated with TCA use (HR 0.76, 95% CI: 0.56-1.03), although no association was observed with total AD use (HR 0.90, 95% CI: 0.75-1.09), SSRI use (HR 1.08, 95% CI: 0.85-1.36), or use of other ADs (HR 0.63, 95% CI: 0.53-1.11). The decreased risk associated with TCA use was observed among women using the drug for less than two years (HR 0.42, 95% CI: 0.22-0.81) but not among those using the drug for longer duration (HR 0.97, 95% CI: 0.69-1.37).

Similarly, TCA use was associated with a decreased risk of colon cancer (HR 0.68, 95% CI: 0.48-0.96; Table 5), with the strongest effect seen among short-term users (HR 0.39, 95% CI: 0.19-0.82). Total AD use (HR 0.91, 95% CI 0.74-1.12), SSRI use (HR 1.17, 95% CI 0.91-1.5), and other AD use (HR 0.56, 95% CI: 0.29-1.08) were not associated with risk of colon cancer. No significant association was observed between AD use with risk of rectal cancer (Table 6).

We also explored how AD use affected colorectal cancer risk among women with and without depressive symptoms (Table 7). There was no statistically significant interaction between AD use and depressive symptoms on risk of colorectal cancer (p=0.92) (data not shown). However, in a model with a joint definition of AD use and depression, we did observe a suggestive increased colorectal cancer risk among women experiencing depressive symptoms without AD use (HR 1.21, 95% CI: 1.05-1.4) compared to women with neither depressive symptoms nor AD use.

CHAPTER 4

DISCUSSION

In this prospective study of postmenopausal women, we observed a statistically significant 32% reduced risk of colon cancer among TCA users, though this effect was limited to those using TCAs for less than two years. A similar decreased risk of rectal cancer was observed among TCA users using for less than two years, however results were limited by small numbers and were not significant. Overall, we found no compelling evidence of an association between total AD use, SSRIs, or other ADs on the risk of colorectal, colon, or rectal cancers specifically.

Prior evidence of the relationship between TCAs and colorectal cancer is contradictory. Some epidemiological studies of TCA use found non-significant reductions of colorectal cancer, [8, 9] while others observed no association.[10, 12] A case-control study which enrolled 649 cases from an integrated healthcare delivery system (N=1,305), observed a reduced risk of colorectal cancer among TCA users (OR 0.7, 95% CI: 0.5-1.1), and those using the drug for less than two years (OR 0.6 95% CI: 0.3-1.0).[8] Additionally, in another case control study, a non-significant reduced risk of colon cancer among TCA users (OR 0.81, 95% CI: 0.51-1.29) was observed (N=10,011).[9] Conversely, two studies found no association between TCA use and risk of colorectal cancer.[10, 12] Differences between our analysis and previous studies may be due to their smaller sample size, which limited their ability to detect an association between TCA use and risk of colorectal cancer.[8, 9] Additionally, we were able to control for important potential confounders, (i.e. depression, colonoscopy history, and polyp removal) which may have enhanced our ability to see a true effect. Limited control of confounding factors, particularly depression, may have reduced the ability of previous studies to observe the independent effect of TCA use on colorectal cancer risk.[8-12] Further, our observation of an inverse association between

colorectal cancer and TCA use was restricted to current users, and was not observed among longer term users, which raises some concern about whether the association is real. Prior studies measured AD use through pharmacy records or databases.[8-12] In the WHI, however, women were asked to bring in current medications to their clinical visit, and self- report duration of use. While this has the advantage of capturing current use, it may not reliably capture past use or adherence. Pharmacy records are similarly limited in this fashion as participants could have filled prescriptions and not taken prescribed ADs, or they could have been taking them inconsistently. This misclassification of use could have led in part to the null results observed by previous studies[10, 12] and the null findings of studies which looked at use for greater than 2-3 years.[8, 9] Additionally, misclassification of use could have attenuated our ability to detect a true association between AD use and risk of colorectal cancer, particularly when considering duration of use greater than two years, and may in part account for our null findings in this group.

