EXPLORING THE ASSOCIATION BETWEEN ANTIDEPRESSANTS AND COLORECTAL CANCER IN ADMINISTRATIVE DATA: NEGATIVE CONTROLS, ACTIVE COMPARATORS AND ALGORITHMS

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ABSTRACT

Monica E. D'Arcy: Exploring The Association Between Antidepressants and Colorectal Cancer in Administrative Data: Negative Controls, Active Comparators and Algorithms
(Under the direction of Jennifer Lund)

Some antidepressants, especially Selective Serotonin Reuptake Inhibitors (SSRIs), may prevent colorectal cancer (CRC), but these effects may be drug rather than class specific. Previous epidemiological studies have only examined class-level effects, and all studies used non-user comparisons, which are susceptible to several biases.

Examining specific SSRI-CRC associations requires a large sample size and precise prescription records, which are features of administrative data; however, these data do not generally contain pathology confirmed cases and algorithms are required to identify probable cases.

The goals of this dissertation were: 1) to examine the class-level associations between three antidepressant classes, including SSRIs, and CRC compared to a negative control, antihypertensive initiators (AHT), 2) to examine the association between specific SSRIs and CRC, and 3) to re-evaluate claims-based CRC-identification algorithms in a contemporary population.

To examine the first two goals, we performed a new-user, cohort study using a 20% random sample of Medicare beneficiaries (2007-2013), aged ≥66. We estimated hazard ratios (HRs) and 95% confidence intervals (CI), and controlled measured confounding using a propensity score weighting approach. SSRI initiators had lower CRC rates compared with AHT initiators (aHR=0.85, 95% CI: 0.70-1.02). Paroxetine and fluoxetine initiators had lower CRC rates compared with citalopram users (aHR: 0.78, 95% CI: 0.56-1.06; aHR: 0.74, 95% CI: 0.52-1.05, respectively). Estimates were consistent across sensitivity analyses.

We re-evaluated CRC-identification algorithm performance in a ≥65, 2006-2009 North Carolina Medicare population, a proportion of which were cancer registry identified CRC cases. We employed a novel cohort creation strategy, whereby cases contribute information from both their pre-diagnostic non-case and case states to accurately capture CRC incidence. Specificity was lower (98.3-99.4% versus 98.5-99.6%) and Positive Predictive Value (PPV) substantially lower (18-37% versus 45-71%) in this population compared to the original population.

Results from the first two goals warrant further investigation into the SSRI-CRC association, including incorporating additional part D data as it becomes available. Algorithms are a necessity when performing a drug-cancer study in administrative data, but should be used cautiously, because they are population and time specific. These CRC-identification algorithms need to be updated to reflect a more contemporary and economically diverse population. Future validation studies should employ strategies to accurately ascertain incidence to avoid overestimating PPV.

To Uncle Frank, Uncle Andy and Grandmommy: You were all taken far too early by cancer and I miss you terribly.

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5. Michael G: I’m sure you’re glad it’s over.

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LIST OF ABBREVIATIONS

5-FU	5-flourouracil
5-HT	5-hytroxytryptophan, serotonin
ACF	Aberrant Crypt Foci
AOM	Azoxymethane
AD	Antidepressant
BMI	Body Mass Index
BOL	2-bromolyseric acid diethylamide
DMH	1,2 dimethylhydrazine
CI	Confidence Interval
CIN	Chromosomal Instability Phenotype
CIMP	CpG Island Methylator Phenotype
COPD	Chronic Obstructive Pulmonary Disorder
COX-2	Cyclooxygenase-2
CRC	Colorectal Cancer
EC	Enterochromaffin Cells
FAP	Familial Adenomatous Polyposis
GEE	Generalized Estimating Equations
GI	Gastrointestinal
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
IBS	Irritable Bowel Syndrome
IBD	Inflammatory Bowel Disease
ICD-9	International Classification of Diseases, Clinical Modification, Ninth Revision
ICISS	Integrated Cancer Information Surveillance System
MDR	Multidrug Resistance
MSI	Microsatellite Instable
NCCCR	North Carolina Central Cancer Registry

NE	Norepinephrine
NET	Norepinephrine Transporter
NPV	Negative Predictive Value
NSAID	Non-Steroidal Anti-Inflammatory Drug
OR	Odds Ratio
PA	Pennsylvania
PACE	Pharmaceutical Contract for the Elderly
PPV	Positive Predictive Value
NC	North Carolina
RCT	Randomized Clinical Trial
RR	Risk Ratio
SE	Sensitivity
SERT	Serotonin Reuptake Transporter
SMR	Standardized Morbidity Ratio
SSRI	Selective Serotonin Reuptake Inhibitor
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SP	Specificity
TCA	Tricyclic Antidepressant
TNBS	Trinitrobenzene Sulfonic Acid
UC	Ulcerative Colitis
VEGF	Vascular Endothelial Growth Factor

CHAPTER 1: SPECIFIC AIMS

Despite declines in incidence and mortality over the past 30 years, colorectal cancer (CRC) remains the second leading cause of cancer mortality in the United States [1] with almost 50,000 deaths expected in 2015 [2]. CRC treatment is expensive, with the average cost per colon cancer Medicare beneficiary in the first year after diagnosis estimated at $30,000 in 2010 [3]. High costs of cancer treatment have therefore generated interest in identifying existing drugs and supplements with the potential to prevent cancer [4].

Antidepressants are commonly prescribed drugs**,** with an estimated 17% of Americans aged ≥65 reporting antidepressant use in a 2012 nationally representative survey [5]. Experimental evidence, both in-vivo [6-12] and in-vitro [8, 9, 13-20], suggests that some antidepressants may have anti-neoplastic effects, and that these effects could be drug and not class specific.

The few epidemiological studies [21-26] examining the association between both Selective Serotonin Reuptake Inhibitors (SSRIs) and Tricyclic Antidepressants (TCAs), and CRC have produced conflicting results, and all studies compared antidepressant users to non-users. Failure to adequately synchronize the start of follow-up can lead to improper attribution of events to new user and non-user groups. The frequency and intensity of interaction with the healthcare system (i.e., healthcare utilization) may also differ between initiators of a drug—new users [27]—and non-users, and thus non-user comparisons are also susceptible to outcome detection bias.

Administrative data are increasingly being used to identify both negative and positive effects of drug exposures on the risk of cancer. Although drug exposure information from

claims is reliable, claims data do not generally contain pathology confirmed cases, because they are used for reimbursement, and not research purposes. Therefore, algorithms are necessary to identify incident cancer cases in administrative data. Claims data are critical to answering questions that could not be feasibly ascertained within the context of a randomized clinical trial (RCT) or an observational study, because certain questions require a very large sample size, precise exposure ascertainment, and do not have enough evidence to warrant an RCT, for example the association between specific SSRIs and CRC. Studies performed in these data can also be substantially cheaper than traditional cohort studies because these data already exist.

The overarching goals of this dissertation are to rigorously examine the association between antidepressants and CRC, including plausible reasons for conflicting results, while exploring some methodological considerations specific to adequately addressing this sort of question in administrative data. The specific aims are as follows:

Specific Aim 1: Compare the incidence of CRC across cohorts of new users of SSRIs, new users of TCAs, new users of Serotonin Norepinephrine Reuptake Inhibitors (SNRIs), and new users of a negative exposure control, antihypertensives (AHT) exclusive of beta-blockers. Explore potential reasons for high cancer incidence shortly after initiation.
Aim 1 will be accomplished by generating cohorts of incident users to the classes of drugs of interest in the Medicare claims databases (parts A/B/D) for the years 2007-2013 in individuals aged ≥66 years. Our comparison of antidepressant users with the control group (non-users) will incorporate current pharmacoepidemiology techniques to improve exchangeability. We hypothesize that new users of SSRIs will have a reduced incidence of CRC compared with TCA new users and AHT initiators. We hypothesize that new users of SNRIs will have an increased incidence of CRC compared to AHTs.

Rationale: To date, no study has examined the association between antidepressant classes and CRC using a negative exposure control, and no study has ever evaluated the association between SNRIs and incident CRC. There are biologically feasible reasons why SNRIs may increase CRC risk through increased vascularization.

Specific Aim 2: Evaluate variation in the association between specific SSRIs (i.e. sertraline, fluoxetine, paroxetine) and CRC.

Aim 2 will be accomplished by generating cohorts of incident users to the classes of drugs of interest in the Medicare claims databases (parts A/B/D) for the years 2007-2013 in individuals aged ≥66 years. We hypothesize that differences in previously reported studies could be partially explained by inherent differences between specific drugs in the SSRI class with respect CRC risk. **Rationale:** Experimental evidence suggests some SSRIs may have anti-neoplastic effects. Epidemiologic studies examining the association between SSRIs and colorectal cancer (CRC) have produced inconsistent findings. Potential heterogeneity of specific SSRI effects, paired with differences in SSRI use across populations, may explain variation in previously reported results.

Specific Aim 3: Re-evaluate the validity of the algorithms defined by Setoguchi [28] **for colorectal, colon and rectal cancer cases in the Medicare claims database for the years 2006-2009 in more economically diverse and recent population without stringent enrollment criteria**

We will use Medicare beneficiaries, ≥65 years of age, and NC cancer registry CRC cases to validate the algorithm for identifying incident colon and rectal cancers in 2006-2009 Medicare population. We hypothesize that specificity of the algorithm has declined because of changes in the screening, treatment, and overall management of CRC over time, as well as differences between the NC and original PA/PACE populations. **Rationale:** We will be using

these algorithms to identify probable CRC cases in Aims 1-2; however, their performance in a more contemporary and economically diverse population is unknown. These algorithms were developed in a Pennsylvania (PA) population that was continuously co-enrolled in both Medicare and Pharmaceutical Contract for the Elderly (PACE)—a drug benefit program for low-income individuals—for the years 1997-2000. Therefore, we would also like to re-evaluate the algorithm in: (1) a less selected, and economically diverse group of individuals aged 65+ years in NC and (2) a more contemporary time period (2006-2009).

CHAPTER 2: BACKGROUND

2.1 Significance

Stress and depression are hypothesized to contribute to the progression of cancer via pathways involved in immune function, apoptosis, and inflammatory response. These hypotheses are supported by experimental studies [29-33], although they are difficult to test in humans [33-39]. Depressive symptoms—often treated with antidepressants—are reported by approximately 10% of Americans. Antidepressants are commonly prescribed drugs**,** with an estimated 17% of Americans aged ≥65 years reporting antidepressant use in a 2012 nationally representative survey [5]. It is estimated that 25% of cancer patients suffer from depression [40], and depression is associated with increased mortality [41]. As the 3rd most common cancer among men and women, and the 2rd leading cause of cancer mortality in the United States [42], CRC is a major public health burden.

There is increasing in-vivo [6-12] and in-vitro [8, 9, 13-18, 20, 43] evidence that antidepressants are cytotoxic to cancer cells, and that some antidepressants may act as chemosensitizers [44-46]. There is limited [21, 22, 25] epidemiological evidence supporting these associations, but these studies failed to use current pharmacoepidemiologic techniques to ensure comparability between exposed and non-exposed populations. They were also not powered to evaluate potential heterogeneity within the SSRI class.

Experimental evidence suggests that some antidepressants may act late in the multistep carcinogenic process, because several of the drugs reduced tumor size, slowed tumor growth or were cytotoxic. If these drugs modify CRC risk late in the carcinogenic process, then it would be possible to observe a population level association between antidepressant use and CRC

without decades of data. With seven years of a 20% random sample of the Medicare population, we have the opportunity to rigorously evaluate the associations between individual drugs and incident CRC.

Antidepressants are drugs used to treat depression, and depression is common among cancer patients [40]. Because these drugs are so commonly used, it is important to understand the potential harms and benefits. If they reduce the incidence of CRC by acting late in the carcinogenic process—on a late adenoma or early carcinoma—then they may have adjuvant benefits to individuals getting treated for CRC who also have depression. For example, some CRC tumors are highly resistant to Cetuximab [47], but there is evidence that some antidepressants (sertraline) may be cytotoxic to similar cell lines (HT-29), and reduce tumor size in HT-29 xenografted mice [48].

2.2 Antidepressants, serotonin and cytotoxicity

2.2.1 Antidepressants

Three of the most commonly used antidepressant classes include: SSRIs, TCAs and SNRIs. These drug classes increase the intercellular availability of neurotransmitters—most commonly serotonin, norepinephrine or dopamine—by preventing their uptake. TCAs are named for their physical structure, having three rings, but are quite variable in their function and affinity for various neurotransmitters. They increase neurotransmitter availability by preventing reuptake via binding to specific receptors or reuptake transporters, but they do this non-selectively. In contrast, drugs within the SNRI or SSRI class behave similarly to one another in that they strongly prevent only specific neurotransmitters, norepinephrine + serotonin, or serotonin respectively, from reuptake into the cell. They also generally only have strong affinity to the neurotransmitter reuptake transporter as opposed to the receptor. Each of these classes is indicated for a wide variety of conditions beyond depression. TCAs are an older class of antidepressant, with more severe side effects, and are thus less frequently a first line treatment,

and are more often prescribed to treatment resistant or more severe forms of depression. They additionally have a wider indication of use including neuropathic pain (desipramine). SNRIs are also indicated for neuropathic pain and fibromyalgia. In contrast, SSRIs and not indicated for pain conditions.

2.2.2 Serotonin in the body

The majority of serotonin (5-hytroxytryptophan (5-HT)) in the body is synthesized from tryptophan by the enterochromaffin cells (EC), which are distributed throughout the gastrointestinal (GI) Tract [49]. Serotonin then enters the lumen and interacts with the various serotonin receptors, and finally is taken up by enterocytes expressing the serotonin reuptake transporter (SERT) [50] . Serotonin has many functions including motility control of the GI tract. SSRIs bind to SERT, thereby inhibiting the reuptake of serotonin into the cell. TCAs are non-selective and may bind to SERT, the dopamine transporter (DET) and the norepinephrine transporter (NET). SNRIs preferentially bind to SERT and NET. All three classes additionally have marginal affinity for some of the several known serotonin receptors classes[51].

The distribution and types of serotonin receptors and SERT in the GI tract, specifically the colon, is not completely known[50], but serotonin receptors and SERT are present in the colon. Although SERT is present in the colon, there is evidence that it is expressed at much lower levels compared with the small intestine [52]. SSRIs modify SERT and serotonin expression in experimental animal models [53, 54], enhancing the biological rationale that these drugs could alter CRC risk in humans.

Serotonin, serotonin receptor, and SERT dysregulation is implicated in several gastrointestinal (GI) diseases[50, 55-57] including irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), celiac disease and diverticulitis. Serotonin and SERT *deficiency* has also been observed in ulcerative colitis (UC), IBS-D, IBS-C patients, and the number of EC cells was

dramatically reduced in severe UC compared with non-severe UC cases [58]. The association between 5-HT, 5-HT receptor, SERT and these disorders is complex and not completely understood. IBD, UC in particular, is a strong risk factor for CRC. Therefore, drugs that modify 5-HT, 5HT receptors and SERT expression may be associated with an increased or decreased risk of CRC.

2.2.3 Serotonin and cancer cell cytotoxicity

There was conflicting evidence early on concerning the association between serotonin and/or serotonin antagonists and both cell proliferation and tumor growth. In two separate experiments, Tutton and Barkla [59, 60] found that serotonin intraperitoneally injected into rats with chemically induced (dimethylhydrazine (DMH)) descending colon adenocarcinomas increased the mitotic rate of the tumors, but not in the normal colonic crypt epithelium. Injecting higher levels of serotonin into the animals resulted in a reduction of cell proliferation. The same studies also found that either depleting serotonin with DL-6-fluorotryptophan, or blocking serotonin receptors with a serotonin antagonist (2-bromolyseric acid diethylamide (BOL)) decreased tumor mitotic rate without a change in colonic crypt proliferation rate. A later study found [16] that fluoxetine greatly reduced human COLO320 DM viability, and increased serotonin and its main metabolite, but that serotonin-only treatment did not reduce viability. Tutton and Barkla also [61] observed that BOL was not cytotoxic to tumors induced by DMH in male rats, although it decreased the tumor mitotic rate. In 1981[6] they observed that a serotonin antagonist in mice xenografted with 1 of 4 human colon or rectal cancer cell lines reduced tumor growth in some of the cell lines compared with a control group; this was one of the first experiments demonstrating differential effects of a serotonin antagonist on different colon cancer cell lines. Finally, in 1982 [7] they evaluated how well now-commonly used SSRIs, fluoxetine (Prozac) and citalopram (Celexa), reduced tumor growth in mice xenografted with 1 of 3 human colon or rectal cancer cell lines, and how these drugs affected cell proliferation in the

tumor and the normal tissue compared with controls. They found that the drugs reduced tumor size relative to the control in two of the cell lines; the drug had no effect on one cell line relative to the control. In one cell line, fluoxetine reduced tumor growth whereas citalopram just slowed the tumor growth relative to the control. They also found that the drugs increased cell proliferation in the jejunal crypts, but decreased cell proliferation in the colonic tumors relative to controls.

2.2.4 Antidepressants and cancer cytotoxicity

2.2.4.1 In-vitro evidence

Since the first SSRI entered the American market in 1987, there has been increasing evidence that some antidepressants can induce cancer cell death or reduce their viability. More recent studies have provided biological evidence documenting mechanisms underlying the reduction of cell or tumor viability. Many of the studies support pro-apoptotic pathways [8, 13-15, 17, 43, 48, 62-64], although there is some evidence that the antidepressants may also act by modifying intracellular Ca^{2+} concentration [65-68], increasing immune function [69], reducing cell proliferation via p27 [11], and decreasing VEGF and Cyclooxygenase-2 (COX-2) expression [10].

Antidepressants have been shown to reduce cancer cell viability in-vitro in lung cancer cells [43], prostate cancer cells [8, 67, 68], melanoma cancer cells [20], osteosarcoma cells [70], neuroblastoma cells [15], burkitt's lymphoma cells [14, 71], leukemia cancer cells [13] and in CRC cells [17, 48, 62, 72]. One controlled study (comparison to untreated cells) [48] , compared the cytotoxic ability of antidepressants (sertraline, paroxetine, fluoxetine, reboxetine) to chemotherapies (doxorubicin, 5-FU) on CRC LS1034 cells, and found that sertraline and paroxetine were superior to both doxorubicin and 5-FU with respect to cell cytotoxicity. Doxorubicin was somewhat cytotoxic, but 5-FU had no impact on LS1034 cell viability, a cell line that is known to be resistant to chemotherapy. In the same study, sertraline and paroxetine had

similar cytotoxic abilities on the HT29 cells to doxorubicin; however, the antidepressants induced apoptosis and minimal necrosis, whereas doxorubicin induced cell death by necrosis [48]. Necrosis is an undesirable side effect, and can result in an inflammatory response that has the potential to reverse chemotherapeutic effects. Although no single study systematically evaluated all antidepressants in all possible cell lines, there is consistent evidence of differential effects by drug, class, dose and cell line.

2.2.4.2 In-vivo evidence of antidepressant cytotoxicity

A few studies have reported that some antidepressants reduce tumor volume [12, 48, 73, 74] or the number of circulating cancer cells in a metastatic CRC animal model [12]. In an experiment comparing the cytotoxic ability of various SSRIs to 5-flourouracil (5-FU, chemotherapy), one study[48] found that mice treated with sertraline (SSRI), and not paroxetine (SSRI) or 5-FU or control (saline solution), reduced the size of HT29 xenografted tumors in mice after 3 weeks of treatment.