In contrast to our null association between SSRI use and colorectal cancer, some previous studies observed a reduced risk of colorectal cancer among SSRI users.[8, 9, 12] One case-control study reported that regular users of SSRIs had a significant decrease in risk of colorectal cancer (OR 0.55, 95% CI: 0.35-0.88) and colon cancer (OR 0.47, 95% CI: 0.26-0.85) when compared with non-users.[9] Similar results were seen among SSRI users taking a high cumulative dose (>0.01 mol) within the five years before diagnosis (OR 0.69, 95% CI: 0.50-0.96).[12] Another study found a similar reduced risk (OR 0.7 05% CI 0.4-1.1) of colorectal cancer among SSRI users, however results were not significant.[8] Differences in the results of this current analysis as compared to previous work may be due to the timing and study design. Previous studies,[8-12] collected information retrospectively from pharmacy databases on SSRI use within the 10-20 years before colorectal cancer diagnosis, occurring in 2000[12], 2003[8], and or 2008.[9,10] In contrast,

our study design assessed AD use once, at baseline, and followed women forward until development of colorectal cancer, death, or end of the study period. As use of SSRIs as treatment for depression became more prevalent after 1995, many SSRI users may have been new users at baseline exposure assessment, in 1993. Recency of SSRI exposure may have limited our ability to detect an effect of SSRIs on risk of colorectal cancer within our study population, as a majority of SSRI users had been using SSRIs for less than two years (n=2,886). Further, current medications that were brought in and recorded were required to have been taken for a minimum of two weeks in order to be considered in our analysis. Although this may capture current use it does not capture consistency of use within the two week period, discontinued use soon after baseline assessment, or information on recency of use; our limited ability to verify use may have led in part to our null results. Previous studies which observed a null association may have been similarly limited by their ability to reliably capture past use, as participants could have been filling prescriptions and not taking prescribed ADs, or taking them inconsistently, [10, 11] possibly contributing to their null results. As both previous studies and our current analysis were limited by misclassification of use more information is needed to verify our results and explore the true effects of SSRIs.

An important limitation of previous studies is that none have controlled for the effects of depression in the relationship between AD use and colorectal cancer.[8-12] As mentioned earlier about 78% of AD users are prescribed ADs for depression.[5] Compared to healthy individuals, those with depression have higher levels of inflammatory markers, such as C-reactive protein, pro-inflammatory cytokines, and raised serum levels of interleukin-6 (IL6), interleukin-1 beta (IL1b), and tumor necrosis factor alpha (TNFa) potentially increasing risk of cancer.[6,7] Prior studies support a relationship between depression and increased risk of overall cancer.[14-17] Those

that looked at colorectal cancer observed an increased risk of colorectal cancer.[7,15-17] A significant 40% increased risk of colorectal cancer was observed among those with depressive symptoms.[7] Although this study did not control for AD use, its prospective design and large sample size give strength to the possibility that depression itself may be risk factor for colorectal cancer. Further, as depression is highly correlated to AD use and studies have shown depression may be associated with the development of colorectal cancer, if we did not control for depression it might appear that ADs increase risk of colorectal cancer or attenuate our ability to observe a relationship. Conversely, in our analysis models that controlled for age and BMI versus models that controlled for age, BMI, and depressive symptoms saw little change in the magnitude of effect of AD use on risk of colorectal cancer. Our ability to fully control for the effects of depression may be limited as we could only control for the effects of depressive symptoms, which, although our method of detection had a high sensitivity and specificity differ from the gold standard, a clinical diagnosis. This may have led to some residual confounding within our observed results.