2.2.4.3 Antidepressants to prevent neoplastic precursors

There is some evidence [75] that fluoxetine, an SSRI, may reduce the occurrence of aberrant crypt foci (ACF) in rats exposed to a carcinogen (1,2 dimethylhydrazine (DMH)). Kannen et al observed that animals co-treated with fluoxetine developed fewer ACF compared with DMH-only treated animals. Fluoxetine treatment was associated with significantly higher serotonin in the stromal cells within pericryptal colonic stroma near the crypt bottom compared to fluoxetine-untreated animals. Higher serotonin was accompanied by reduced VEGF, c-MYC and COX-2 expression. VEGF is a marker of vascularization, c-MYC is an oncogene and COX-2 is associated with inflammation and is frequently elevated in colon cancer. ACF may be precursor lesions to neoplasms. This study suggests that fluoxetine may have a very early chemopreventive effect.

2.2.4.4 Antidepressants as chemosensitizers

Chemotherapy frequently fails due to multidrug resistance (MDR), an influx-efflux imbalance in which certain transporters remove the drug from the cancer cell thus reducing tumor cell toxicity. There is evidence that some antidepressants may increase the potency of standard chemotherapies by inhibiting the removal of the chemotherapeutic drug. For instance, fluoxetine (SSRI)-doxorubicin co-treatment significantly slowed the progression of tumors in HCT-15 xenografted mice, comparable to bevacizumab treatment [76]; the concentration of doxorubicin was higher in tumor cells of animals co-treated with fluoxetine. Another study[46] reported that desipramine (TCA) increased the cytotoxicity of all platinum based chemotherapies against HT-116 cell lines; p53 and caspase expression increased in desipramine-cisplatin treated cells, suggesting the combination triggers apoptosis.

2.2.5 Antidepressants: Mechanisms implicated

The in-vivo and in-vitro evidence of antidepressant induced cancer cell death, the dysregulated apoptotic genes associated with their death [8, 13, 15, 17, 19, 48, 62-64, 77], the association between the dysregulated apoptotic genes and cancer etiology[78], and the role that serotonin plays in the colon**,** all provide strong biological rationale that some antidepressants could prevent incident CRC. Fluoxetine has been used to increase serotonin availability in mice with trinitrobenzene sulfonic acid (TNBS) induced colitis to block SERT [54]. These drugs may therefore also modify circulating serotonin and SERT in humans, thus providing a biological basis for potentially plausible mechanisms.

If any of the drugs or classes are chemopreventive, it is not clear is where in the natural history of CRC these drugs are acting to reduce the incidence. The evidence suggests two plausible time points: early, because there is some evidence that fluoxetine prevents ACF in mice co-treated with a carcinogen [75], and late, because there is abundant evidence that various antidepressants kill cancer cells [8, 13, 15, 17, 43, 48, 62-65, 67, 68, 72, 77, 79, 80] and

reduce tumor growth [8, 12, 48, 69, 73, 75, 81]. The apoptotic genes dysregulated in many of the studies are genes that are altered in the final stages of the carcinogenic process in the normal-carcinoma CRC sequence [82]. The evidence presented herein is very similar to the evidence that had been presented about various COX-2 inhibitors [83-86] and CRC. COX-2 is an inflammatory response that is produced in the carcinogenic process of the majority of colonic tumors, and COX-2 inhibitors reduce COX-2 expression and inflammation, a tumor-promoting feature. Predictably, aspirin only appears to reduce the risk of tumors expressing COX-2 [87]. Carcinogenesis is a multistep process and it is possible for a carcinogen or protective agent to affect multiple steps. Day and Brown[88] empirically demonstrated that smoking likely has both an early and late carcinogenic effect with respect to lung cancer.

2.2.6 Mechanisms implicated

A hallmark of cancer is its ability for unchecked cell proliferation [78, 89]; this commonly corresponds to a mutation in a tumor suppressor gene. An example of a tumor suppressor gene is p53, and mutations in this gene are very common in colorectal tumors [90, 91]. As the guardian of the genome, p53 controls both apoptosis and cell proliferation, lying upstream of p21 and the caspases. In several of the laboratory studies [8, 9, 13, 14, 19, 70], caspase-3 was frequently upregulated after exposure to certain antidepressants. One of the last genomic alterations in the progression to carcinoma in the majority of CRC tumors [90] is a p53 mutation, and it is found primarily in the well-characterized APC-KRAS-P53 adenoma – carcinoma progression [91-93]. There are many types of mutations, but those that inactivate P53 are associated with worse outcomes [94]. A mutation that inactivates P53 would be associated with reduced apoptosis and allow aberrant cells to have unchecked growth. The BRAF gene is associated with apoptosis, and BRAF mutations are more common in the CpG island methylator phenotype (CIMP). BRAF is an oncogene and BRAF mutations may cause the caspases downstream to become inactive, thereby reducing apoptosis. Some genes that have been

found to be dysregulated in CRC tumors are caspase-8 and caspase-9, both of which are in the apoptotic pathway. Overcoming apoptosis [78, 95, 96], and any pharmacological agent that increases apoptosis may prevent cancer progression, incidence, or decrease the likelihood of metastasis.

2.2.7 Total evidence

The laboratory evidence suggests biologically plausible mechanisms by which some antidepressants may reduce CRC development, and thus reduce CRC incidence at the population level. These drugs could be acting at various points in the multistep process: 1) late, by acting on tumors or late adenomas 2) middle, by increasing microenvironment apoptosis which is inversely associated with adenomas [97], and 3) early, by preventing ACF. Although some of these drugs may act on multiple points in the carcinogenic process, we can only test late acting effects in this study given only seven years of data. This is akin to showing that smoking cessation immediately begins reducing the relative risk of lung cancer compared to continuing smokers[88].

2.3 Epidemiological evidence

Antidepressants are commonly prescribed drugs**,** with an estimated 17% of Americans aged 65+ reporting antidepressant use in a 2012 nationally representative survey [5]. The few epidemiological studies [21-26] examining the association between both SSRIs and TCAs, and CRC have produced conflicting results, and all studies compared antidepressant users to non-users.

To date, no study has examined the association between SNRIs and CRC. Some drugs within the SNRI class are commonly used, for example Effexor, and there are biological reasons why norepinephrine could accelerate the carcinogenic process via increased vascularization [32, 33]. This is supported by a study reporting that serum norepinephrine concentration may

increase the likelihood of tumor development in rats treated with the carcinogen, azoxymethane (AOM) [98] . Antidepressants more reliant on norepinephrine reuptake inhibition may also be less effective at reducing tumor cell viability [43, 99]. This is consistent with the evidence that beta-blockers may reduce the incidence of cancer by reducing circulating norepinephrine[100]. It is important to understand if some antidepressants may have more carcinogenic potential compared with other antidepressants, because so many cancer patients suffer from depression, and may be treated with antidepressants.

Some previous studies [21, 24] have excluded CRC cases occurring in the year immediately following initiation to prevent protopathic bias (reverse causality). Latent CRC can cause symptoms mimicking depression, for example lethargy, weight loss, or gastrointestinal distress[101]. Thus, CRC cases diagnosed shortly after initiation of an AD may not be attributable to the AD itself, but could have been latent CRC with the physical symptoms of depression. We additionally hypothesize that high cancer incidence, if observed shortly after drug initiation, could also result from new users who have not been actively engaged with the healthcare system prior to drug initiation. These new users may thus experience a catch-up period of medical encounters, including diagnostic and cancer screening services, which we term “medicalization”.

2.3.1 Reasons for study variability

In-vivo evidence has shown that some, and not all, SSRIs may reduce CRC tumor volume or growth [48, 74, 102], with one study reporting superior benefit of sertraline compared to doxorubicin in HT29 cell-line xenografted mice[9]. The evidence suggests SSRIs may have different effects with respect to CRC risk, and that any potential association between an SSRI and CRC, could be drug and not class specific.

Epidemiologic studies examining the association between SSRIs and CRC risk have produced inconsistent findings, with three studies reporting no association [23, 24, 26], and the remaining studies reporting moderate (15%-45% reduction) inverse associations [21, 22, 25]. All studies relied on the comparison between antidepressant users to non-users or past users, which could be prone to confounding by depression. Both stress and depression may accelerate cancer progression [29, 33, 103] and therefore potentially increase observed CRC incidence. Confounding by indication could therefore attenuate any protective effect. All previously published studies also ignored the potential heterogeneity of specific SSRI effects. As a result, inconsistent findings from prior studies could be partially explained by changes in SSRI patterns over time and differential effects of specific SSRIs on CRC risk. For example, a study with a predominately 1989 population would have reported an SSRI-CRC association heavily weighted to the effects of fluoxetine on tumors in a population, because that was one of the few SSRIs on the market at that point in time. All previous studies are quite heterogeneous with respect to populations and exposure definitions (Table 1, Table 2)

Table 1: Epidemiological evidence

Paper	Years	Type	Features	Ever use definition	Outcome definition/ascertainment
Xu 2006	1991-2000	Nested case control	Saskatchewan Health, Canada 3188 cases, 12648 population controls, risk set sampling	Any prescription for SSRI within 10 years. Recorded in database	Saskatchewan Cancer Registry, ICD-10 codes
Coogan 2009	1995-2008	Case control	Philadelphia, US 529 case, 1955 hospital control	At least 3 months regular use, self report	Individuals reporting CRC in past year during nurses interview
Haukka 2010	1998-2005	Cohort (new user – 3 year washout)	Finland, unexposed = non-user during 1998-2005, randomly selected 1 non-user for each user, matched on birth year, sex and hospital district.	1 prescription during study period, recorded in database	Linked to Finnish cancer registry, ICD-7. Covers 99% of all cancers
Cronin-Fenton 2011	1991-2008	Case control	Denmark, 9979 cases, 99790 population control, risk set sampling Matched on birth year, sex, residence	Any two RX during 1991-2008, recorded in database	1st discharge dx = ICD8: 153.x-154.19, ICD10: C18.x, C19.9, C20, C20.9
Chubak 2011	2000-2003	Case control	WA state health plan, 649 cases, 649 controls. Matched on age, gender, time on health plan	Any 2 RX filled within 6 months during 2000-2003, recorded in database	SEER registry linked to group health plan
Walker 2011	?	Case control	Great Britain (GPRD), 6232 cases, 12010 population controls	Defined only for **TCA**, but defined as **> 1** prescription in the years prior to DX	GPRD – codes available upon request

Table 2: Exposure assessment characteristics and variability in epidemiological studies

Paper	Included cases within 1 year of use	OR/RR (95% CI)*	Exposure definition used in meta-analysis [104]
Xu 2006	Yes	0.84 (0.68, 1.03) CRC	**Exposure definition** = Ever use definition, adjusted. **Alternatives**: Cumulative dose low: adjusted OR =0.98 (0.75, 1.30) Cumulative dose high: adjusted OR = 0.75 (0.56,1.01) Low dose 0-5 years prior to CRC: adjusted OR = 0.96 (0.72, 1.28) High dose 0-5 years prior to CRC: adjusted OR = 0.70 (0.50, 0.96) Low dose 6-10 years prior to CRC: adjusted OR = 1.20 (0.73, 1.98) High dose 6-10 years prior to CRC: adjusted OR = 0.93 (0.55, 1.58)
Coogan 2009	No	0.55 (0.35, 0.88) CRC	**Exposure definition** = Any self-reported 3 month use adjusted **Alternatives CRC**: Recently initiated: adjusted OR =0.41, (0.12, 1.43) Sporadic: adjusted OR = 0.80, (0.33, 1.90) Regular use, < 3 year, adjusted OR = 0.50, (0.20,1.17) Regular use: >= 3 years, adjusted OR = 0.58, (0.34,0.99) **Alternatives colon cancer**: Regular use: adjusted OR = 0.47 (0.26, 0.85) **Alternatives rectal cancer**: Regular use: adjusted OR = 0.72 (0.37, 1.41)
Haukka 2010	Yes	1.11(0.56, 2.21) colon cancer	**Exposure definition** = 1460+ DDD cumulative exposure, adjusted. **Alternatives colon cancer**: 1-91 DDD, adjusted IRR = 1.39 (0.95, 2.04) 92-181 DDD, adjusted IRR = 1.29 (0.83, 2.02) 182-365 DDD, adjusted IRR = 0.81 (0.49, 1.33) 366-730 DDD, adjusted IRR = 0.85 (0.52, 1.40) 731-1460 DDD, adjusted IRR = 1.18 (0.71, 1.94) **Alternatives rectal cancer**: 1-91 DDD, adjusted IRR = 1.26 (0.79,2.00)

			92-181 DDD, adjusted IRR = 0.78 (0.43, 1.40) 182-365 DDD, adjusted IRR = 1.17 (0.68, 2.02) 366-730 DDD, adjusted IRR = 0.94 (0.53, 1.67) 731-1460 DDD, adjusted IRR = 0.89 (0.48,1.67) 1460+ DDD, adjusted IRR = 0.83 (0.35, 1.95)
Cronin-Fenton, 2011	No	0.97 (0.90, 1.05) CRC	**Exposure definition** = Ever use definition, adjusted **<u>Alternatives:</u>** Recent use (1 -< 2 years) adjusted OR = 0.97 (0.88, 1.07) Former use (2+ years) adjusted OR = 0.97 (0.86, 1.09) Short term, low dose adjusted OR = 1.04 (0.89, 1.21) Short term, medium dose (adjusted OR = 0.98 (0.85, 1.13) Short term, high dose adjusted OR = 0.90 (0.78 1.03) Long term, low dose adjusted OR = 0.94 (0.88, 1.07) Long term, medium dose (adjusted OR = 0.97 (0.74, 1.16) Long term, high dose adjusted OR = 1.13 (0.85, 1.51)
Chubak 2011	No	0.70 (0.5-0.9) CRC	**Exposure definition** = Ever use definition, adjusted **<u>Alternatives</u>**: Duration < 2 years: adjusted OR = 0.6 (0.3, 1.1) Duration > 2 years: adjusted OR = 1.0 (0.4, 2.8)
Walker 2011	No	0.95 (0.8 1.12) CRC	Effect estimate buried in the text. It isn't clear exactly what this estimate is: adjusted/unadjusted, ever/never, low dose/high dose, duration (1-117 days, >= 177 days)

2.4 Claims databases and identification of incident cancers

Administrative data are increasingly being used to identify both negative and positive effects of drug exposures on the risk of cancer. Although drug exposure information from claims is reliable, claims data do not contain the same information as a cancer registry, because they are used for reimbursement, and not research purposes. Therefore, algorithms are necessary to identify incident cancer cases in administrative data, with a specific algorithm necessary to minimize bias when we are estimating a relative effect measure [105]. Claims data are critical to answering questions that could not be feasibly ascertained within the context of an RCT or even an observational study, because certain questions require a very large sample size or do not have enough evidence to warrant an RCT, for instance Aim 2.

One of the most commonly used claims-based algorithms to identify incident cancers is from Setoguchi and colleagues [28]. She provided four definitions (Figure 1) of varying sensitivity and specificity that were developed in individuals who were continuously co-enrolled in both Medicare and the Pharmaceutical Contract for the Elderly (PACE) program between Jan 1,1997-Dec 31, 2000. PACE provided comprehensive drug coverage, but was limited to a very low-income group of individuals. Definitions 2 and 4 rely only upon *International Classification of Diseases, Clinical Modification, Ninth Revision* (ICD-9) diagnosis codes, whereas definitions 1 and 3 incorporate diagnosis, procedure and treatment events. Time, income and continuous enrollment criteria contribute to this source population inadequately representing a more economically diverse and contemporary Medicare population.

An additional limitation to these definitions is that they group colon and rectal cancers together. Although risk factors are similar for colon and rectal cancers, the effect estimates of risk factors vary qualitatively. For instance, a 2008 meta-analysis [106] reported that the association between smoking and cancer is stronger among rectal cancer cases than among colon cancer cases. Also, the median age of incidence is much younger for rectal cancer [64

years] than for colon cancer [71 years] [1], suggestive of etiological heterogeneity. Thus, there may be instances where an investigator wants to distinguish between the association between a particular drug exposure and colon cancer or rectal cancer.

Definition 1: Any of the following

>=1 cancer diagnosis + any diagnosis or procedure codes related to complications of cancer or palliative care in two weeks followed by another diagnosis of cancer within 12 months.

≥ 1 diagnostic procedure with biopsy followed by >=2 cancer diagnoses at two different occasions within 12 months (recorded on different dates from the procedures).

≥ 1 cancer diagnosis + any surgery related to cancer during the same hospitalization and/or visit.

≥ 1 cancer diagnosis + any cancer chemotherapy during the same hospitalization and/or visit

≥ 1 cancer diagnosis + any radiation therapy during the same hospitalization and/or visit

≥ 1 cancer diagnosis + hematopoietic cell transplantation during the same hospitalization and/or visit (for leukemia only)

≥ 1 cancer diagnosis + oral chemotherapy dispensing within 2 weeks after the diagnosis

Definition 2:

≥ 2 diagnoses of cancer within 2 months

Definition 3:

Cases defined by using Definition 1 or 2

Definition 4:

≥ 1 diagnosis of cancer

Figure 1: Incident cancer identification algorithms.

These algorithms were validated in the 1997-2000 PA/PACE population. See APPENDIX B for diagnoses and procedure codes used.

2.5 Epidemiology of CRC

CRC is the 3rd most incident cancer in the US and the 2rd leading cause of cancer mortality for both men and women combined [42]. In 2013, there were an estimated 142,820 new CRC cases and 50,830 CRC-attributable deaths; there are currently over 1 million CRC survivors, whose survivor status puts them at a higher risk of future CRC [107]. Although screening has reduced mortality, and relative 5-year survival has improved 20 percentage points since 1975, CRC remains a major and costly public health burden, with the average treatment cost per colon cancer Medicare beneficiary estimated at ~ $30,000 in 2010 [3]. As with most cancers, age is a major risk factor for sporadic CRC, with 90% of cases occurring in individuals older than 50 [1].

2.5.1 Broad molecular classifications of colorectal cancer

Although there have been efforts to more precisely characterize genomic features of all CRC tumors [108-110], there are currently only two universally recognized molecular subtypes: The chromosomal instability phenotype (CIN) and the Microsatellite Instable (MSI). The CpG Island methylator phenotype (CIMP) is becoming more commonly recognized as a distinct group, but it is not mutually exclusive of the other groups such that CIMP tumors may be MSI or Microsatellite Stable (MSS) [47, 111-113]. It is estimated that 85% of all tumors are CIN and the remaining 15% are MSI [112, 114]. Additionally, MSI and CIMP tumors are not consistently categorized as yes or no, but are often classified according to the degree of MSI or methylation in tumors. These tumors may be further stratified into MSI-H, MSI-L, MSS and CIMP-H, CIMP-L. Other features that are used to classify tumors and provide insight into etiology are: tumor genetic mutations, location of the tumor [115], response to therapy [47, 116, 117], and the mutation rate[91].

Corresponding to these molecular subtypes, mutations and physical characteristics, are at least two or more distinct pathways by which normal tissue develops into carcinoma: the adenoma pathway [92] and the serrated pathway [47, 109, 118-120].

2.5.1.1 Highly Penetrant Hereditary Disorders

Much of what has been learned about the carcinogenic process of CRC derives from studies of two highly penetrant, genetic disorders: Familial adenomatous polyposis (FAP) [92, 121] and Lynch Syndrome [121, 122], also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC). These disorders contain several features that are present in the subtypes of sporadic CRC, which are estimated to account for ~70% of all cases [121].

2.5.1.2 Lynch Syndrome

Lynch Syndrome is the most common hereditary disorder that predisposes a person to develop CRC, accounting for approximately 2%-4% of all incident CRC cases. Individuals with this syndrome have a 50-80% probability of developing CRC in their lifetime [121]. These cases are defined by a germ-line mutation in one of the mismatch repair (MMR) genes, including: MLH1, MSH2, MSH6 and PMS2, with the majority of mutations occurring in the MLH1 and MSH2 genes. These genes are responsible for correcting single base-pair errors during replication. In the context of Lynch syndrome, this damage is manifested by microsatellite instability (MSI) in the tumor. Lynch Syndrome is diagnostically confirmed by evaluating MSI, MMR gene staining and BRAF V600 mutation. A BRAF V600 mutation is an exclusion criteria for Lynch Syndrome, and the case is considered sporadic CRC (www.arupconsult.com/Algorithms/Lynch.pdf). These tumors may however have KRAS mutations. Tumors with MSI may not be as responsive to chemotherapy [123]. Although these individuals do not have more polyps than the average sporadic case, the aberrant MMR system accelerates the carcinogenic process such that it may only take 2-3 years to move from a small lesion to carcinoma [111]

2.5.1.3 Familial adenomatous polyposis

Familial Adenomatous Polyposis (FAP) is a highly penetrant inherited disorder accounting for 1% of all CRC cases [121]. These individuals have a germ-line mutation in the APC gene, which is a tumor suppressor gene in the Wnt signaling pathway; this mutation allows hundreds of polyps to develop, and because of this, individuals with this disorder are at an increased risk of CRC, with the average age of diagnosis at 39 years. Only a small percentage of these polyps will become a carcinoma, but the absolute number of polyps an FAP affected individual experiences increases the lifetime probability to ~100% [121]. This disorder allowed investigators to finely map genetic mutations associated with each stage of colon cancers

evolving through the classic adenoma-carcinoma sequence [92, 93]. FAP cases are characterized by chromosomal instability (CIN), which manifests itself by aneuploidy and is detected with karyotyping.

2.5.1.4 Sporadic cases

The majority of sporadic CRC are CIN [112]. CIN tumors generally occur in the left/distal colon, are highly differentiated, rarely mucinous and more likely to spread to lymph nodes and thus metastasize. APC and P53 mutations are very common in CIN tumors. Approximately 40% of these tumors contain a KRAS mutation. BRAF mutations are rare in CIN tumors and are generally mutually exclusive of KRAS mutation.

2.5.2.5 MSI

Approximately 15% of tumors are MSI. Like Lynch syndrome, sporadic MSI cases are characterized by microsatellite instability, but they differ from Lynch syndrome in that they do not have a germ line mutation in a MMR gene. Gene function of MMR genes is generally inactivated by methylation at the promoter region of MLH1. These tumors are more likely to occur in women, are generally found on the right/proximal colon, are poorly differentiated, larger, and less likely to have lymph node involvement or metastasize. Survival is generally longer despite larger, poorly differentiated tumors. P53 mutations are less common in these tumors than in CIN tumors.

Categorization of MSI is still evolving and some groups propose the use of more MSI categories including MSI-H (high), MSI-L (low) and MSS instead of MSI (yes/no) [108, 124] . Cut points for MSI-H includes 40% of markers demonstrating MSI, 20%-40% is considered MSI-L and 0% is considered Microsatellite stable (MSS).

2.5.1.6 CIMP

CIMP tumors are sporadic cases without clear classification guidelines, but are broadly defined as tumors with substantial methylation at the promoter regions of particular genes. Some of the genes that are frequently used to classify as CIMP are CACNA1G, CRABP1, NEUROG1, CDKN2A, and MLH1[125]. CIMP tumors can be MSI high, MSI low or MSS[108, 126]. They commonly have a BRAF location[113], and are thus less likely to have a KRAS mutation since these mutations are generally mutually exclusive.

Like MSI tumors, some groups classify CIMP tumors in gradation including CIMP-high tumors, CIMP-low tumors and CIMP-0 (no evidence of methylation at gene specific sites).

2.5.2 CRC Risk and protective factors

2.5.2.1 Demographic risk factors

Except for individuals genetically predisposed to CRC (Lynch syndrome, FAP), CRC is rare in younger persons, and 90% of incident cases occur in persons older than 50 years of age[1], with the majority of cases being sporadic [121]. The median age of diagnosis is 68 overall, although this varies by race and gender, with males having a younger median age of diagnosis than females, and blacks having a younger median age of diagnosis than other races. Median age of diagnosis also varies between colon [71 years] and rectal cancer [64 years]. The overall incidence in individuals over the age of 65 is 225 per 100,000 persons.

2.5.2.2 Behavioral/Lifestyle risk factors

The incidence of CRC is generally higher in westernized countries [127] compared with developing countries, suggesting lifestyle factors contribute to this difference. There are several lifestyle risk factors contributing to increased risk of CRC including: alcohol intake, smoking, diet, obesity, central adiposity and diabetes. A summary of non-demographical CRC risk and protective factors is in Table 3 and Table 4 below.

Table 3: Summary of CRC risk factors

Risk Factor	Magnitude of association/other
Alcohol [128]	Dose response RR = 1.07, 95% CI = (1.04, 1.10) comparing 10 grams/day to none RR = 1.82, 95% CI = (1.41, 2.35) comparing 100 grams/day to none Effects stronger in men than women and in Asians compared to other groups.
Smoking [106]	Ever versus never smokers (26 studies; RR = 1.18, 95% CI = (1.11, 1.26)) North America; 13 studies; RR = 1.18, 95% CI = (1.10, 1.26) Rectal cancer; 10 studies; RR = 1.25, 95% CI = (1.14, 1.38) in ever versus never Colon cancer; 10 studies; RR = 1.12, 95% CI = (1.04, 1.21) in ever versus never Rectal cancer; 25 studies, RR = 1.11, 95% CI = (1.00, 1.23) in current versus never Colon cancer; 25 studies, RR = 1.00, 95% CI = (0.91, 1.10) in current versus never Men; 10 studies; RR = 1.18, 95% CI = (1.07, 1.31) Women; 11 studies; RR = 1.14, 95% CI = (1.03, 1.25)
Body Mass Index/Waist Circumference	Positive association (RR = 1.33, (95% CI = 1.25, 1.42) between BMI and CRC, comparing obese to normal weight individuals in meta analysis (N=41 studies) [129] Strong association (RR = 1.46, 95% CI = 1.33, 1.60; N= 13 studies) between waist circumference—a measure of central adiposity—and incident cancer, comparing those in the highest versus lowest category of waist circumference [129] Johnson 2013 reported a 1.10, 95% CI = (1.08, 1.12) for each 8-unit increase in BMI. **Other:** high BMI is associated with reduced preventive screening[130], and thus could be associated with an increased incidence via decreased screening behavior.

Diet – Red meat/processed meat	Convincing evidence supporting the positive association between red meat and processed meat consumption [131], and both colon and rectal cancers [132]**.** 21 studies [133] (14 on red and processed meat; 13 on red meat; 13 on processed meat) RR = 1.22, 95% CI = (1.11,1.34) for CRC comparing those with the highest versus lowest intake of red or processed meat, RR = 1.14, 95% CI = (1.04,1.24) for every 100 gram/day intake of red or processed meat. There was a linear positive association up until 140 g/day, and above 140 grams/day, the association plateaued.
Insulin Resistance/Diabetes [134]	Moderate positive association in both European (N=10), RR = 1.47, 95% CI = (1.20, 1.80) and North American (N=14), RR = 1.21, 95% CI = (1.16, 1.26) studies between Diabetes Mellitus (DM) and CRC.
Inflammatory disorders	A Pooled standardized incidence ratio = 2.4, (95% CI = 2.1,2.7) for ulcerative colitis (UC) of population based cohort studies in the U.S. and Europe [135]. The association was slightly stronger in males and among individuals diagnosed with UC at a young age. Johnson et al [136] : RR = 2.93, 95% CI = 1.79, 4.81
Family History and Genetics	~20-30% of sporadic cases have a hereditary component [121]. Dose response with the number of affected family members, and risk increasing from 3rd to 2nd to 1st degree relatives [137]**.** Individuals with a 1st relative, RR = 1.90, 95% CI = (1.61, 2.02) [136]
Previous Adenomas/CRC	~ > 70% of all carcinomas go through the adenoma pathway[119], and as such previous adenomas are a strong risk factor for carcinoma.
Other	Stress and depression are associated with decreased immune function [35], and therefore possibly the increased risk of cancer. Animal models show that stress increased the proliferative potential of cancer [31-33, 36, 138]. In addition, depression is associated with unhealthy behaviors (poor diet, alcohol consumption, smoking), all of which are all risk factors for CRC.

Table 4: Summary of protective factors

Protective Factor	Magnitude of association/other
Physical activity	Physical activity and CRC in men (RR = 0.76, 95% CI = 0.72, 0.81) and women (RR = 0.79, 95% CI = 0.71, 0.88) [139]. Inverse association between physical activity and adenomas [140]. Association was stronger for more advanced adenomas (RR = 0.70, 95% CI = 0.56, 0.88). **Potential mechanisms:** improved immune function [141]**,** by reducing BMI or insulin resistance, or by the inverse association between physical activity and certain behaviors: smoking/alcohol consumption.
Hormone replacement therapy (HRT)	**Cancer Prevention Study II** [142]**:** stronger protective results among current estrogen only users (RR = 0.76, 95% CI = 0.59, 0.97) compared with estrogen + progesterone formulations (RR = 0.93, 95% CI = 0.70, 1.23), Protective effects stronger for rectal cancer cases among current estrogen only users (RR = 0.59, 95% CI = 0.34, 1.01) compared with CRC cases among estrogen only users (RR = 0.81, 95% CI = 0.61,1.08). Time dependent dose response reduction of CRC cases among estrogen only users **The Women's Health Initiative (WHI)** [143] 93,651 from an observational study, an RCT of 16,590 evaluating estrogen + progesterone, an RCT of 10,722 individuals evaluating an estrogen only formulation, and an additional 40,785 participants in a diet study. Stronger protective effect for rectal cancer, HR = 0.57, $p < 0.001$ compared to colon cancer, HR = 0.70, 95% CI = (0.62, 0.80). No statistical association at $p < 0.10$ for the type of HRT, or duration of use in the two RCTs. **European Prospective Investigation into Cancer and Nutrition (EPIC)** [144]. EPIC reported generally null results, although they did report a HR = 0.76, 95% CI = (0.57, 1.01) associated with testosterone derivatives of current progestin use. They also reported that ever, current, or former use of any HRT was associated with a reduced risk of rectal cancer.

Diet - Calcium	8% decreased risk associated with a 300 mg/day increase in calcium intake (N = 20 prospective studies (134)) 15% reduction in relative risk for each 400 g/day of dairy product consumption N=19 studies (135). 1000-2000 mg/day of calcium supplementation is associated with a 20% reduction in the risk of colorectal adenomas among individuals with a history of colorectal polyps [145, 146]. **Plausible mechanisms:** 1) calcium may reduce cell proliferation by modulating cell signaling [147, 148] 2) calcium may modify the expression of the APC/BCatenin pathway in the normal mucosa of adenoma patients [149]. APC/B-catenin genetic mutations are early events (associated with early adenomas) in the multi-stage process of colorectal carcinogenesis[82]
Diet – Vitamin D	Evidence described as limited and suggestive [131]. Vitamin D, like calcium, is found in milk and dairy products, although much of vitamin D is obtained through ultraviolet irradiation.
Diet - Fiber	Evidence as probable that fiber intake was associated with a decreased risk of CRC despite inconsistent findings [131]. 10% relative risk reduction for CRC associated with 10g of total fiber intake/day in meta-analysis of 25 studies [150]. The risk reduction was variable over the source of fiber.
Diet - other	Other potentially protective factors include: folic acid, selenium and others.
Non selective anti-inflammatories (NSAIDS)/aspirin	Aspirin and NSAID use is associated with a decreased risk of adenomas and CRC in both average risk and higher risk individuals. NSAID use is associated with longer survival among CRC patients [151, 152]
Apoptosis	Baseline apoptosis in the normal mucosa is associated with a decreased number of adenomas at colonoscopy and a reduced risk of adenomas in the future; this association is independent of NSAID use [97]. Overcoming apoptosis is one of the hallmarks of cancer [78].

2.5.3 Heterogeneity of risk factors and CRC subtypes

The aforementioned protective and risk factors broadly apply to incident colon/rectal cancer as a whole, although there is evidence that these factors to not act uniformly across tumor subtypes and features.

Table 5: Heterogeneity of CRC risk factors

Risk factor	Heterogeneity associations
Smoking	**Iowa Women's Health Study** [153] Ever smoking was associated with a moderate increased risk of any incident CRC compared with never smoking, (RR = 1.18, 95% CI = 1.05, 1.35) Stronger association comparing current smokers to never smokers for the risk of: MSI-high tumors (RR = 1.99, 95% CI = 1.26, 3.14), CIMP+ tumors (RR = 1.88, 95% CI = 1.22, 2.90) and BRAF mutated tumors (RR = 1.92, 95% CI = 1.22, 3.02). No association between ever and never smokers and incident MSS/MSI-low tumors (RR = 1.00, 95% CI = 0.79, 1.25), CIMP-negative tumors (RR = 1.02, 95% CI = 0.81, 1.30), BRAF wild-type tumors (RR = 1.00, 95% CI = 0.65, 1.27).
Aspirin	**Nurses' Health Study and the Health Professionals Follow-Up Study** [154] Inverse association between aspirin and CRC only applied to BRAF wild-type tumors (HR = 0.73, 95% CI = 0.64, 0.83) and not to BRAF mutated tumors (HR = 1.03, 95% CI = 0.76, 1.38). Association between aspirin and wild-type BRAF tumors became stronger as frequency of use increased, whereas the association remained null between aspirin and BRAF mutated tumors regardless of frequency the frequency of use. Aspirin is also only associated with a reduced risk of CRC among tumors expressing COX-2 [87]. **Aspirin and post-diagnosis survival** [152] HR = 0.39, 95% CI = 0.20, 0.76) for COX-2 expressing tumors versus HR = 1.22, 95% CI = 0.36, 4.18 for tumors not expressing COX-2 **Aspirin and recurrence** [154, 155] Reduced recurrence among individuals with PIK3CA-mutant tumors (HR = 0.11, 95% CI = 0.001, 0.832), not PIK3CA wild-type tumors (HR = 0.92, 95% CI = 0.60, 1.42), Rofecoxib (Vioxx), an NSAID, no benefit in either PIK3CA-mutant tumors (HR = 1.2, 95% CI = 0.53, 2.72) or PIK3CA wild-type tumors (HR = 0.87, 95% CI = 0.64, 1.13)

	Higher alcohol consumption, and red or processed meat consumption appear to be associated with mutations or methylation in the promoter region of the APC gene [156].
	>= 5 years of Hormone therapy is inversely associated (RR = 0.50, 95% CI = 0.27, 0.95) with high P53 expression [156].
Other	Potential association between BMI and BRAF mutation status [157].

2.5.3.1 Why heterogeneity matters

The evidence between antidepressants and incident CRC appears to be drug/cell line dependent and there is evidence to suggest that the drug or drug class will not behave uniformly across all cancers. This fact should temper any conclusions we may be tempted to draw from potential results. For instance, maybe some of these drugs only act to prevent MSI tumors. These tumors only comprise 15% of all tumors and our results will reflect the distribution of tumor subtypes in our population. Additionally, tumor subtypes vary by population. If, for example, certain drugs only act upon BRAF+/CIMP tumors, we would expect a stronger result in our population compared to a younger population since these tumors are more common in older women. Our proposed data source is greatly limited by absent molecular tumor information.

CHAPTER 3: METHODS

3.1 Study design and population

3.1.1 Aim 1, Aim 2

For Aim 1 we will conduct a new user [27], cohort study of exclusive (class monotherapy) initiators of SSRIs, TCAs, SNRIs or AHT excluding beta-blockers, using a 20% random sample of Medicare beneficiaries aged ≥66 years from 2007-2013 with simultaneous fee-for-service (FFS) parts A, B, and D (drug) coverage for at least one month during a calendar year. We chose AHT, excluding beta-blockers, as our negative control exposure, because there is no compelling evidence that their use is associated with CRC risk, and we anticipated a substantial number of initiators. We excluded beta-blockers, because there is evidence that their use could reduce cancer risk [100].

For Aim 2 we will conduct an active comparator, new user [158], cohort study of initiators of specific SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, sertraline) using a 20% random sample of Medicare beneficiaries aged ≥66 years from 2007-2013 with simultaneous fee-for-service (FFS) parts A, B, and D (drug) coverage for at least one month during a calendar year. Active comparator studies have been shown to reduce confounding by indication, because initiators of the drug of interest and initiators of an alternative drug initiated for the same indication, are generally more similar across measured and unmeasured characteristics than patients who do not initiated a similarly indicated medication [159, 160]. New user designs remove time-related biases to which observational drug-cancer studies are susceptible [161].

Medicare is a guaranteed benefit available to all Americans older than the age of 66, and our dataset for both Aim 1 and Aim 2 includes a random sample of all Americans with

concurrent fee-for-service Medicare parts A, B, and D coverage in at least one month during the calendar year, regardless of gender, race or geographic location. This data source is ideal for our study because it contains a large, representative sample of Americans aged 66+ years, the population is generally followed from entry at age 65 until death, the incidence of CRC in this population is high (225 per 100,000 persons) [1], and exposure assessment—antidepressant use—is reliable.

Medicare Part A includes claims for inpatient services and hospitalizations. We will use this information for procedures associated with colon or rectal cancer treatment. These procedures will be used to identify incident cases. Medicare Part B includes claims for outpatient services and preventive procedures such as cancer screenings. Treatment for colon or rectal cancer is commonly performed in the outpatient setting. We are using treatment and screening procedures to identify incident cases. Medicare Part D includes claims for all filled (dispensed) prescriptions. This information will be used to define our cohorts.

3.1.2 Aim 3

Aim 3 is a validation study where we will be re-evaluating algorithm performance of commonly used definitions to identify incidence cancer cases in a more recent and economically diverse population. We will use the integrated cancer information and surveillance system (ICISS), a resource at the University of North Carolina (UNC). ICISS houses several linked data sources with the goal of understanding cancer incidence, risk factors and patterns of care of NC residents [162]. ICISS contains a 100% sample of NC Medicare beneficiary enrollment and claims information, and NC cancer registry (NCCCR) cases that are linkable to NC Medicare beneficiary information.

3.1.2.1 Case selection and data linkage

We identified all colon or rectal cancer cases age 65+ at diagnosis in the NCCCR from July 1, 2006-December 31, 2009 that were linkable to NC Medicare enrollment and beneficiary files. We then further required that all cases had ≥13 months of continuous enrollment in Medicare parts A/B at any point between Jul 1, 2006 and Dec 31, 2009, having at least one claim to ensure benefit utilization. Finally we restricted to first and primary colon or rectal cancer cases using the sequence id variable that is part of the cancer registry. The NCCCR has a gold star rating from the association of cancer registries [163]. This rating is only given to those registries with timely and >= 95% case ascertainment [164].

3.1.2.2 Non-case selection criteria

We identified all NC Medicare beneficiaries, not appearing in the cancer registry, who were continuously enrolled for 13+ months in Medicare parts A/B at some point between Jul 1, 2006-Dec 31, 2009, were aged 65+, and had at least one in or outpatient claim in order to ensure benefit utilization. We then randomly selected 150,000 of these non-cases meeting cohort criteria.

3.1.2.3 Main validation cohort

We will not require continuous enrollment during the entire study period (Jul 1, 2006-Dec 31, 2009), but instead will create a series of continuous enrollment windows of a smaller size, thereby capturing a less select, and more representative, 65+ Medicare beneficiary.