To determine the independent effects of depression and AD use on risk of colorectal cancer. To our knowledge, this is the first study to examine the separate and combined relationship between depressive symptoms and AD use and colorectal cancer risk. We observed an increased colorectal cancer risk among women experiencing depressive symptoms without AD use (HR 1.21, 95% CI: 1.05-1.4) compared to women with neither depressive symptoms nor AD use. This is important as it corroborates that women with depression may have an increased risk of colorectal cancer particularly among those not using AD medications.

The biological mechanism through which TCA may act is unclear. *In vitro* studies of the effects of TCAs on human carcinoma cell lines have shown evidence to support both an increase

and decrease in the risk of colorectal cancer.[12] TCAs were examined in an *in vitro* model of Human HT29 colon adenocarcinoma cells using three TCA drugs, imipramine, desipramine, and amitriptyline.[30] All three of these TCA drugs exhibited cytotoxic effects acting through a non-mitchondrial pathway associated with cell cycle progression, suggesting this effect is specific to malignant colorectal tumors.[30] In order for this to occur it is necessary for the drug to reach cytotoxic levels within the cell, ~10μm. It still remains to be seen if oral use of TCA drugs can achieve cytotoxic levels in colorectal colon and rectal tissues; [30] however, our results of a possible protective association may indicate that cytotoxic levels can be reached in human subjects. Conversely, in rat models of colorectal cancer using the TCA, desipramine, serum levels of norepinephrine increased the proliferation of colon epithelial cells, indicating a carcinogenic effect.[31] These results show that TCA composition and type may matter in terms of the carcinogenic or cytotoxic effect.[12] As information on TCA composition, type, and genotoxicity was unavailable, our study is limited in its capability to determine the protective effects of specific TCA drugs, but is indicative of a possible cytotoxic mechanism of overall TCA use. Although our results show no association between SSRI use and risk of colorectal cancer, laboratory studies support protective effects of SSRIs on colorectal cancer. One such study observed reduced tumor cell growth after administering SSRIs to mice xenografted with human colorectal carcinomas compared to controls, indicating possible cytotoxic effect of SSRIs.[8] In human colorectal cancer cell line a similar effect was observed when treated with SSRIs.[8] Serotonin levels have been hypothesized to play a role in colon cancer, as serotonin levels promote cell division of adenocarcinomas of the large intestine. SSRIs inhibit the uptake of serotonin, reducing the mitotic rate of tumor cells within the colon.[12, 13]

Limitations of this study primarily relate to our measurement of AD use and depressive symptoms and our power. Null results observed with SSRI use and risk of colorectal cancer may relate to the fact that SSRI drugs were new to the market at the time of WHI baseline. In general, TCA use to treat depression was greater prior to 1995 and SSRI use for treatment of depression was greater after 1995. As our analysis only assessed AD use at baseline we lack the ability to see if a recency of SSRI use may have led to our null results. Additionally, we had small numbers to detect an association between duration of use and risk of colorectal cancer for TCAs and other ADs. Further we had small numbers of AD users who developed rectal cancer which limited our ability to detect an effect of AD use on risk of rectal cancer. To ascertain current medication use, women in the WHI brought in pill bottles of current medications and supplements. This is advantageous as it is an accurate way to measure current use; however, if women failed to bring in their pill bottles we may have some misclassification and numbers may be underestimated. Furthermore, this method lacks the ability to capture specific information on chemical make-up, past use, dose, and intensity. Although names of the specific ADs were available and may give some information on aspects of chemical make-up, this information was not used for this analysis, and as such we were unable to account for any effects. Additionally, duration of use was based on self-report, and as such are subject to some recall error, and does not reliably capture past use or adherence. Therefore, our results for duration of use should be interpreted with caution. Depressive symptoms were measured according to a self-administered questionnaire from which a CES-D score was calculated. Although this method has high levels of sensitivity and specificity, it differs from the gold standard of a clinical diagnosis. Thus, the inability to accurately control for depression lead to residual confounding which may have attenuated the true relationship between AD use and risk of colorectal cancer.

Strengths of our study include its prospective design, large sample size, and comprehensive data on potential confounders. Data for this study contained extensive information on depressive symptoms, history of a previous colonoscopy, diet, and BMI, which had not been previously controlled for, this limited potential confounding within our study. Further, as mentioned previously, the methods use in this study showed increased accuracy of actual, current AD use.

CHAPTER 5

CONCLUSION

In summary, our results support a slightly suggestive inverse association between TCA use and risk of colorectal cancer. These findings contribute to a better understanding of the safety of AD use and provide some reassurance, as they suggest that AD use does not increase risk of colorectal cancer. Given the high prevalence of depression and AD use, future work is needed to understand and verify these associations, and to explore the effects of SSRIs with more recent data is warranted.

Table 1. Distribution of Covariates According to AD use; Women's Health Initiative.

Characteristic	No Antidepressant Use N= 135,154	Antidepressant User N=10,036
Age; Mean (SD)	63.14(7.2)	62.01(7.2)
Race & Ethnic Sub-population; (%)		
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)
Body Mass Index (BMI), kg/m^2 (%)		
Underweight (<18.5)	1,155(0.9)	75(0.8)
Normal (18.5-<24.9)	46,425(34.6)	2,771(27.9)
Overweight (>=24.9-<30)	46,658(34.8)	3,414(34.3)
Obese I (30-34.9)	24,712(18.4)	2,025(20.4)
Obese II (35.0-39.9)	9,925(7.4)	1,037(10.4)
Extreme Obesity (>=40)	5,129(3.8)	621(6.3)
Healthy Eating Index Score (%)		
Less than 60.05	33,666(25.0)	2,762(27.6)
60.05-68.63	33,868(25.1)	2,493(24.9)
68.634-75.66	33,759(25.0)	2,468(24.6)
75.66 or Greater	33,609(24.9)	2,296(22.9)
Physical Activity MET (hours/week) (%)		
<2.25(hours/ week)	31,853(24.8)	3,143(32.7)
2.3-8.3(hours/week)	32,220(25.1)	2,465(25.6)
8.375-17.75(hours/week)	31,905(24.9)	2,168(22.6)
Greater Than 17.83(hours/week)	32,422(25.3)	1,838(19.1)
Alcohol (%)		
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 per Week	27,638(20.6)	2,004(20.1)
1 to <7 Drinks per Week	34,965(26.1)	2,158(21.7)
Greater than 7 Drinks per Week	15,821(11.8)	939(9.4)
Smoking (Pack-years) (%)		
Never	69,069(51.8)	4,477(45.3)
<5 Pack-years	18,872(14.1)	1,406(14.2)
5-20 Pack-years	18,766(14.1)	1,396(13.8)
Greater than 20 Pack-years	23,628(17.7)	2,418(24.4)
Don't Know Duration of Smoking	3,087(2.3)	222(2.2)

Table 1. (cont'd) Distribution of Covariates According to AD use; Women's Health Initiative.

Characteristic	No Antidepressant Use N= 135,154	Antidepressant User N=10,036
Has a Primary Care Provider (%)	124,894(93.3)	9,739(97.8)
Has Had a Medical Visit (within 1 year) (%)	105,461(80.8)	8,958(91.5)
History of Diabetes (%)	7,515(5.6)	854(8.5)
History of Diverticulitis (%)	9,982(7.9)	1,119(11.8)
History of Hypertension (%)	44,181(32.7)	4,047(40.3)
Colonoscopy (colonoscopy, sigmoidoscopy or flex sig) (%)		
No	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)
Has had Polyps of Colon Removed (%)	10,623(16.7)	1,117(18.8)
Depressive Symptoms (CES-D scale)		
Not Depressed (< 0.06)	119,126(90.6)	6,882(70.9)
Depressed (>=0.06)	12,389(9.4)	2,832(29.1)
Postmenopausal Hormone Therapy History (%)		
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)
Nonsteroidal Anti-inflammatory Drug (NSAID) use (%)		
Never	80,716(59.7)	4,653(46.4)
Use for up to 1 Year	16,962(12.5)	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)
Greater than 20 Years	3,869(2.9)	317(3.2)
First Degree Relative had Colorectal Cancer (%)	20,267(15.7)	1,453(15.2)
HRT Study Arm (%)		
Not randomized to HRT	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)

*-Percentages may not add to 100 because of missing data

Table 2. Distribution of Antidepressant Subtype Use Among Antidepressant Users (N=10,036); Women's Health Initiative.