Rationale for dynamic enrollment periods

Cancer-associated claims information changes over time for cases, and there are periods of time before an incident case becomes a case when claims information would be more representative of a non-case. Claims information dated after the case has been diagnosed are more representative of prevalent and not incident cases. Cancer cases,

especially those such as CRC that go through a series of events from screening, diagnosis to treatment, require a minimum period of time to fully "diagnose" an incident CRC case within claims data. This pattern of series of events should vary by cancer type, based on screening and treatment guidelines. Therefore, there is a minimum period of time that is necessary to follow an individual who becomes a true incident case. In order to loosen the continuous enrollment criteria previously imposed, and consider cases in their pre-diagnosis non-case status, pre and during diagnosis incident case status, and post-diagnosis prevalent case status, we will create a series of cohorts that move over time. Cases can move from pre-diagnosis non-case status to pre/during incident-case status, and thus in and out of the cohort, depending where in time they are relative to the registry diagnosis date.

A complete window

The cohort will consist of a series of cohorts with a minimum enrollment criteria of 365 days that is bounded by a period of time before this window (pre-buffer) and after the window (post-buffer) whereby if a case is diagnosed within the pre-buffer or post-buffer, they would be excluded from the specific cohort, because they are potentially not contributing all critical information. Non-cases are eligible for all cohorts as long as they are continuously enrolled during the entire period of observation (primary window + pre-buffer + post-buffer). Cases can move from non-case status to case status. After they have become a case, they can no longer enter future cohorts, because they are now prevalent cases (Figure 2).

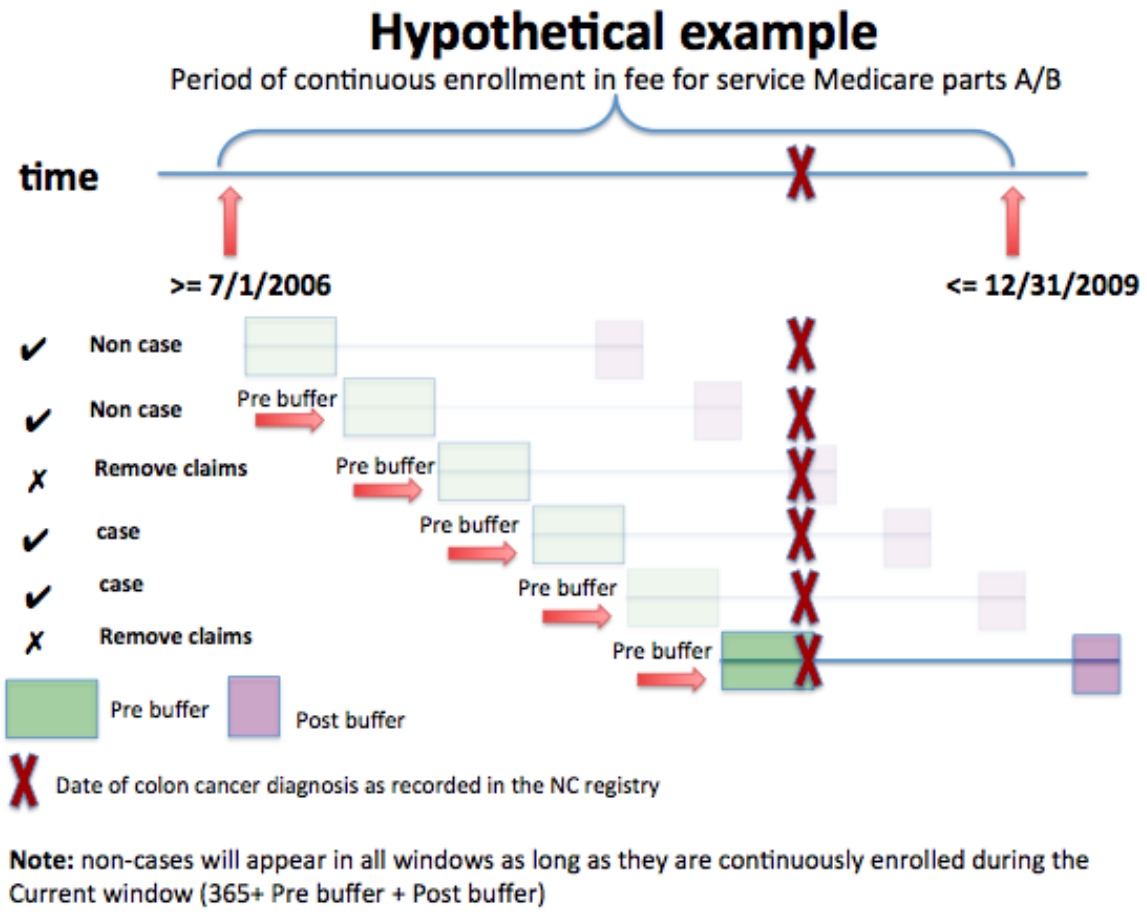

Figure 2: Hypothetical example, series of observation windows.

An individual that is diagnosed with colon cancer contributes information as a non-case in windows 1 and 2, and as a case in windows 4 and 5. There is not enough information to adequately ascertain case status of this individual in windows 3 and 6.

Calculation of pre-buffer size

We will calculate for each CRC case the mean amount of time in days between the registry diagnosis date and all dates of diagnostic-associated procedures (e.g. colonoscopy), (APPENDIX C) occurring within 365 days of the registry diagnosis date. We will then calculate the earliest 1% of the distribution of these mean days, corresponding to the largest 99th percentile of the amount of time in days between diagnostic events and registry diagnosis dates, and used this value as the pre-buffer size. We will exclude all cases and associated claims whose registry diagnosis date falls within this pre-buffer window, which is the pre-buffer time in days immediately preceding the 365-day primary window.

Calculation of post-buffer size

We will calculate for each CRC case the mean amount of time in days between the registry diagnosis date and all dates on which a treatment code was observed (e.g., chemotherapy, APPENDIX C), occurring within 365 days of the registry diagnosis date. We will use the 99th percentile of the distribution of these mean days as the post-buffer size. This corresponds to the largest 99th percentile of the mean amount of time in days between registry diagnosis dates and treatment events. We will exclude all cases and associated claims whose registry diagnosis date fell within this post-buffer window, or between the end of the primary 365-day window plus the post-buffer time in days.

3.2 Exposure ascertainment and Inclusion criteria (Aim 1, Aim 2)

For Aim 1 all cohort members must be aged 66+ at the date of the first observable, dispensed prescription for an SSRI, SNRI, TCA, or AHT, and have ≥ 360 days of continuous enrollment in Medicare Parts A and B prior to the first (SSRI, SNRI, TCA, AHT) prescription to evaluate baseline covariates and clinical factors. Initiators will have ≥180 days of continuous part D enrollment, and no claims for an SSRI, SNRI, TCA, or AHT prior to the first prescription to restrict to "new" users of the medication class. They will have no diagnoses or treatments associated with CRC in claims during the baseline assessment period to exclude prevalent cases, and a second claim for a medication within the same class as the initial claim occurring within the days' supply of the first claim date plus a grace period of 60 days. We chose 60 days as a grace period because initiators of these medication classes frequently augment or switch between drugs within the class. We used National Drug Codes (NDC) associated with formulations for the generic drugs of interest to classify cohort members. The date of cohort entry was the date the second prescription was dispensed.

For Aim 2 all cohort members must be aged 66+ years at the date of the first prescription claim for an SSRI and have at least 360 days of continuous enrollment in Medicare Parts A and

B prior to the first SSRI prescription to evaluate baseline covariates. They must have at least 180 days of part D and no claims for an SSRI prior to the first prescription to restrict to "new" users of the medication, and no evidence of CRC (only CRC, not other cancer sites) in the baseline assessment period to exclude potentially prevalent events (identified with *International Classification of Diseases, Clinical Modification, Ninth Revision* (ICD-9) diagnosis codes or current procedural terminology codes (CPT)). We are only excluding potentially CRC cases, because other cancer sites do not commonly metastasize to the colon [165]. Finally, we require a second prescription claim within the day's supply of the first claim plus a grace period of 30 days to allow for imperfect adherence. The second claim requirement increases the likelihood that the initiator was adherent for a meaningful exposure period. We used National Drug Codes (NDC) associated with formulations for the following generic drug names to generate the new user cohorts: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline. The date of cohort entry was the date the second prescription was dispensed.

3.3 Outcome ascertainment (Aim 1, Aim 2)

For both Aim 1 and Aim 2, we will identify non in-situ CRC events with an algorithm developed by Setoguchi et al [28]. This algorithm was defined as two or more *International Classification of Diseases, Ninth Revision* (ICD-9)—codes {153.x, 154.0,154.1, 154.2} present within 60 days. The date of diagnosis was the date of the first of the 2+ diagnoses. This definition obtained high specificity, which is necessary to minimize bias in studies evaluating relative measures of association [105]. This is because at non-perfect specificity, a proportion of non-cases will be classified as cases in both the exposed and non-exposed groups, and we will be adding a proportion of the total number of exposed or unexposed groups into the numerator of each of the risks. By adding these additional cases to both numerators we bias the ratio estimate. As an example, assume that the true risk ratio estimate is (a/b)/(c/d) where 'a' is the number of events in the exposed group, 'c' is the number of events in the unexposed

group, ‘b’ is the total number of persons or person-time in the exposed group, ‘d’ is the total number of events in the unexposed group. We also then assume that ‘b’ is some proportion ‘q’ of ‘d’ and ‘p’ is the proportion of individuals falsely classified as cases.

The unbiased risk ratio = (a/b)/(c/d) = (a/q*d)/(c/d) = [a/(q*c)]

At non-perfect specificity, the risk ratio becomes: [a+ p*b] /[q*(c+p*d)]

The above equation is only unbiased when p or the proportion of falsely misclassified non-cases is 0, perfect specificity, or when the unbiased ratio is 1.

3.4 Covariate assessment (Aim 1, Aim 2)

For both Aim 1 and Aim 2 we will covariates using claims for the 360 days preceding the date of the first prescription claim for an SSRI, SNRI, TCA, or AHT.

Demographic information available in the baseline assessment period included: race (White, Non-Hispanic, Black, Non-Hispanic, Hispanic, Asian, Native American/Pacific Islander or Other), sex, and age at the first prescription (coded as a continuous variable).

ICD-9 diagnosis and procedure codes, Current Procedural Terminology (CPT) codes, or Healthcare Common Procedure Coding System (HCPCS) codes present in any claim during the baseline assessment period were used to identify clinical factors and comorbidities at the time of SSRI, TCA, SNRI or AHT medication initiation. These covariates included: any potential non-CRC cancer diagnosis (e.g., breast cancer), obesity status, diabetes mellitus type 2, chronic obstructive pulmonary disease—a proxy for current or past smoking [166], inflammatory gastrointestinal diseases, alcohol abuse indicators, colonoscopy (coded as 0 or ≥ 1) anxiety and depression. Individuals with ICD-9 diagnosis or procedure codes, or CPT or HCPCS procedure codes associated with CRC during the baseline period were identified as having prevalent CRC, and were excluded from the cohort. Users of estrogen-based medications and non-steroidal

anti-inflammatory drugs were identified as having ≥1 claim for a drug in the class in the baseline period.

3.5 Confounding control (Aim 1, Aim 2)

Although evidence suggests that more conventional multivariable methods produce similar results to propensity score methods, there are advantages to their use [167]. In an observational study, propensity scores (PS) can be used to balance measured and unmeasured covariates, thereby reducing the risk of unmeasured confounding [168-170]. We will use known and available risk factors for CRC to generate propensity scores[171]. A benefit of PS is that they enable a visual inspection of overlap between the treatment groups. This overlap for the propensity of treatment allows identification of individuals who would never be eligible for other treatments. This is important because confounding by indication (e.g. depression) may exist, and it is plausible that TCA users may be inherently different than SSRI or SNRI users.

3.5.1 Aim 1 confounding control

To control measured confounding, we will use a propensity score (PS) approach that weights the covariate distribution of AHT initiators to reflect the covariate distribution of each of the AD class initiators, with the goal of estimating the "treatment effect in the treated" [172] . We seek to balance covariates across treatment groups and estimate an unconfounded association between the AD class (SSRI, SNRI, TCA) compared with AHT initiators and the risk of incident CRC. We will run three logistic regression models to estimate the predicted probability of initiating an AD class (SSRI, SNRI, TCA) compared with AHT initiators. We will then weigh the AHT initiators to the baseline covariate distribution of each of the three AD classes (SSRI, SNRI, TCA) using a weight of PS/(1-PS) for AHT initiators and a weight of 1 for all AD class initiators, a procedure referred to as standardized morbidity ratio weighting (SMRW). We will thus compare initiators of SSRIs, SNRIs, or TCAs each individually to AHT initiators. PS weighting methods are particularly useful in this study, because the comparator group is not an

active comparator and we need to evaluate the extent to which AD and AHT initiators differ at cohort entry, and how well covariates were balanced after SMRW.

3.5.2 Aim 2 confounding control

We will control confounding using a propensity score (PS) weighting approach such that the distributions of measured covariates in the non-referent groups (escitalopram, fluoxetine, paroxetine, sertraline) are weighted to the covariate distribution of the referent group of citalopram initiators. Citalopram was chosen as the referent group because it has the largest number of initiators. The goal of PS weighting is to balance covariates across treatment groups and estimate the unconfounded associations between specific SSRIs (compared with citalopram) and incident CRC. We will run four separate logistic regression models to estimate the PS of initiating each non-referent SSRI drugs versus citalopram based on measured covariates. We will then weight the non-referent initiators to the baseline covariate distribution of the citalopram initiators with (1-PS)/PS, a variant of standardized morbidity ratio weighting (SMRW) when there are more than two non-referent groups [173]. Citalopram initiators will be given a weight of 1.

3.6 Person-time at risk Aim 1, Aim 2

For both aim 1 and aim 2, we implemented a variation of the “disease induction” and “latent” concepts defined by Rothman [174] to specify person-time at risk. The induction is the time from the start of a specific exposure from which malignant transformation begins until the detection of cancer, whereas the latent period is the time in which a cancer is present but not yet detected. It is impossible to precisely identify when cancer induction has ended and latent period begun. Therefore we commonly merge the two concepts into the term “empirical induction”, the time from cancer initiation to a detectable cancer. For the purposes of these two aims, “empirical induction” will refer from drug initiation to a detectable cancer.

CRC is thought to evolve through a series of genomic and physical changes over a period of years [93]. We hypothesized that SSRIs may have effects that are observable during the later stages of carcinogenesis by preventing the transition of an adenoma to a carcinoma. We also assumed that there would be some minimum time after drug initiation before observable effects could reasonably be expected to occur (empirical induction, immune time). We set this interval to 180 days after the second prescription, and thus person-time and cases began to accrue 180 days after the second prescription.

We continued to follow individuals for up to 90 days after drug discontinuation or augmentation to account for cases that may be attributable to drug use, but whose tumor remained undetected at SSRI cessation. We censored individuals at the earliest of: the date of the last prescription plus the days' supply plus a grace period to allow for imperfect adherence (Aim 1 or Aim 2) or drug switching (Aim 1) plus 90 days; date of death; date of Medicare parts A, B or D disenrollment, or the end of the study period (12/31/2013). Figures 3, 4 illustrate general conceptualization of cohort entry and exit.

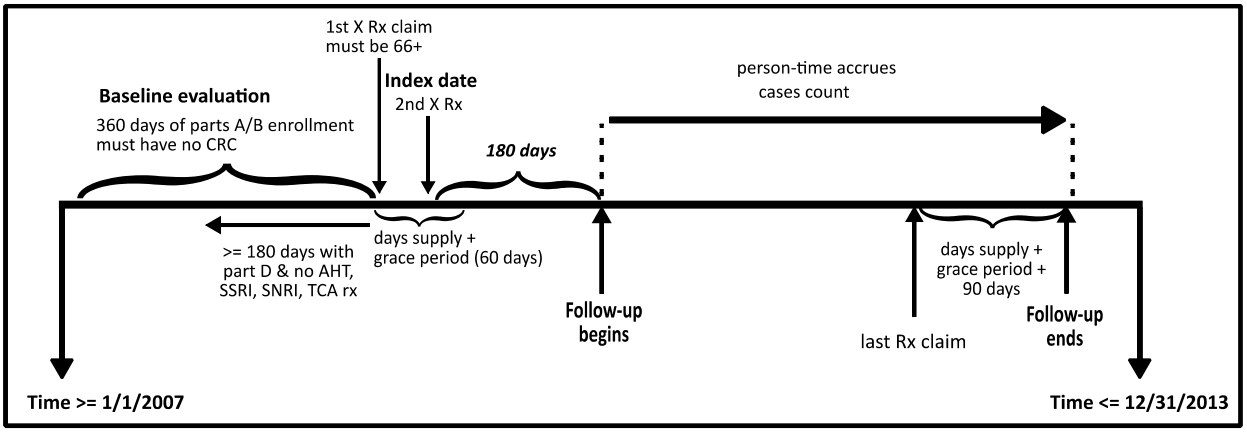

Figure 3: Cohort entry and exit for Aim 1

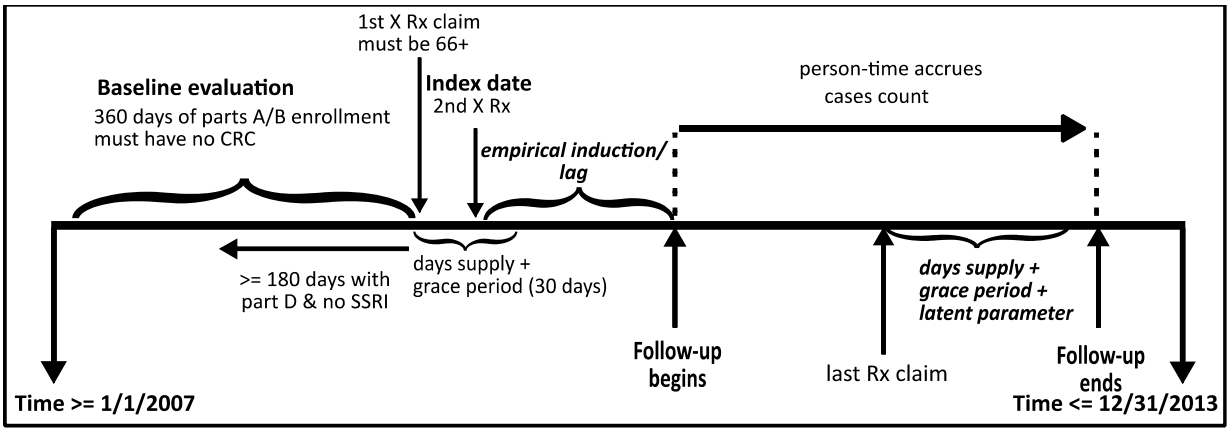

Figure 4: Cohort entry and exit for Aim 2

3.7 Statistical analyses

3.7.1 Aim 1

We will hazard ratios (HR) and robust 95% confidence intervals using three SMRW Cox proportional hazards models, one for each AD-AHT comparison. We will censor individuals at the earliest of the date of the last prescription plus the days' supply plus the grace period (60 days) plus the latent period parameter, date of death, date of Medicare parts A, B or D disenrollment, or the end of the study period (12/31/2013).

We will examine whether there is high CRC incidence following AD or AHT initiation by calculating the incidence stratified by time and drug group. We will examine one of the potential hypotheses for increased incidence following medication initiation, the "medicalization" hypothesis, by examining patterns of office visits in the 360 days prior to the first AD or AHT prescription. Based on our hypothesis, we expect that new users of any class, on average, will have fewer visits in the 360 days prior to the first prescription. If the CRC rate is high shortly after initiation, and it is in part due to depressive symptoms attributable to a latent cancer leading to an AD prescription, then we expect patterns of healthcare utilization to differ between the AD and AHT initiators, which assumes that hypertension does not induce CRC-like symptoms.