Antidepressant Class	**N (%)**
SSRI Use	
Non-User	4,908(48.9)
SSRI User	5,128(51.1)
Up to 2 Years of Use	2,886(28.8)
Greater than 2 years of Use	2,242(22.3)
TCA Use (%)	
Non-User	5,954(59.3)
TCA User	4,082(40.7)
Up to 2 Years of Use	1,546(15.4)
Greater than 2 years of Use	2,536(25.3)
Other Antidepressant (AD) Use (%)	
Non-User	8,521(84.9)
Other AD User	1,515(15.1)
Up to 2 Years of Use	803(8.0)
Greater than 2 years of Use	712(7.1)

Table 3. Distribution of Colorectal Cancer According to Antidepressant Use; Women's Health Initiative

Total Cancer	No Antidepressant Use	Antidepressant User	P-Value*
Colorectal cancer			0.018
No	132,722(98.2)	9,888(98.5)	
Yes	2,432(1.8)	148(1.5)	
Colon Cancer			0.053
No	133,130(98.5)	9,910(98.7)	
Yes	2,024(1.5)	126(1.3)	
Recto sigmoid Cancer			
No	135,011(99.9)	10,030(99.5)	0.196
Yes	143(0.1)	6(0.1)	
Rectal Cancer			
No	134,831(99.8)	10,018(99.8)	0.234
Yes	323(0.2)	18(0.2)	

*chi-square tests for categorical variables, T tests for continuous variables. For variables with small cell size Fischer's exact test

Table 4. Age and Multivariable Adjusted HRs and 95% Confidence intervals of Baseline AD use and Colorectal Cancer; WHI.

Table 5. Age and Multivariable adjusted HRs and 95% Confidence intervals of Baseline AD use and Colon Cancer; WHI.

			Age-adjusted		BMI-adjusted*		Depression-Adjusted**		Adjusted†	
			HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Total Colorectal Cancer	**Cases**	**Person-Years**								
	N=2,580		**N=2,197**		**N=2,197**		**N=2,197**		**N=2,197**	
AD use (SSRI and TCA)	123	42,764,833	0.90	.75-1.08	0.88	0.73-1.05	0.84	0.70-1.01	0.90	0.75-1.09
AD duration										
Less than 2 Years of Use	56	20,475,508	0.87	0.66-1.13	0.85	0.65-1.10	0.80	0.61-1.04	0.85	0.65-1.11
Greater Than 2 Years of Use	67	22,289,325	0.93	0.73-1.19	0.91	0.71-1.16	0.88	0.69-1.11	0.95	0.75-1.22
SSRI use	73	22,111,189	1.10	0.87-1.38	1.06	0.84-1.34	1.00	0.79-1.27	1.08	0.85-1.36
SSRI duration										
Less than 2 Years of Use	44	12,305,981	1.18	0.87-1.59	1.15	0.85-1.55	1.08	0.79-1.45	1.14	0.85-1.55
Greater Than 2 Years of Use	29	9,805,208	0.99	0.69-1.43	0.95	0.66-1.37	0.92	0.63-1.32	0.99	0.68-1.43
TCA use	43	17,160,382	0.74	0.55-1.00	0.72	0.54-0.98	0.71	0.52-0.96	0.76	0.56-1.03
TCA duration										
Less than 2 Years of Use	9	6,558,417	0.41	0.21-0.79	0.40	0.21-0.78	0.40	0.21-0.76	0.42	0.22-0.81
Greater Than 2 Years of Use	34	10,601,965	0.94	0.67-1.31	0.92	0.65-1.29	0.90	0.64-1.26	0.97	0.69-1.37
Other Antidepressant (AD) use	12	6,365,452	0.62	0.35-1.10	0.61	0.35-1.08	0.57	0.33-1.0	0.63	0.35-1.11
Other AD Duration										
Less than 2 Years of Use	5	3,380,000	0.50	0.21-1.20	0.48	0.20-1.16	0.45	0.19-1.08	0.47	0.19-1.13
Greater Than 2 Years of Use	7	2,985,452	0.76	0.36-1.59	0.76	0.36-1.59	0.72	0.34-1.51	0.82	0.39-1.73