3.7.2 Aim 2

We will estimate HRs and robust 95% confidence intervals with one SMR weighted Cox proportional hazards model using four sets of weights, one for each non-referent group. To evaluate the stability of associations, we will perform sensitivity analyses in which we varied the amount of time: 1) between the second prescription and when person-time and cases begins accrual, and 2) between medication discontinuation and when person-time and case accrual ceases. We examined the proportional hazards assumption by stratifying by time since initiation and visually inspecting changes in HR.

3.7.3 Aim 3

We will identify all probable cases over all cohorts for all definitions. We will calculate sensitivity (the proportion of true positives captured by the algorithm); specificity (the proportion of true negatives classified as a non-case); positive predictive value (PPV) (the probability that an individual is a case given the algorithm calls an individual a case); and negative predictive value (NPV) (the probability the person is not a case given the algorithm classifies him as a non-case), and corresponding 95% confidence intervals in all cohorts using the epiR package [175]. We will adjust both NPV and PPV for the sampling fraction of non-cases. Because individuals in the primary cohort may appear in multiple windows, we will use generalized estimating equations (GEE) to calculate the standard error to account for within subject variability. Because we expect that dataset to be fairly large we will employ a resampling technique to estimate the standard error of the GEE estimate.

3.8 Sensitivity analyses

3.8.1 Aim 1, Aim 2

We performed sensitivity analyses where we varied the amount of time between the second prescription and when person-time and events began accrual (0-730 days), and after medication discontinuation when person-time and events ceased accrual (0-360 days).

3.8.2 Aim 3 sensitivity cohorts

3.8.2.1 Cohort replication of Setoguchi definitions

To mimic the continuous enrollment criteria imposed on the PA/PACE population, we required cohort-eligible individuals to maintain continuous part A/B enrollment for at least 36 months. This was to emulate the 48 months of continuous enrollment in Medicare and PACE in the PA/PACE validation. We will also test the definitions among all individuals continuously enrolled for only ≥13 months. We will finally examine how incorporating treatment and procedure codes that did not exist in 1997-2000, but did between 2006-2009, impacts the performance of definitions #1 and #3. Definitions #1 and #3 use both diagnosis and treatment or procedural codes to identify a case.

3.8.2.2 Low-income status (LIS)

The PA/PACE population was highly select with respect to both continuous enrollment criteria and income, with cohort members having a very low maximum income. Thus, their patterns of cancer diagnosis and treatment may differ from a more typical and economically diverse Medicare population. They may not have the same level of mobility as a more economically diverse population. We attempted to capture a lower income population by using a flag ("Cost Share Group Code"; CST_SHR_GRP_CD_1-CST_SHR_GRP_CD_12 variables) representing LIS-eligibility in the beneficiary summary file. There is a flag for each month of Medicare enrollment. Specifically we classified individuals as ever LIS if they had a code of 01-03 (fully-subsidized part D), or 04-08 (LIS eligible, but not receiving full part D subsidy) in any month of the period of continuous enrollment.

3.8.2.3 Modification of algorithms to identify colon and rectal cancer cases

We have used modifications of definition #2 (2+ ICD-9 diagnoses within 60 days) to identify cancer sites not originally validated. For example, we have used two ICD-9 codes to identify potential pancreatic cancer cases[176]. We have also previously attempted to identify

colon-only cancer cases (ICD-9 = 153.x within 60 days) with the motivation that colon cancer may have distinct etiology from rectal cancer with respect to a specific drugs exposure [177].

CHAPTER 4: SYNCHRONIZING FOLLOW-UP IN PHARMACOEPIDEMIOLOGIC STUDIES USING NEGATIVE CONTROL EXPOSURES: ANTIDEPRESSANTS AND CRC RISK

4.1 Background

Randomization, on average, balances measured and unmeasured patient characteristics across treatment arms. Therefore, randomized controlled trials (RCTs) provide the strongest evidence about the effects of drugs on disease outcomes. However, RCTs can be challenging to execute when evaluating cancer outcomes because of the potentially long period of follow-up time required to observe a sufficient number of events. We often thus rely upon observational studies, but non-user comparisons—the observational analog to an RCT placebo comparison—are susceptible to time-related biases [161, 178]. Although researchers have identified proxies for drug initiation in non-user groups (e.g., an office visit), a natural initiation time does not exist, and the mechanism to synchronize initiation times is not obvious. Failure to adequately synchronize the start of follow-up can lead to improper attribution of events to new user and non-user groups.

The frequency and intensity of interaction with the healthcare system (i.e., healthcare utilization) may also differ between initiators of a drug—new users [27]—and non-users. In the extreme case where a drug non-user simply does not interact with the healthcare system, we would be unable to identify asymptomatic cancers, leading to an underestimation of early events in non-user groups. Therefore, elevated cancer rates observed immediately following drug exposure compared to non-use may not represent a true relative effect of the drug on the development of cancer, but rather differential interaction with the healthcare system (i.e., outcome detection bias). New users must visit a healthcare provider to receive a prescription.

This interaction with the healthcare system could lead to event detection in users that would not be possible for non-users who lack interaction with the healthcare system.

Although an active comparator new user design is ideal for minimizing several sources of bias in pharmacoepidemiological studies [158], a natural active comparator does not always exist. Furthermore, when the goal of a study is to establish whether a drug exposure, compared to no exposure, is causally associated with an outcome, an active comparator design cannot be used. An alternative to the active comparator in a nonrandomized setting is to use a negative control exposure [179]—a drug or drug class that it assumed to have no association with the outcome. Using a negative control can reduce the potential for outcome detection bias and immortal time bias by synchronizing the start of follow-up for both treatment groups and by conditioning on an initial interaction with the healthcare system (e.g., the start of a new prescription medication). This study design has previously been used to evaluate the association between statins and lung, CRC and breast cancers, where the negative control exposure was anti-glaucoma medication [180].

As an empirical example illustrating the usage of a negative exposure control, we examined the associations between antidepressant (AD) classes (serotonin reuptake inhibitor (SSRI**)** initiators, tricyclic (TCA) antidepressant initiators, serotonin norepinephrine reuptake inhibitor (SNRI) initiators) compared with a negative exposure control (antihypertensive (AHT) initiators) and CRC. Antidepressants are commonly prescribed drugs**,** with an estimated 17% of Americans aged ≥65 reporting antidepressant use in a 2012 nationally representative survey [5]. The few epidemiological studies [21-26] examining the association between both SSRIs and TCAs, and CRC have produced conflicting results, and all studies compared antidepressant users to non-users.

Previous studies [21, 24] have excluded CRC cases occurring in the year following initiation to prevent protopathic bias (reverse causality). Latent CRC can cause symptoms mimicking depression, for example lethargy, weight loss, or gastrointestinal distress [101]. Thus, CRC cases diagnosed shortly after initiation of an AD may not be attributable to the AD itself, but could have been latent CRC with the physical symptoms of depression. Alternatively, relatively high CRC incidence, if observed shortly after drug initiation, could result from new users who have not been actively engaged with the healthcare system prior to drug initiation. These new users may experience a catch-up period of medical encounters, including diagnostic and cancer screening services, which we term “medicalization”. It would be from this catch-up period that a latent cancer is diagnosed. A secondary goal of this study is to test a hypothesis that CRC diagnoses in new users occurring shortly after drug initiation may in part be due to an increase in medical encounters in the time period proximal to the first AD or AHT prescription.

4.2 Methods

4.2.1 IRB approval (#14-1991) and CMS approval

This project was reviewed by the Institutional Review Board at the University of North Carolina, and data use was approved by the Centers for Medicare and Medicaid Services.

4.2.2 Selection of a negative control exposure

We chose AHT, excluding beta-blockers, as our negative control exposure, because there is no compelling evidence that their use is associated with CRC risk, and we anticipated a substantial number of initiators. We excluded beta-blockers, because there is evidence that their use could reduce cancer risk [100].

4.2.3 Data source and study population

We conducted a new user [158] cohort study of exclusive (class monotherapy) initiators of SSRIs, TCAs, SNRIs or AHTs, using a 20% random sample of Medicare fee-for-service (FFS) beneficiaries, aged ≥66 from 2007-2013.

All cohort members were aged ≥66 at the date of the first observable, dispensed prescription for an SSRI, SNRI, TCA, or AHT, and had ≥360 days of continuous enrollment in Medicare Parts A and B prior to the first (SSRI, SNRI, TCA, AHT) prescription to evaluate baseline covariates and clinical factors. Initiators also had ≥180 days of continuous part D enrollment, and no claims for an SSRI, SNRI, TCA, or AHT prior to the first prescription to restrict to "new" users of the medication class. They had no diagnoses or treatments associated with CRC in claims during the baseline assessment period to exclude prevalent cases, and a second claim for a medication within the same class as the initial claim occurring within the days' supply of the first claim date plus a grace period of 60 days. We chose 60 days as a grace period because initiators of these medication classes frequently augment or switch between drugs within the class. We used National Drug Codes (NDC) associated with formulations for the generic drugs listed in APPENDIX A to classify cohort members. The date of cohort entry was the date the second prescription was dispensed.

4.2.4 Outcome assessment

We identified non in-situ CRC events with an algorithm developed by Setoguchi et al [28]. This algorithm was defined as two or more *International Classification of Diseases, Ninth Revision* (ICD-9)—codes {153.x, 154.0,154.1, 154.2} present within 60 days. The date of diagnosis was the date of the first of the ≥2 diagnoses. This definition obtained high specificity, which is necessary to minimize bias in studies evaluating relative measures of association [105].

4.2.5 Covariate assessment

We evaluated covariates using claims for the 360 days preceding the date of the first prescription claim for an SSRI, SNRI, TCA, or AHT.

4.2.5.1 Demographics

Demographic information available in the baseline assessment period included: race (White, Non-Hispanic, Black, Non-Hispanic, Hispanic, Asian, Native American/Pacific Islander or Other), sex, and age at the first prescription (coded as a continuous variable).

4.2.5.2 Clinical factors and concomitant medications

ICD-9 diagnosis and procedure codes, Current Procedural Terminology (CPT) codes, or Healthcare Common Procedure Coding System (HCPCS) codes present in any claim during the baseline assessment period were used to identify clinical factors and comorbidities at the time of AD or AHT medication initiation. These covariates included: any potential non-CRC cancer diagnosis (e.g., breast cancer), obesity status (ICD-9 = 278,278.0,278.00,278.01), diabetes mellitus type 2 (ICD-9 = 250.xx), chronic obstructive pulmonary disease (ICD=496.0)—a proxy for current or past smoking [166], inflammatory gastrointestinal diseases (ICD-9=555.0-555.2,555.9,556.0-556.6,556.8,556.9), alcohol abuse indicators (ICD-9=303,303.9,303.90-303.93,305.0,305.00-305.03,535.3,535.30-535.31,571.0-571.3,V11.3), colonoscopy (coded as 0 or ≥ 1, APPENDIX C) anxiety (ICD-9=300,300.01,300.02,300.09) and depression (ICD-9=296.2, 296.20-296.26, 296.0,296.30-296.36, 298.0, 300.4,309.0,309.1,311). Individuals with ICD-9 diagnosis or procedure codes, or CPT or HCPCS procedure codes associated with CRC (ICD-9=V10.05, V10.06, 153,153.1-153.4,153.6-153.9, 154.0, 154.1,154.8;CPT = 3382F, 3384F, 3386F, 3388F, 3390F, G8371, G8372, G9085-G9095) during the baseline period were identified as having prevalent CRC, and were excluded from the cohort. Users of estrogen-based medications and non-steroidal anti-inflammatory drugs were identified as having ≥1 claim for a

drug the class in the baseline period. All medications used to classify cohort members are listed in APPENDIX A.

4.2.5.3 Confounding control

To control measured confounding, we used a propensity score (PS) approach that the weighted the covariate distribution of AHT initiators to reflect the covariate distribution of each of the AD class initiators, with the goal of estimating the "treatment effect in the treated" [172] . We sought to balance covariates across treatment groups and estimate an unconfounded association between the AD class (SSRI, SNRI, TCA) compared with AHT initiators and the risk of incident CRC. We ran three logistic regression models to estimate the predicted probability of initiating an AD class (SSRI, SNRI, TCA) compared with AHT initiators. We then weighted the AHT initiators to the baseline covariate distribution of each of the three AD classes (SSRI, SNRI, TCA) using a weight of PS/(1-PS) for AHT initiators and a weight of 1 for all AD class initiators, a procedure referred to as standardized morbidity ratio weighting (SMRW). We thus compared initiators of SSRIs, SNRIs, or TCAs each individually to AHT initiators. PS weighting methods were particularly useful in our study, because our comparator group was not an active comparator and we needed to evaluate the extent to which AD and AHT initiators differed at cohort entry, and how well covariates were balanced after SMRW.

4.2.5.4 Person-time at risk

Person-time and outcomes began accruing 180 days (i.e. empirical induction, lag) after the second prescription. We then followed individuals for up to 90 days after medication discontinuation to account for cases that might be attributable to drug exposure, but were detected after drug discontinuation (i.e. latent period). See Figure 5 for a general conceptualization of cohort entry and exit.

4.2.6 Statistical analysis

We estimated hazard ratios (HR) and robust 95% confidence intervals using three SMRW Cox proportional hazards models, one for each AD-AHT comparison. We censored individuals at the earliest of the date of the last prescription plus the days' supply plus the grace period plus the latent period parameter, date of death, date of Medicare parts A, B or D disenrollment, or the end of the study period (12/31/2013). We performed sensitivity analyses where we varied the amount of time between the second prescription and when person-time and events began accrual (180-730 days), and after medication discontinuation when person-time and events ceased accrual (0-360 days).

4.2.6.1 Description of medicalization

We examined if high CRC incidence immediately followed AD or AHT initiation by calculating the incidence stratified by time (0-90, 91-180, 181-360, 361-730, 731+) days and drug group (AHT versus AD classes). We tested the "medicalization" hypothesis by examining patterns of office visits in the 360 days prior to the first AD or AHT prescription and in the 60 days after the first prescription. If our hypothesis is in part true, then we expect that new users of any class, on average, will have fewer visits in the 360 days prior to the first prescription. If the CRC rate was high shortly after initiation, and the high rate was driven by depressive symptoms attributable to latent CRC that precipitated an AD prescription, then we would expect patterns of healthcare utilization to differ between the AD and AHT initiators. A strong assumption is that hypertension does not induce physical CRC-like symptoms.

Analytic cohorts were generated in SAS V9.3 (Cary, NC) and all statistical analyses were completed in R [181] version 3.14.

4.3 Results

We identified 830,609 initiators of SSRIs, SNRIs, TCAs, or AHTs initiators with no evidence use of the other medication classes in the 180 days prior to the date of the first prescription. Of these initiators, only 492,213 individuals had a second prescription and met age, enrollment and CRC-free status **(**Table 6**).** The number of cohort members was not evenly distributed across the AHT and AD users with far more individuals exclusively initiating an AHT (n=354,934) than the other classes (SSRI: n=72,630; SNRIs: n=11,155; TCAs: n=11,320). The median number of days of medication use after the second prescription (overall=315 days) varied across classes [AHT=340 days; SSRI= 247 days; TCA=166 days; SNRI=221 days].

Demographic characteristics and clinical factors differed by class (Table 6), but SMRW significantly improved the balance of covariates (Table 7). Initiators of an AD class were more likely to be white (~90% versus ~80%) and women (70% versus 57%) than AHT initiators. A smaller proportion of AHT and TCA initiators had an ICD-9 diagnosis code for anxiety or depression compared to SSRI or SNRI initiators during the baseline assessment period.

4.3.1 Primary analyses

We observed 1,341 CRC events in 480,087 person years (PY) (incidence = 279 per 100,000 PY) (Table 8), with incidence varying from 191 per 100,000 PY for SNRI initiators to 287 cases per 100,000 PY for AHT initiators. There was a small reduced rate of CRC for SSRI initiators compared with AHT initiators: aHR = 0.85 (0.71, 1.02). TCA and SNRI initiators had lower adjusted rates of CRC compared with AHT initiators; aHR = 0.86 95% CI = (0.54,1.39), aHR=0.86 (0.52,1.43), respectively, however estimates were less precise. Incidence was variable over time for all classes, and was generally highest in the first 90 days of follow-up (Figure 6), dropping sharply until approximately 180 days of use after the second prescription**.**

4.3.2 Medicalization and high short-term CRC rate

We examined our "medicalization" hypothesis by examining the pattern of office visits in the 360 days preceding the first prescription of an AD or AHT. With the exception of slight increases in office visits corresponding to approximately 6 month and yearly visits, generally, for all drug classes (Figure 7), cohort members had fewer office visits in the 360 days prior to the first prescription compared to the 30 days prior to and following the first prescription, indicating increased interaction with the healthcare system. This pattern was more pronounced among individuals diagnosed with CRC within the first 30 days after the second prescription compared to those diagnosed with CRC more than 180 days after the second prescription (Figure 8). Although a second prescription is necessary for cohort entry, increased healthcare interactions should begin occurring proximal to the first prescription.

4.4 Discussion

Our study goals were to: (1) examine the association between three AD classes (SSRIs, SNRIs, TCAs) and the risk of CRC compared to initiators of AHT (negative exposure control) for the years 2007-2013 among a cohort study of Medicare FFS beneficiaries aged ≥66 and (2) examine the "medicalization" phenomena by describing healthcare utilization in the time period before and after the first AD or AHT prescription. We found that all AD initiators had a reduced rate of CRC compared with AHT initiators, although the point estimates for the SNRI and TCA versus AHT comparisons were imprecise. We also provided some evidence for the "medicalization" phenomena by showing that, on average, initiators of both AD and AHT had a surge in physician encounters in the time proximal to the first prescription when compared to their physician encounters in the time before the first prescription.

We tested the stability of our results of the effects of AD on CRC risk by varying empirical induction and latent period assumptions (Figure 9). The adjusted association between SSRIs and CRC compared to AHT initiators did not vary dramatically as we varied either the

induction or latent parameters. For most analyses there was a small, reduced rate (5%-20%) of CRC among SSRI users compared with AHT initiators, with estimates falling between previously reported estimates [21-26]. There was little we could conclude about the SNRI-AHT and TCA-AHT association, because precision was poor, resulting from the small numbers of SNRI and TCA initiators and events.

This was the first study to evaluate class level associations between three AD classes and incident CRC in a North American cohort. We chose a negative control group of medication initiators to reduce time-related biases that may occur in a cohort study without start of follow-up synchronization. By using PS weighting confounding control methods, we were able to assess how well we balanced measured risk factors and confounders. Our study used high-quality exposure data (from pharmacy dispensing), and we used sensitivity analyses to assess the stability of our reported associations between a specific AD classes and CRC.

We chose AHT initiators as our negative control exposure, because there is no compelling evidence that, as a class, AHTs affect the risk of CRC, and we hypothesized that we would have a large number of initiators. However, there were marked differences between the AD cohorts and the AHT cohort on some key factors including sample size and follow-up time. A superior negative control would be one in which a smaller proportion of AD initiators had the likelihood to initiate the comparator class (to reduce loss of AD initiators). There were a substantial number of AD initiators who were ineligible for our study because they initiated both an AD and AHT. We were additionally unable to control for confounding by indication (depression in particular), although we argue that the likely association between depression or anxiety, and CRC—if any—would be positive, and by not fully accounting for this, our results are biased towards the null. Our reported estimates may represent an underestimation of the true association between AD and CRC.

Because our data lacked pathology confirmed CRC events, we used an algorithm to identify probable events. Although the definition we used reported high specificity (>99%) in the population in which it was developed, its performance in our population is unknown. Additionally, CRC risk factors can vary by molecular features of the tumor, for instance smoking and BRAF status [153], and our results represent the average effect of a drug class over all CRC tumors.

High CRC rates succeeded by a sharp drop after initiation mirrored our previous observations. We hypothesized this phenomena may be driven by “medicalization”, whereby new users of specific drugs had not been actively engaged in healthcare seeking activities until the first prescription. New users may then undergo a catch-up period of medical care, including screening and diagnostic tests, ultimately leading to a latent CRC diagnosis that is not attributable to drug effects. We may therefore be capturing either undiagnosed latent or prevalent cases as opposed to incident cases. Global healthcare utilization patterns in the year leading up to the first prescription paired with stronger patterns among CRC events diagnosed early compared with CRC events diagnosed later support our hypothesis. Because healthcare utilization patterns were similar between AD and AHT initiators we also have support that CRC symptoms masquerading as depression symptoms (reverse causality) may not fully explain the spike in CRC incidence. We have only speculated about and tested a few of the many unknown factors that may be driving this spike in CRC incidence after initiation.

4.5 Future directions

We recommend that future pharmacoepidemiologic studies with cancer outcomes should examine incidence rates after follow-up begins, and exclude all person-time and cancer events preceding the sharp incidence decline and flattening (e.g., 180 days in our study). Cancers diagnosed shortly after initiation, within a period of increased healthcare utilization following a new prescription, may have been diagnosable during the period of relatively reduced

interaction with the healthcare system prior to the first prescription, making them ineligible for the study. We also suggest that studies using a negative exposure control should compare patterns of healthcare utilization between the primary exposure groups and the control. Marked differences in utilization patterns may put the study at risk for outcome detection bias. Medicalization patterns, and their potential for bias in pharmacoepidemiologic studies, should be further examined in other drug exposure and disease outcome settings.

4.6 Tables

Table 6: Demographic characteristics of 492,213 people initiating a single class

	Medication class							
	AHT		SNRI		SSRI		TCA	
	N	%	N	%	N	%	N	%
Mean age (sd)	75.5 (7.5)		74.8 (7.4)		76.8 (8.2)		74.4 (7.0)	
66-69	94,890	26.7	3,527	31.6	17,822	24.5	3,436	30.4
70-74	92,798	26.1	2,804	25.1	16,140	22.2	3,189	28.2
75-79	66,659	18.8	1,913	17.1	12,590	17.3	2,079	18.4
80-84	50,564	14.2	1,475	13.2	11,448	15.8	1,446	12.8
85+	50,023	14.1	1,436	12.9	14,630	20.1	1,170	10.3
Sex								
Male	151,474	42.7	3,142	28.2	21,669	29.8	3,670	32.4
Female	203,460	57.3	8,013	71.8	50,961	70.2	7,650	67.6
Race [a]								
White	286,212	80.6	10,252	91.9	66,510	91.6	9,938	87.8
Black	34,209	9.6	325	2.9	2,327	3.2	468	4.1
Asian	11,176	3.1	183	1.6	943	1.3	325	2.9
Hispanic	12,977	3.7	235	2.1	1,710	2.4	315	2.8
Native American, Other, Unknown	10,360	2.9	160	1.4	1,140	1.6	274	2.4
Comorbidities [b]								
Depression [c]	5,948	1.7	1,575	14.1	7,873	10.8	447	3.9
Anxiety [c]	24,769	7.0	2,608	23.4	19,762	27.2	1,495	13.2
Diabetes	109,574	30.9	2,854	25.6	16,112	22.2	2,534	22.4
Inflammatory GI disorders	2,880	0.8	162	1.5	874	1.2	166	1.5
Previous Cancer [d]	54,784	15.4	2,283	20.5	13,032	17.9	2,248	19.9

COPD	57,443	16.2	2,191	19.6	14,990	20.6	1,958	17.3
Medications [e]								
NSAID use	65,162	18.4	3,552	31.8	15,320	21.1	3,387	29.9
Estrogen-based medication use	7,188	2.0	568	5.1	2,443	3.4	546	4.8
Screening								
Colonoscopy (Yes, 1+)	28,241	8.0	1,215	10.9	6,391	8.8	1,400	12.4

All AHT, SSRI, SNRI, TCA initiators had a second claim within the same class occurring within the days' supply + 60 data.

sd, standard deviation; COPD, smoking proxy;

[a] Race was entered as Black versus White/Other for propensity score calculation and weighting

[b] Comorbidities evaluated in the 360 days of part A/B enrollment up to the 1st prescription. Other variables used to estimate propensity score and SMR weights include: codes associated with chronic alcohol abuse, obesity status and calendar year of first prescription.

[c] not used in propensity score model. They were strong instruments and we wanted to reduce risk for bias (Patrick et al 2011) that can occur when including a strong instrument into PS model. Results with or without these variables were similar (Table 7, Table 8), but covariate balance was superior without depression or anxiety.

[d] All cancer diagnosis codes prior to the date of the 1st prescription except those for CRC.

[e] Medication use defined as any observed claim in the up to 360 days of part A/B enrollment up to the date of the first prescription.

Table 7: Balance of select covariates of application of weights.

	Comparison					
	SSRI-AHT		SNRI-AHT		TCA-AHT	
	SSRI	AHT	SNRI	AHT	TCA	AHT
N	55,833	55,892	8,424	8,424	8,324	8,325
Age	76.5	76.6	74.6	74.7	74.3	74.3
Race (%)						
Black	3.1%	3.1%	2.7%	2.7%	3.8%	3.8%
White/Other	96.9%	96.9%	97.3%	97.3%	96.2%	96.2%
Sex (%)						
Male	28.9%	28.8%	27.0%	27.3%	31.9%	31.9%
Female	71.1%	71.2%	73.0%	72.7%	68.1%	68.1%
Comorbidities (%)						
Obesity	4.2%	4.2%	5.8%	5.7%	4.3%	4.3%
Diabetes	21.8%	21.8%	25.3%	25.1%	22.3%	22.3%
Alcoholism	1.9%	1.9%	1.6%	1.7%	1.1%	1.1%
Inflammatory GI	1.3%	1.3%	1.5%	1.5%	1.5%	1.5%
Previous Cancer	17.1%	17.3%	20.1%	20.1%	19.4%	19.4%
COPD	19.6%	19.8%	19.2%	19.2%	17.0%	17.1%
Medications (%)						
NSAID use	21.1%	21.2%	31.3%	31.3%	29.8%	29.8%
Estrogen use	3.6%	3.6%	5.2%	5.2%	5.2%	5.2%
Screening (%)						
Colonoscopies	9.0%	9.0%	11.3%	11.3%	12.6%	12.6%

Represents covariate balance of individuals appearing in Table 7 analysis. Members of each antidepressant class were given weights of 1. Propensity scores (PS) were estimated by running three logistic regression models to estimate the predicted probability of antidepressant class use. AHT initiators given weight of: propensity score /(1-propensity score).

Table 8: The association between AD use and algorithm-identified CRC

Class	N	Median days followup[a] (Q1, Q3)	Events	Total PY	Incidence[a]	Unadjusted HR (95% CI)	Adjusted[bc] HR (95% CI)
AHT	290,958	330 (111, 786)	1,166	406,851.4	287	1.00	1.00
SNRI	8,424	193.5 (65, 484)	18	8,095.6	191	0.77 (0.49, 1.23)	0.86 (0.54, 1.39)
SSRI	55,833	225 (77, 544)	142	58,549.4	243	0.85 (0.71, 1.01)	0.85 (0.71, 1.02)
TCA	8,324	133 (50, 379)	15	6,590.8	228	0.79 (0.48, 1.32)	0.86 (0.52, 1.43)

[c] PS model does not include depression or anxiety status during baseline assessment period. See Table 8 for results that include depression and anxiety in PS model.

Table 9: Like Table 7 except excludes anxiety and depression in PS model.

Class	N	Median days followup[a] (Q1, Q3)	Events	Total PY	Incidence[a]	Unadjusted HR (95% CI)	Adjusted[b] HR (95% CI)
AHT	290,958	330 (111, 786)	1,166	406,851.4	287	1.00	1.00
SNRI	8,424	193.5 (65, 484)	18	8,095.6	191	0.77 (0.49, 1.23)	0.90 (0.54, 1.45)
SSRI	55,833	225 (77, 544)	142	58,549.4	243	0.85 (0.71, 1.01)	0.87 (0.74, 1.05)
TCA	8,324	133 (50, 379)	15	6,590.8	228	0.79 (0.48, 1.32)	0.86 (0.52, 1.43)

Person time and cases start accruing 180 days after the date of the second prescription fill and stop at date of the last observed prescription + the days supply + the grace period (60 days) + 90 days.

[a] per 100,000 persons.

[b] We used three SMRW Cox models with robust variance to estimate HRs and 95% CI. In each model, AHT initiators are weighted by PS/(1-PS). PSs are calculated for each AHT-AD comparison by calculating the probability of AD use.

4.7 Figures

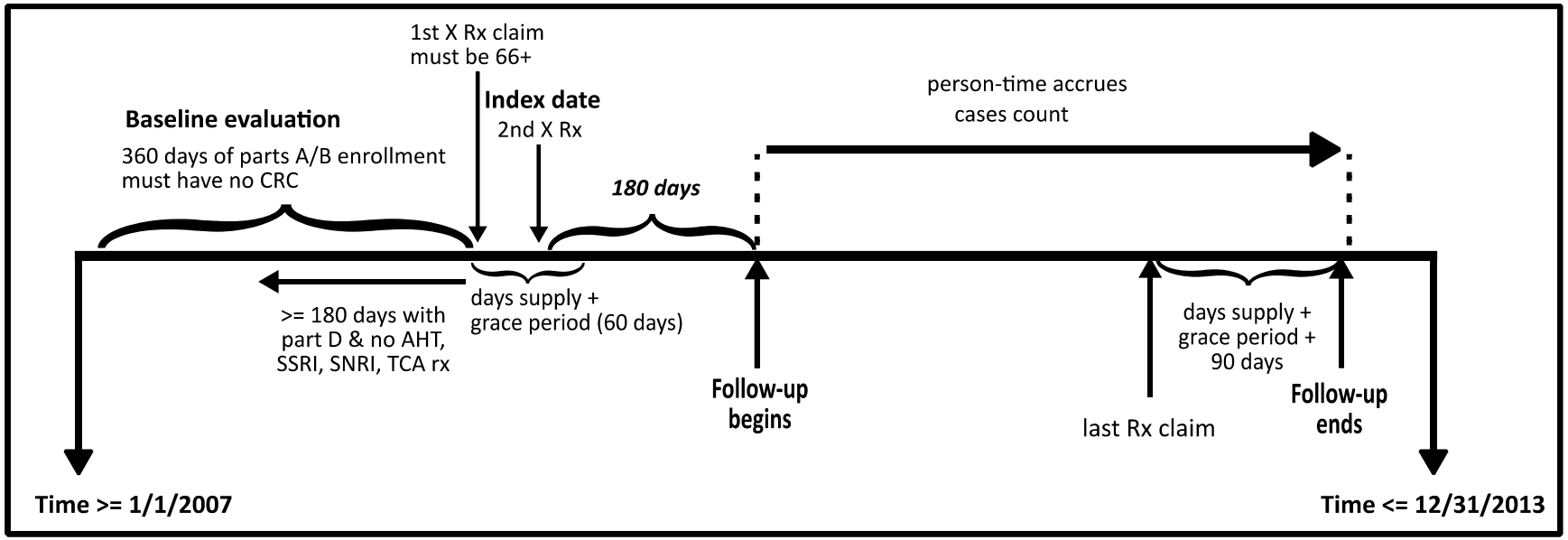

Figure 5: Conceptualization of entry/exit into AD class

In the primary analysis, person-time and cases begin accrual after 180 days (***empirical induction/lag/immune time)*** and continue accruing until 90 days after (***latent parameter)*** the date of the last prescription + the days supply + grace period (60 days). We vary person-time start and stop parameters in sensitivity analyses to evaluate the stability of associations between specific drugs and CRC. The lag period can be >= 0 days. The latent period is >= 0 days and <=360 days. The grace period = 30 days in all analyses. This is to allow for individuals not filling the prescription exactly as prescribed. Baseline parameters are evaluated prior to the first observable claim. Individuals must be age 66+ at the 1st prescription fill. A 2nd claim must be observed within the days supply + the grace period in order to be eligible for cohort entry. Person time and cases start accruing at the date of the 2nd prescription + (***empirical induction)*** parameter days. Person time ends at the first of (1) death; (2) 1st CRC algorithm identified case; (3) end of study period (12/31/2013); (4) disenrollment from Medicare parts A, B or D; (5) a date defined as the days supply plus + grace period + the (***latent)*** parameter beyond the date of the last prescription fill.

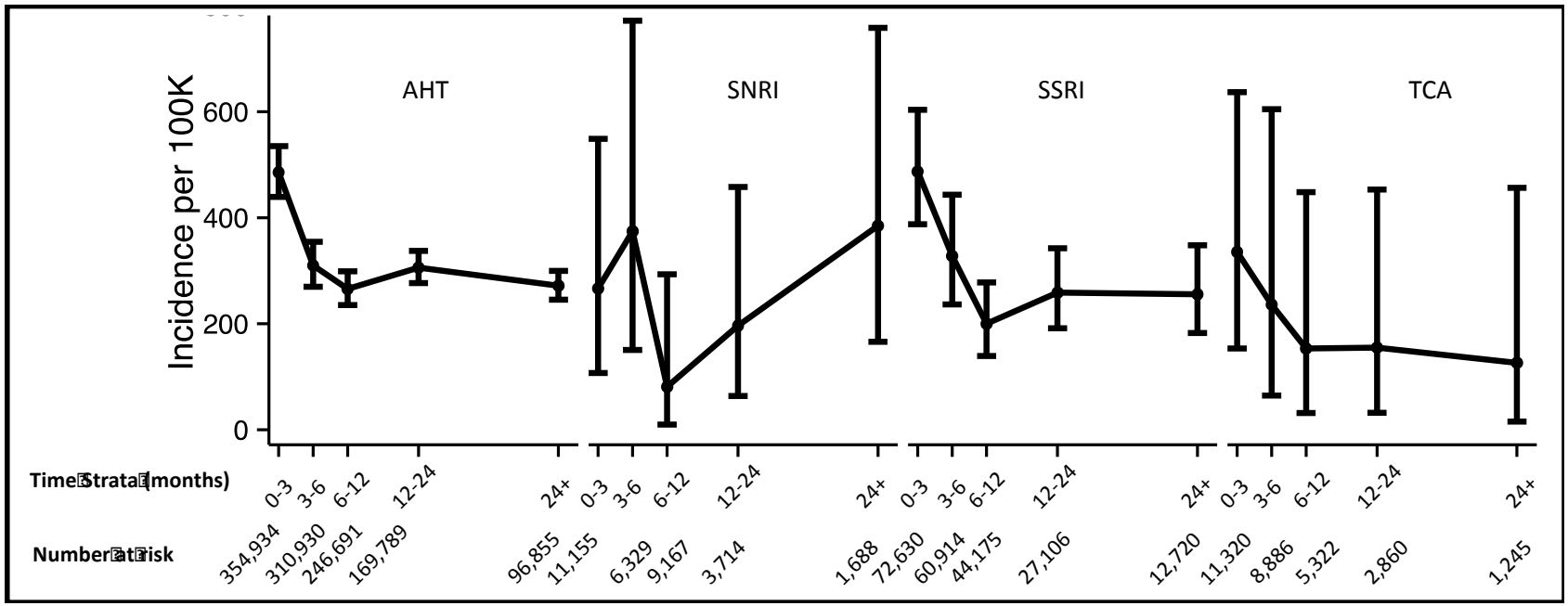

Figure 6: CRC incidence stratified by time and drug class.

All sub-images show incidence per 100,000 persons and 95% CI for all drugs (y-axis). The x-axis contains a tick mark for each time strata and the corresponding number of cohort members below. The incidence is generally highest in the first 0-6 months following the ***second prescription date*** **(time 0).** This helps to justify our (lag/empirical induction/immune time) assumptions of at least 180 days, such that person time and cases do not begin accruing until 180 days after the second prescription.

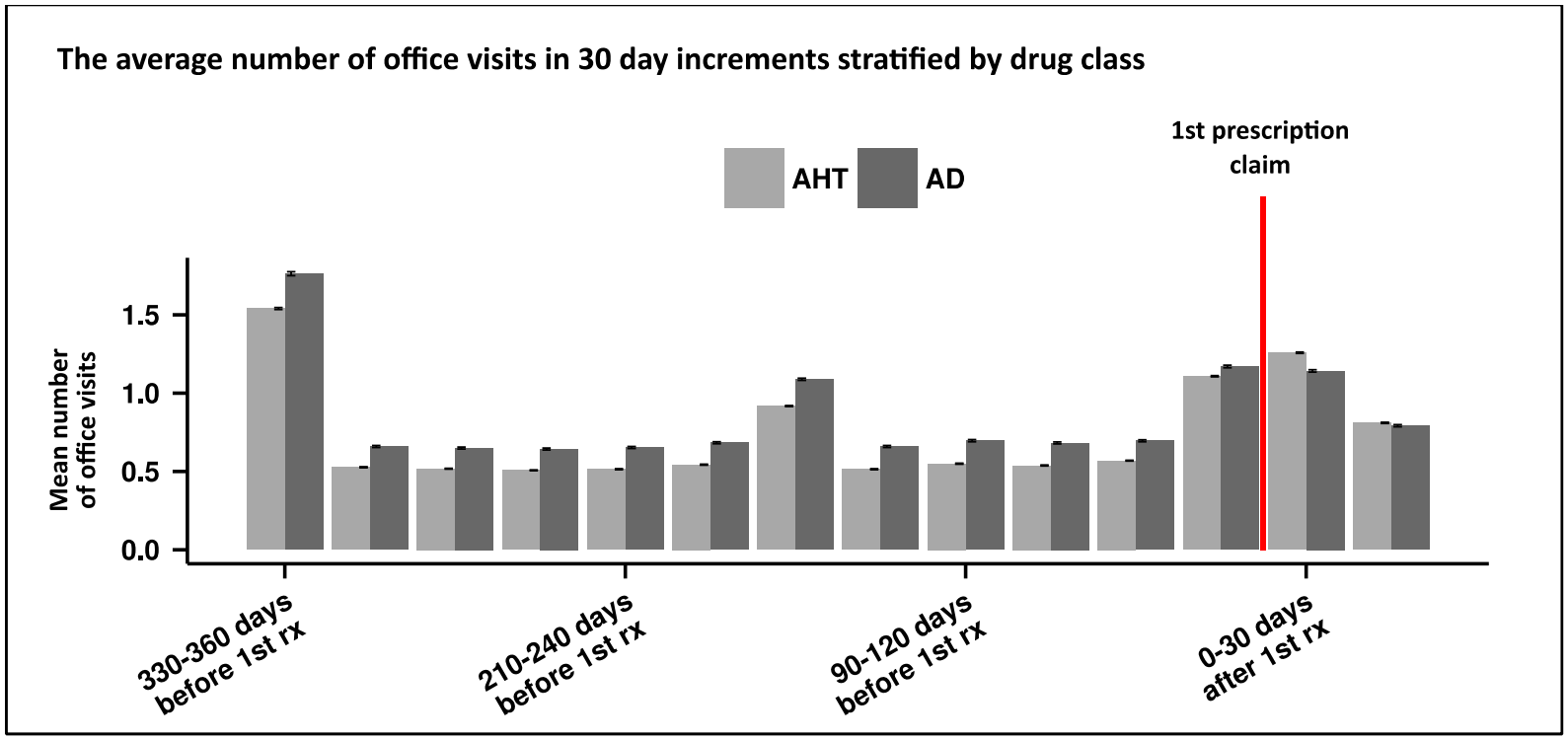

Figure 7: Average number of office visits stratified by medication class.