*Adjusted for age and BMI

**Adjusted for age, BMI, and depression (CES-D scale)

†Adjusted for age, HRT clinical trial study arm, BMI, health eating index (hei2005), physical activity, smoking, diabetes history, hypertension history, colonoscopy, polyp removal, depression (CES-D), family history of colorectal cancer, hrt use, history of diverticulitis, NSAID use

			Age-adjusted		BMI-adjusted*		Depression-Adjusted**		Adjusted†	
Total Colon Cancer	**Cases (%)**	**Person-Years**	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
	N=2,150		**N=1842**		**N=1842**		**N=1842**		**N=1842**	
AD use (SSRI and TCA)	104	42,764,833	0.92	.75-1.12	0.89	0.73-1.09	0.85	0.7-1.04	0.91	0.74-1.12
AD duration										
Less than 2 Years of Use	48	20,475,508	0.90	0.67-1.19	0.87	0.66-1.16	0.82	0.62-1.10	0.87	0.65-1.16
Greater Than 2 Years of Use	56	22,289,325	0.94	0.72-1.22	0.91	0.7-1.19	0.88	0.67-1.15	0.95	0.73-1.25
SSRI use	66	22,111,189	1.20	0.94-1.54	1.16	0.91-1.49	1.10	0.86-1.40	1.17	0.91-1.50
SSRI duration										
Less than 2 Years of Use	40	12,305,981	1.30	0.95-1.77	1.26	0.92-1.73	1.18	0.86-1.6	1.25	0.91-1.72
Greater Than 2 Years of Use	26	9,805,208	1.08	0.73-1.59	1.04	0.7-1.53	0.99	0.67-1.47	1.06	0.72-1.57
TCA use	32	17,160,382	0.66	0.46-0.93	0.64	0.45-0.91	0.63	0.44-0.89	0.68	0.48-0.96
TCA duration										
Less than 2 Years of Use	7	6,558,417	0.38	0.18-0.8	0.37	0.18-0.79	0.37	0.17-0.77	0.39	0.19-0.82
Greater Than 2 Years of Use	25	10,601,965	0.82	0.55-1.22	0.8?	0.54-1.19	0.79	0.53-1.17	0.85	0.57-1.26
Other Antidepressant (AD) use	9	6,365,452	0.56	0.29-1.09	0.55	0.29-1.07	0.52	0.27-1.00	0.56	0.29-1.08
Other AD Duration										
Less than 2 Years of Use	3	3,380,000	0.36	0.12-1.12	0.35	0.11-1.09	0.32	0.1-1.00	0.34	0.11-1.05
Greater Than 2 Years of Use	6	2,985,452	0.78	0.35-1.75	0.78	0.35-1.74	0.74	0.33-1.66	0.84	0.38-1.87

*Adjusted for age and BMI

**Adjusted for age, BMI, and depression (CES-D scale)

†Adjusted for age, HRT clinical trial study arm, BMI, health eating index (hei2005), physical activity, smoking, diabetes history, hypertension history, colonoscopy, polyp removal, depression (CES-D), family history of colorectal cancer, hrt use, history of diverticulitis, NSAID use

Table 6. Age and Multivariable Adjusted HRs and 95% Confidence intervals of Baseline AD use and Rectal Cancer; WHI.