Bars represent average number of office visits and 95% CI stratified by AHT versus AD status. The bars are positioned at (y-axis) 30-day increments before the 1st prescription up to 360 days before the 1st prescription and up to 60 days after the 1st prescription.

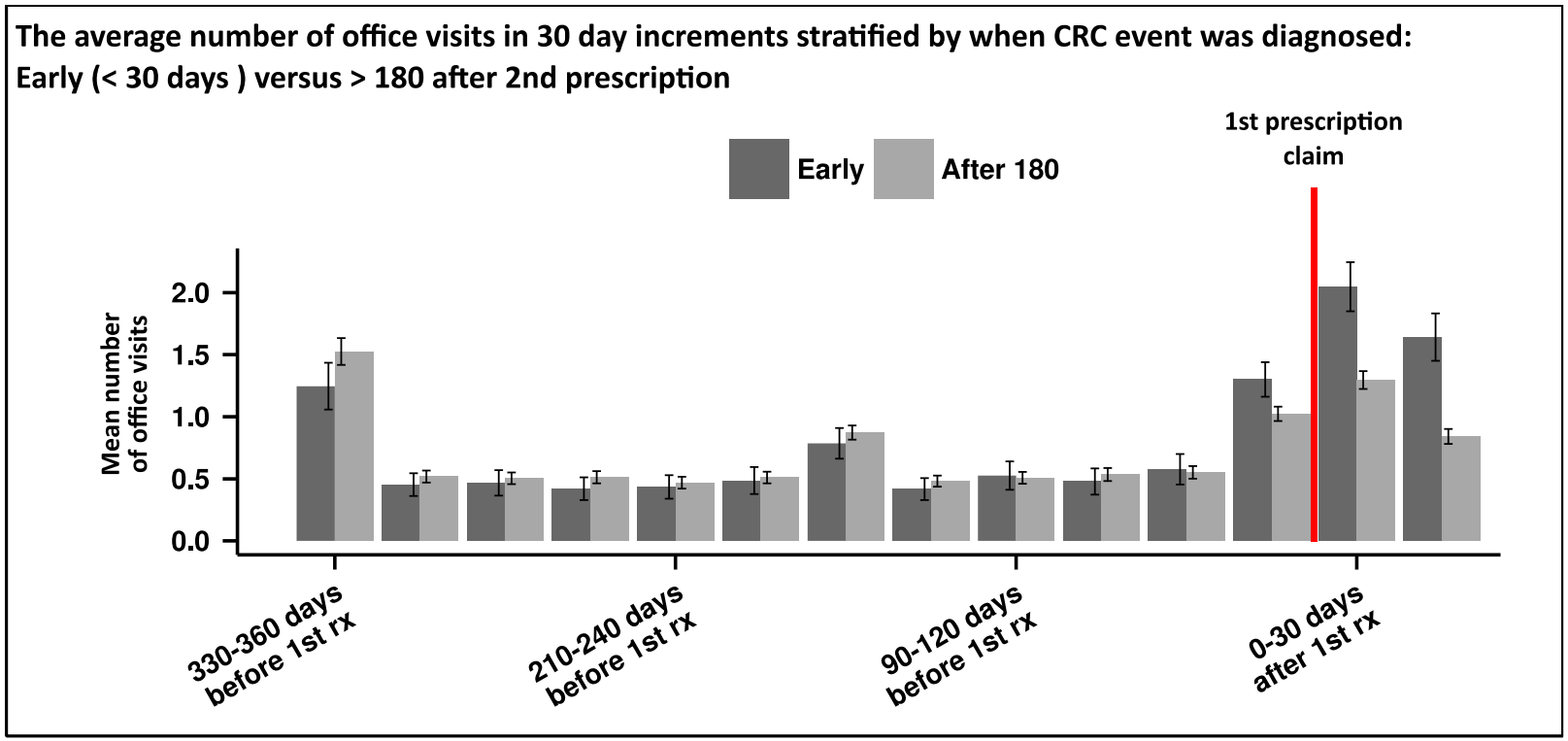

Figure 8: Average number of office visits among algorithm identified CRC cases.

Bars represent average number of office visits among algorithm-identified CRC events with a diagnosis date < 30 after the 2nd prescription or > 180 days after the 2nd prescription. The bars are positioned at (x-axis) 30-day increments before the 1st prescription up to 360 days before the 1st prescription and up to 60 days after the 1st prescription.

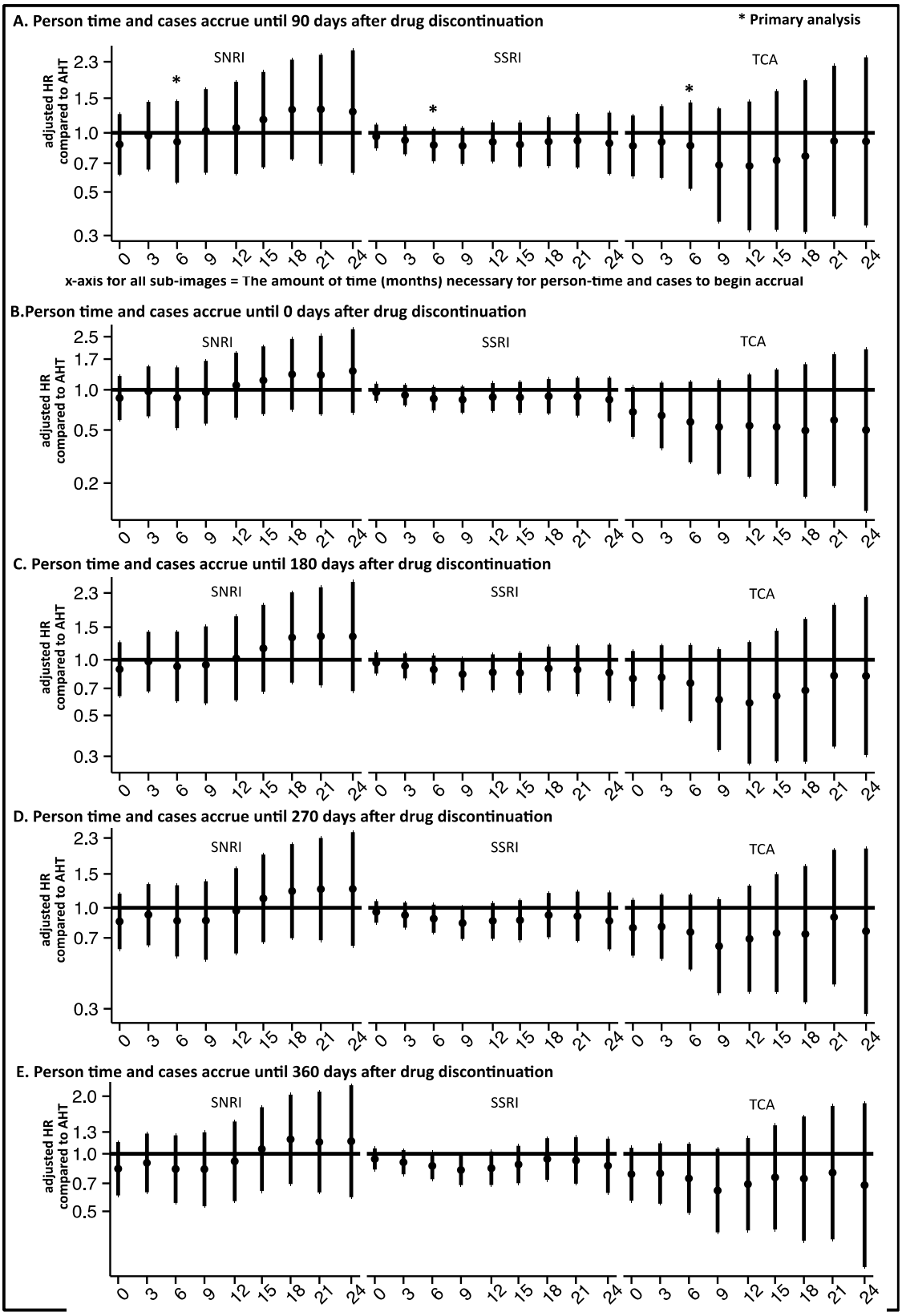

Figure 9: Sensitivity analyses with varying induction and latency assumptions.

All sub-images show HR and 95% CI comparing Antidepressant classes to Antihypertensive initiators. The x-axis for all images is the lag period in increments of ~ 3 months for a specific latent period. **Figure 9A:** Sensitivity analyses where the latent period = 90 days. The primary analyses occur at lag time = 180 days and are distinguished with a '*'. Person time and cases accrue until the date of the last prescription plus the days supply plus the grace period (60 days) plus 90 days. **Figure 9B:** Sensitivity analyses with latent period = 0 days. Person time and cases accrue until the date of the last prescription plus the days supply plus the grace period (60 days). **Figure 9C:** Sensitivity analyses with latent period = 180 days. Person time and cases accrue until the date of the last prescription plus the days supply plus the grace period (60 days) plus 180 days. **Figure 9D:** Sensitivity analyses where latency = 270 days. Person time and cases accrue until the date of the last prescription plus the days supply plus the grace period (60 days) plus 270 days. **Figure 9E:** Sensitivity analyses where latency = 360 days. Person time and cases accrue until the date of the last prescription plus the days supply plus the grace period (60 days) plus 360 days.

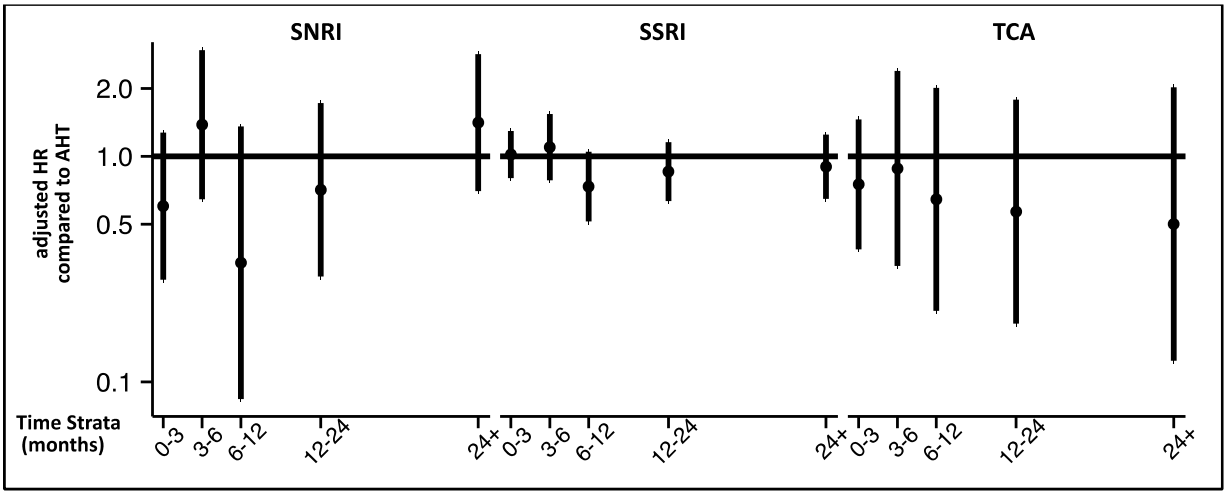

Figure 10: Adjusted hazard ratios stratified by time on AD class.

All sub-images show adjusted hazard ratios and 95% confidence intervals for SNRIs, SSRIs, TCAs compared AHT initiators during the following time: 0-3 months, 3-6 months, 6-12 months, 12-24 months, 24+ months. We used this to determine how well the proportional assumption held over time.

CHAPTER 5: SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND THE RISK OF COLORECTAL CANCER IN A COHORT OF MEDICARE BENEFICIARIES (2007-2013)

5.1 Background

Despite declines in incidence and mortality over the past 30 years, colorectal cancer (CRC) remains the second leading cause of cancer mortality in the United States [1], with almost 50,000 deaths expected in 2015 [2]. CRC treatment is expensive [3], and can be physically and emotionally draining [182]. Therefore, there is ongoing interest in identifying existing drugs and supplements with the potential to prevent this cancer [4].

Antidepressants are commonly used [5, 183] and well-tolerated drugs prescribed to treat a variety of conditions from depression and anxiety to neuropathic pain and menopausal hot flashes, with SSRIs being the most commonly prescribed antidepressant class [5]. Although SSRIs are primarily associated with regulation of central nervous system serotonin through selective binding to the serotonin reuptake transporter (SERT), both serotonin and SERT are present in the human colon [184], with serotonin playing an important role in motility. In animal models, fluoxetine, an SSRI, has been used and shown to modify extracellular SERT and serotonin concentration in the colon [54]. In-vivo evidence has shown that some, but not all, SSRIs may reduce experimental CRC tumor volume or growth [7, 9, 74], with one study reporting a superior benefit of sertraline, an SSRI, compared to doxorubicin, an antineoplastic drug, in HT29 cell-line xenografted mice [9]. If these anti-tumor properties are also active in precursor lesions, then some SSRIs may reduce CRC risk. These data also suggest that the associations between SSRIs and CRC could be drug- rather than class-specific.

Epidemiologic studies examining class level association between SSRIs and risk of CRC have produced inconsistent findings, with three studies reporting no association [23, 24, 26],

and the remaining studies reporting moderate (15%-45% reduction) inverse associations [21, 22, 25]. These studies relied on the comparison between antidepressant users to non-users or past users, design features that could lead to confounding by depression. Both stress and depression may accelerate cancer progression [29, 33, 103] and therefore potentially increase observed CRC incidence in SSRI users. Confounding by indication could therefore attenuate any protective effect. Furthermore, all previously published studies ignored the potential heterogeneity of specific SSRI effects. As a result, inconsistent findings from prior studies could be partially explained by different patterns of SSRI use and differential effects of specific SSRIs on CRC risk. For example, a study of SSRIs as a class based on a 1990 population would report an association heavily weighted to the effects of fluoxetine on CRC risk, because there were few other SSRIs on the market at that time. To examine whether specific SSRIs exhibit different effects on CRC risk, we compared the incidence of CRC across cohorts of older US adults initiating specific SSRIs using methods to reduce common sources of bias.

5.2 Methods

5.2.1 IRB approval (#14-1991) and CMS approval

This project was reviewed by the Institutional Review Board at the University of North Carolina, and data use was approved by the Centers for Medicare and Medicaid Services.

5.2.2 Data source and study population

We conducted an active comparator, new user [158], cohort study of initiators of specific SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, sertraline) using a 20% random sample of Medicare beneficiaries aged ≥66 years from 2007-2013 with simultaneous fee-for-service (FFS) parts A (hospital insurance), B (outpatient insurance), and D (pharmacy benefit) coverage for at least one month during a calendar year. Active comparator studies have been shown to reduce confounding by indication, because initiators of a given drug and initiators of a clinically-relevant alternative drug share indications for treatment, and are thus are generally more similar

across measured and unmeasured characteristics than patients without these indications [159, 160]. New user designs also remove time-related biases to which some observational drug-cancer studies are susceptible [161].

To evaluate baseline covariates, we required cohort members to be aged ≥66 years at the date of the first prescription claim for an SSRI and to have at least 360 days of continuous enrollment in Medicare Parts A and B prior to the first SSRI prescription. We also required, at least 180 days of part D and no claims for an SSRI prior to the first prescription to restrict to "new" users of the medication. Finally, we excluded anyone with evidence of CRC in the baseline assessment period to exclude potentially prevalent cases. These were individuals with any of the following *International Classification of Diseases, Clinical Modification, Ninth Revision* (ICD-9) diagnosis or current procedural terminology codes (CPT) procedure codes appearing in their claims in the baseline assessment period: ICD-9=V10.05, V10.06, 153,153.1-153.4,153.6-153.9, 154.0, 154.1,154.8;CPT = 3382F, 3384F, 3386F, 3388F, 3390F, G8371, G8372, G9085-G9095). We only excluded CRC cases, because cancer at other sites does not commonly metastasize to the colon or rectum [165]. Finally, we required a second prescription claim within the days' supply of the first claim plus a grace period of 30 days to increase the likelihood that the patient tolerated and consumed the drug. We used National Drug Codes (NDC) associated with formulations for the following generic drug names to generate the new user cohorts: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline. The date of cohort entry was the date the second prescription was dispensed.

5.2.3 Outcome assessment

We identified incident CRC events using an algorithm developed by Setoguchi et al [28]. For a CRC diagnosis, this algorithm required two or more ICD-9 inpatient or outpatient diagnosis codes {153.x, 154.0, 154.1, 154.2} within 60 days. The algorithm has high reported specificity (> 99%) and moderate sensitivity (84%) in the Medicare population in which it was

developed. The date of cancer diagnosis was defined as the date of the first diagnosis code observed in the claims.

5.2.4 Covariate assessment

We evaluated covariates using inpatient and outpatient diagnoses and procedure claims during the 360 days preceding the date of the first prescription claim for an SSRI. Because we only required 180 days of part D enrollment, we may have only 180 days of concomitant medication claims, but we included up to 360 days if available.

5.2.4.1 Demographics

Demographic information at baseline included age (coded as a continuous variable), sex and race as classified by CMS (White/not Hispanic, Black/not Hispanic, Hispanic, Asian, Native American/Pacific Islander or Other).

5.2.4.2 Clinical factors and concomitant medications

We identified potential clinical factors and comorbidities and cancer screening by the presence of one or more ICD-9 diagnosis or procedure codes present on any claim in any position during the baseline assessment period. These covariates included: (1) any potential non-CRC cancer diagnosis (e.g., breast cancer), (2) indicators of obesity (ICD-9 = 278,278.0,278.00,278.01 (3) type 2 diabetes mellitus (ICD-9 = 250.xx), (4) chronic obstructive pulmonary disease (COPD) (ICD=496.0), (5) inflammatory gastrointestinal diseases (ICD-9=555.0-555.2,555.9,556.0-556.6,556.8,556.9), (6) indicators of alcohol abuse (ICD-9=303,303.9,303.90-303.93,305.0,305.00-305.03,535.3,535.30-535.31,571.0-571.3,V11.3), (7) colonoscopy (coded as 0 or ≥ 1, APPENDIX C) (8) anxiety (ICD-9=300,300.01,300.02,300.09) and (9) depression (ICD-9=296.2, 296.20-296.26, 296.0,296.30-296.36, 298.0, 300.4,309.0,309.1,311). COPD was used as a proxy for smoking status [166]. We identified users of estrogen-based medications and non-steroidal anti-inflammatory drugs (NSAIDs) as

those with ≥1 claim for a drug in that class in the baseline period. All generic medication names used to classify cohort members are listed in APPENDIX A.