			Age-adjusted		BMI-adjusted*		Depression-Adjusted**		Adjusted†	
Total Rectal Cancer	**Cases (%)**	**Person-Years**	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
	N=482		**N=403**		**N=403**		**N=403**		**N=403**	
AD use (SSRI and TCA)	21	42,764,833	0.8	0.52-1.24	0.78	0.50-1.21	0.76	0.49-1.18	0.84	0.54-1.31
AD duration										
Less Than 2 Years of Use	8	20,475,508	0.64	0.32-1.30	0.63	0.31-1.27	0.6	0.30-1.22	0.66	0.33-1.33
Greater than 2 years of Use	13	22,289,325	0.94	0.54-1.64	0.92	0.53-1.60	0.9	0.51-1.56	1	0.58-1.76
SSRI use	8	22,111,189	0.61	0.3-1.22	0.59	0.29-1.19	0.56	0.28-1.14	0.62	0.31-1.27
SSRI duration										
Less Than 2 Years of Use	4	12,305,981	0.55	0.20-1.46	0.53	0.20-1.42	0.5	0.19-1.36	0.55	0.20-1.48
Greater than 2 years of Use	4	9,805,208	0.69	0.26-1.84	0.66	0.25-1.77	0.64	0.24-1.72	0.72	0.27-1.94
TCA use	12	17,160,382	1.12	0.63-1.98	1.09	0.62-1.94	1.08	0.61-1.92	1.19	0.67-2.13
TCA duration										
Less Than 2 Years of Use	2	6,558,417	0.49	0.12-1.98	0.49	0.12-1.95	0.48	0.12-1.92	0.53	0.13-2.12
Greater than 2 years of Use	10	10,601,965	1.49	0.80-2.79	1.46	0.78-2.73	1.45	0.77-2.71	1.6	0.85-3.00
Other Antidepressant (AD)	3	6,365,452	0.8	0.26-2.49	0.79	0.25-2.45	0.76	0.24-2.37	0.84	0.27-2.64
Other AD Duration										
Less Than 2 Years of Use	2	3,380,000	1.02	0.25-4.09	0.99	0.25-3.97	0.95	0.23-3.81	1	0.25-4.04
Greater than 2 years of Use	1	2,985,452	0.56	0.08-3.98	0.56	0.78-3.97	0.54	0.08-3.87	0.64	0.09-4.59

*Adjusted for age and BMI

**Adjusted for age, BMI, and depression (CES-D scale)

†Adjusted for age, HRT clinical trial study arm, BMI, health eating index (hei2005), physical activity, smoking, diabetes history, hypertension history, colonoscopy, polyp removal, depression (CES-D), family history of colorectal cancer, hrt use, history of diverticulitis, NSAID use

Table 7. Multivariable adjusted HRs and 95% Confidence Intervals for the Joint Distribution of Depressive Symptoms and AD use at Baseline and risk of Colorectal Cancer; WHI.

Group	Colorectal Cancer Cases, N	Person- Years	Adjusted† HR (95% CI)
Healthy (Non-user, No Depressive Symptoms)	1,865	549,400,000	1.00 (Ref)
Untreated (Non-user, Depressive Symptoms)	209	51,982,035	1.21 1.05-1.4
Treated (AD User, No Depressive Symptoms)	85	30,638,454	0.91 0.73-1.13
Insufficient Treatment (AD User, Depressive Symptoms)	38	12,126,379	1.08 0.78-1.49

†Adjusted for age, HRT clinical trial study arm, BMI, health eating index (hei2005), physical activity, smoking, diabetes history, hypertension history, colonoscopy, polyp removal, family history of colorectal cancer, hrt use, history of diverticulitis, NSAID use

*NOTE: interaction p=0.92

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