5.2.4.3 Confounding control

Citalopram was chosen as the referent group because it had the largest number of initiators. We controlled measured confounding using a propensity score (PS) weighting approach such that the distributions of measured covariates in the non-referent groups (escitalopram, fluoxetine, paroxetine, sertraline) were standardized to the covariate distribution of the citalopram initiators. The goal of PS weighting is to balance covariates across treatment groups and estimate unconfounded associations between specific SSRIs (compared with citalopram) and incident CRC. We ran four separate logistic regression models to estimate the PS for initiating each non-referent SSRI drugs versus citalopram based on measured covariates. We then weighted the non-referent initiators to the baseline covariate distribution of the citalopram initiators with (1-PS)/PS, a variant of standardized morbidity ratio weighting (SMRW) when there are more than two non-referent groups [173]. Citalopram initiators were given a weight of 1. Although multivariable regression has been shown to produce similar results to PS weighting methods [167], PS methods allow researchers to evaluate how well covariates are balanced across treatment groups before and after weighting, and thus to examine PS model performance.

5.2.4.4 Person-time at risk

We implemented a variation of the “disease induction” and “latent” concepts defined by Rothman [174] to specify person-time at risk. The induction period is the time from the start of a specific exposure from which malignant transformation begins until the occurrence of cancer, while the latent period is the time in which a cancer is present but not yet detected. It is impossible to precisely identify when cancer induction has ended and latent period begun. We therefore commonly merge the two concepts into the term “empirical induction”, the time from

cancer initiation to a detectable cancer. In the context of this study we use “empirical induction” to mean the time from drug exposure to an algorithm identified CRC case. However, we also assumed that there would be some minimum time after drug initiation before observable effects could reasonably be expected to occur (immune time). We set this interval at 180 days after the second prescription. Because the interval between drug use and incident CRC was on the order of months and not years in our study, our study tests the hypothesis that SSRI effects may occur during later stages of carcinogenesis, preventing transition of an adenoma to invasive disease.

We censored individuals at the earliest of: the date of the last prescription plus the days’ supply plus 30 days to allow for imperfect adherence plus 90 days; date of death; date of Medicare parts A, B or D disenrollment, or the end of the study period (12/31/2013). We continued to follow individuals for up to 90 days after drug discontinuation or augmentation (latent period) to account for cases that may be attributable to drug use, but whose tumor remained undetected at SSRI cessation. Figure 11 illustrates general conceptualization of cohort entry and exit.

5.2.5 Statistical analysis

We estimated hazard ratios (HRs) and robust 95% confidence intervals with one SMR-weighted Cox proportional hazards model using four sets of weights, one for each non-referent group. To evaluate the stability of associations, we performed sensitivity analyses in which we varied the amount of time: (1) between the second prescription and the beginning of accrual of person-time (180-730 days) and (2) between medication discontinuation and the cessation of person-time accrual (0-360 days). We examined the proportional hazards assumption by stratifying by time since initiation and visually inspecting changes in HR. Analytic cohorts were generated in SAS V9.3 (Cary, NC) and all statistical analyses were conducted in R version 3.14 [181].

5.3 Results

We identified 752,509 initiators of an SSRI with no evidence of SSRI use in the 180 days prior to the date of the first prescription. Of these initiators, 375,610 individuals had a second prescription and met age, enrollment and CRC-free status at that point in time (Table 10, Figure 13). The median number of days of medication use after the second prescription was similar for all groups, varying from 180 days for users of escitalopram to 211 days for users of citalopram.

Demographic characteristics and clinical factors were similar at baseline across cohorts (Table 10), and weighting further improved the overall balance of covariates (Table 11**).** The majority of initiators were white (~90%) and female (~75%). The average age was 78 years, and approximately 18% of the population had evidence of a non-CRC cancer diagnosis prior to the first prescription. There were 2,422 CRC events among cohort-eligible individuals. Cancer rates were not uniform over follow-up time (Figure 12) and 50% of CRC cases occurred within 448.5 days after the second prescription, (Q1=158; Q3=848.75; range=1-2096).

5.3.1 Primary analyses

In our primary analysis, we observed 602 CRC cases in 238,359 PY, an overall incidence of 253 per 100,000 PY (Table 12). The crude incidence rates varied between 190 per 100,000 PY for fluoxetine and 271 cases per 100,000 PY for citalopram. Paroxetine and fluoxetine had lower adjusted HRs (aHR) compared with citalopram: aHR = 0.78, (95% CI: 0.56,1.07) and aHR = 0.74 (95% CI: 0.52,1.05), respectively. Adjusted rates of CRC among escitalopram and sertraline users were similar to those for citalopram users; aHR = 0.95 (95% CI: 0.76, 1.24) and aHR = 0.91 (95% CI: 0.74, 1.11), respectively**.**

5.3.2 Sensitivity Analyses

To evaluate the influence of exposure timing and tumor latency on observed associations, and to describe any patterns that emerged, we implemented a series of sensitivity

analyses to examine the stability of the associations between specific SSRI medications and CRC. In almost all sensitivity analyses (Figure 14**),** paroxetine, fluoxetine and escitalopram initiators had lower adjusted rates CRC compared with citalopram initiators. Some of the SSRI-CRC associations varied qualitatively in our sensitivity analyses. For example, as we increased the time between the second prescription and when follow-up began from 180-730 days (essentially a proxy for duration of use), the relative association between escitalopram use and CRC compared with citalopram went from no association to almost a 50% reduction, whereas the relatively reduced rate of CRC comparing fluoxetine or paroxetine to citalopram remained fairly constant. CRC rates did not vary between sertraline and citalopram in any sensitivity analyses. Varying the time for CRC accrual after SSRI discontinuation from 0-360 days did not qualitatively change any patterns. The proportional hazards assumption (Figure 15) generally held after 180 days**.**

5.4 Discussion

In this active comparator, new user cohort study of older US adults aged 66 and older, we hypothesized that initiation of specific drugs within the SSRI class may reduce CRC risk compared to other SSRIs. Both paroxetine and fluoxetine users had a slightly lower rate of CRC compared with citalopram users, 22% and 26% lower respectively, although the associations were not statistically significant in the primary analysis. These protective associations (compared to citalopram) between paroxetine or fluoxetine use and CRC were fairly robust to our assumptions about the duration of use (Figure 14). Although escitalopram and citalopram were not differentially associated with CRC in our primary analysis, escitalopram showed stronger protective associations as we increased accrual time, such that after 2 years of use, there was almost a 50% reduction in CRC rates among escitalopram initiators compared with citalopram initiators.

These findings compare effects by drug, within a class, but interpretation is facilitated by our recent observation of a small, non-significant reduced rate of CRC among SSRI initiators as a class compared to a negative control initiators in a similar population [177]. Because the class is predominately comprised of citalopram and sertraline initiators (~60%), and relative CRC rates did not vary between citalopram and sertraline initiators, we do not suspect that our referent medication, citalopram, increases the risk of CRC. Therefore, the relative reduction of CRC rates for non-citalopram SSRIs we observed support our hypothesis that inherent differences of drugs within the SSRI class could have contributed to variability in the results of previously reported studies [21-26].

This analysis had several strengths. Examination of drug-specific rather than class level effects was a novel contribution of this study, made feasible by substantial sample size, excellent exposure ascertainment, and a relatively high risk of CRC in the source population. Our use of an active comparator, new user cohort study design is a strength, because this design reduces unmeasured confounding, confounding by indication, and time-related biases [178]. Time-related biases have previously led to false and sensational drug-cancer associations [185, 186]. By implementing PS weighting methods we have ensured balance of measured covariates across treatment groups. Finally, we assessed the stability of associations by using sensitivity analyses. Sensitivity analyses also gave us some insight into empirical induction periods by varying our assumptions about timing between exposure and outcome (Figure 14). We have deliberately chosen not to adjust for multiple comparisons, because we present all analyses we conducted, and because we are interested in estimation rather than hypotheses testing [187]. Our choice of primary empirical induction and latency parameters was somewhat arbitrary given our hypothesis of generally late acting effects.

Our findings are subject to limitations. Because we used claims data to maximize sample size and exposure ascertainment, we had to rely on algorithms to identify probable CRC

events, and thus did not have access to pathologically confirmed outcomes. However, the claims-based algorithm that we used was reported to have high specificity for identifying CRC in a Medicare population, and a high specificity definition minimizes bias of relative measures of association [105]. Without pathology information, we cannot report molecular tumor characteristics. Our results represent the average effect of a particular drug on all CRC tumors, and thus we can only capture SSRI-CRC associations that have strong associations in subgroups of tumors or weaker associations that impact a large proportion of tumors. Our study also only included older, Medicare FFS Americans enrolled in Part D. It did not include Medicare beneficiaries who are enrolled in Medicare Advantage plans, those who elect to purchase generic drugs outside of the Medicare system (i.e., out-of-pocket), or those younger than 65.

5.5 Conclusion

In this large cohort study among older adults, we present evidence that SSRIs may vary in their chemopreventive effectiveness against CRC. SSRIs are commonly used, inexpensive and generally well tolerated. Our results warrant further investigation (including mechanistic studies) into the SSRI-CRC association. Incorporating longer-term follow-up will help to clarify the signal, but it will not elucidate the mechanisms. Finally, we believe this study design could serve as a cost-effective and timely framework for identifying other potential chemopreventive drugs, especially as more years of Medicare Part D data become available.

5.6 Tables

Table 10: Demographic characteristics for 375,610 SSRI initiators.

		Medication [a]									
		citalopram N = 122,335		**escitalopram** N = 80,076 (21.3)		**paroxetine** N = 34,026 (9.1)		**fluoxetine** N = 36,372 (9.7)		**sertraline** N =102,801 (27.4)	
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Mean age (sd)		78.2 (8.2)		78.5 (8.1)		77.2 (7.9)		75.8 (7.7)		78.3 (8.1)	
	66-69	22,635	18.5	13,666	17.1	7,290	21.4	9,875	27.2	17,815	17.3
	70-74	25,004	20.4	16,172	20.2	7,512	22.1	8,975	24.7	21,048	20.5
	75-79	22,496	18.4	14,958	18.7	6,570	19.3	6,658	18.3	19,382	18.9
	80-84	22,144	18.1	14,904	18.6	5,859	17.2	5,232	14.4	18,968	18.5
	85+	30,056	24.6	20,376	25.4	6,795	20.0	5,632	15.5	25,588	24.9
Sex											
	Male	34,738	28.4	22,468	28.1	9,588	28.2	10,727	29.5	29,891	29.1
	Female	87,597	71.6	57,608	71.9	24,438	71.8	25,645	70.5	72,910	70.9
Race [b]											
	White	110,029	89.9	69,844	87.2	29,418	86.5	32,536	89.5	90,643	88.2
	Black	7,017	5.7	4,504	5.6	1,812	5.3	1,594	4.4	5,867	5.7
	Asian	1,131	0.9	1,334	1.7	762	2.2	544	1.5	1,602	1.6
	Hispanic	2,520	2.1	3,098	3.9	1,445	4.2	1,032	2.8	3,042	3.0
	Native American, Other, Unknown	1,638	1.3	1,296	1.6	589	1.7	666	1.8	1,647	1.6
Comorbidities [c]											
	Depression	14,083	11.5	12,376	15.5	3,532	10.4	4,716	13.0	11,360	11.1
	Anxiety	34,767	28.4	23,299	29.1	11,167	32.8	8,963	24.6	28,437	27.7
	Diabetes	45,826	37.5	31,349	39.1	12,673	37.2	13,572	37.3	38,911	37.9
	Inflammatory GI disorders	1,496	1.2	1,126	1.4	433	1.3	415	1.1	1,252	1.2

Previous Cancer [d]	21,559	17.6	15,607	19.5	5,885	17.3	6,212	17.1	18,993	18.5
COPD	30,219	24.7	20,314	25.4	8,645	25.4	8,349	23.0	24,676	24.0
Medications [e]										
NSAID use	28,909	23.6	20,968	26.2	8,833	26.0	9,492	26.1	24,801	24.1
Estrogen-based medication use	3,880	3.2	2,895	3.6	1,242	3.7	1,440	4.0	3,200	3.1
Screening										
Colonoscopy (Yes, 1+)	11,052	9.0	7,881	9.8	3,353	9.9	3,733	10.3	9,475	9.2

sd, standard deviation; COPD is a smoking proxy

[a] All cohort members had a second claim for single SSRI that met age, continuous enrollment, and CRC-free status during the baseline assessment period. There were too few fluvoxamine initiators to make any comparisons (N = 671 at second claim), so they were excluded from all analyses.

[b] Race was entered as Black versus White/Other for propensity score calculation and weighting

[c] Comorbidities evaluated in the 360 days of part A/B enrollment up to the first prescription. Other variables used to estimate propensity score and SMR weights include: codes associated with chronic alcohol abuse, obesity status and calendar year of 1st prescription.

[d] All cancer diagnosis codes prior to the date of the 1st prescription except those for CRC.

[e] Medication use defined as any observed claim in the up to 360 days of part A/B enrollment up to the date of the first prescription.

Table 11: Balance of select covariates after PS weighting.

	Medication				
	citalopram	**escitalopram**	**paroxetine**	**fluoxetine**	**sertraline**
N	86,832	86,804	86,815	86,817	86,832
Age	77.9	77.8	77.9	77.9	77.9
Race (%)					
Black	5.5%	5.5%	5.5%	5.6%	5.5%
White/Other	94.5%	94.5%	94.5%	94.4%	94.5%
Sex (%)					
Male	27.6%	27.6%	27.5%	28.0%	27.6%
Female	72.4%	72.4%	72.5%	72.0%	72.4%
Comorbidities (%)					
Depression	11.5%	11.5%	11.5%	11.3%	11.4%
Anxiety	27.8%	27.8%	27.8%	27.7%	27.8%
Diabetes	37.1%	37.1%	37.1%	37.2%	37.0%
Inflammatory GI	1.2%	1.2%	1.2%	1.2%	1.2%
Previous Cancer	16.7%	16.7%	16.7%	16.8%	16.7%
COPD	23.4%	23.3%	23.4%	23.8%	23.4%
Medications (%)					
NSAID use	23.6%	23.7%	23.8%	23.9%	23.6%
Estrogen use	3.3%	3.4%	3.4%	3.4%	3.3%
Screening (%)					
Colonoscopy (Yes, 1+)	9.2%	9.3%	9.1%	9.2%	9.2%

Non-citalopram users weighted with (1-propensity score)/propensity score. Citalopram users are the referent group and given a weight of 1. This is weighting of individuals appearing in the primary analysis (Table 10). Propensity scores (PS) were estimated by running four logistic regression models to estimate the predicted probability of each of the non-referent SSRI drugs compared to citalopram. *NOTE: This is not the only way to weight. Alternatively, four logistic regressions can be run to predict the probability of citalopram use. Non-referent groups would then be given a weight of PS/(1-PS). Results would be identical.*

Table 12: The association between SSRIs and incident CRC

Drug	N	Median followup [a] (Q1, Q3)	Events	Total PY	Incidence [b]	Unadjusted HR (95% CI)	Adjusted [c] HR (95% CI)
citalopram	86,832	213 (68, 498)	223	82,323.8	271	1	1
escitalopram	53,815	174 (61, 425)	125	46,506.2	269	0.99 (0.80, 1.23)	0.95 (0.74, 1.24)
paroxetine	23,427	188 (62, 470)	48	21,705.2	221	0.82 (0.60, 1.12)	0.78 (0.56, 1.07)
fluoxetine	25,045	180 (60, 444)	42	22,112.6	190	0.70 (0.50, 0.97)	0.74 (0.52, 1.05)
sertraline	70,062	199 (64, 482)	164	65,711.4	250	0.92 (0.75, 1.13)	0.91 (0.74, 1.11)

*Primary analysis assumes induction-latent period = 180 days; latent period = 90 days. Person time starts accruing 180 days after the date of the 2nd prescription fill and stops accruing person time at date of the last observed prescription + the days supply + the grace period (30 days) + 90 days.

[a] per 100,000 persons.

[b] We used one SMR weighted Cox model with robust variance to estimate HRs and 95% CIs. Non-referent groups are weighted by (1-propensity score)/propensity score; citalopram users given a weight of 1

5.7 Figures

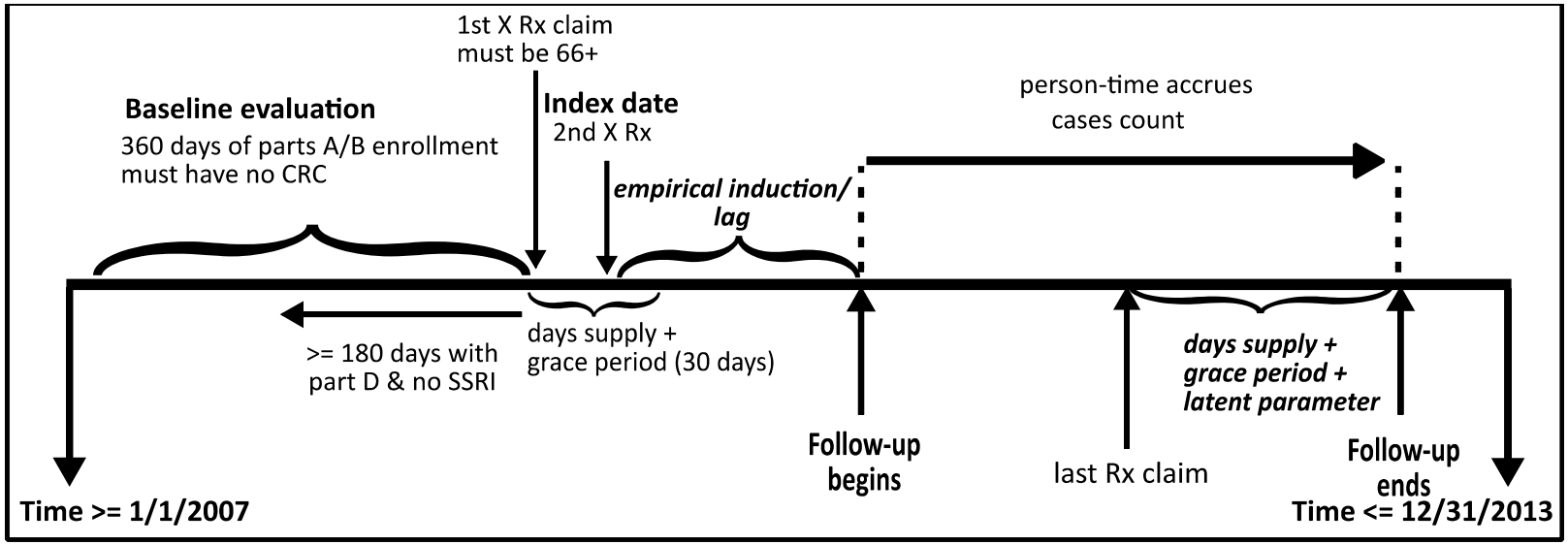

Figure 11: Conceptualization of entry/exit into specific SSRI cohort

In the primary analysis, person-time and cases begin accrual after 180 days (***empirical induction/lag/immune time)*** and continue accruing until 90 days after (***latent parameter)*** the date of the last prescription + the days supply + grace period (30 days). We vary person-time start and stop parameters in sensitivity analyses to evaluate the stability of associations between specific drugs and CRC. The (lag/empirical induction/immune time) period can be >= 180 days. The latent period is >= 0 days and <=360 days. The grace period = 30 days in all analyses. This is to allow for individuals not filling the prescription exactly as prescribed. Baseline parameters are evaluated prior to the first observable claim. Individuals must be age 66+ at the 1st prescription fill. A 2nd claim must be observed within the days supply + the grace period in order to be eligible for cohort entry. Person time and cases start accruing at the date of the 2nd prescription + (***empirical induction/lag/immune time)*** parameter days. Person time ends at the first of (1) death; (2) 1st CRC algorithm identified case; (3) end of study period (12/31/2013); (4) disenrollment from Medicare parts A, B or D; (5) a date defined as the days supply plus + grace period + the (***latent)*** parameter beyond the date of the last prescription fill.

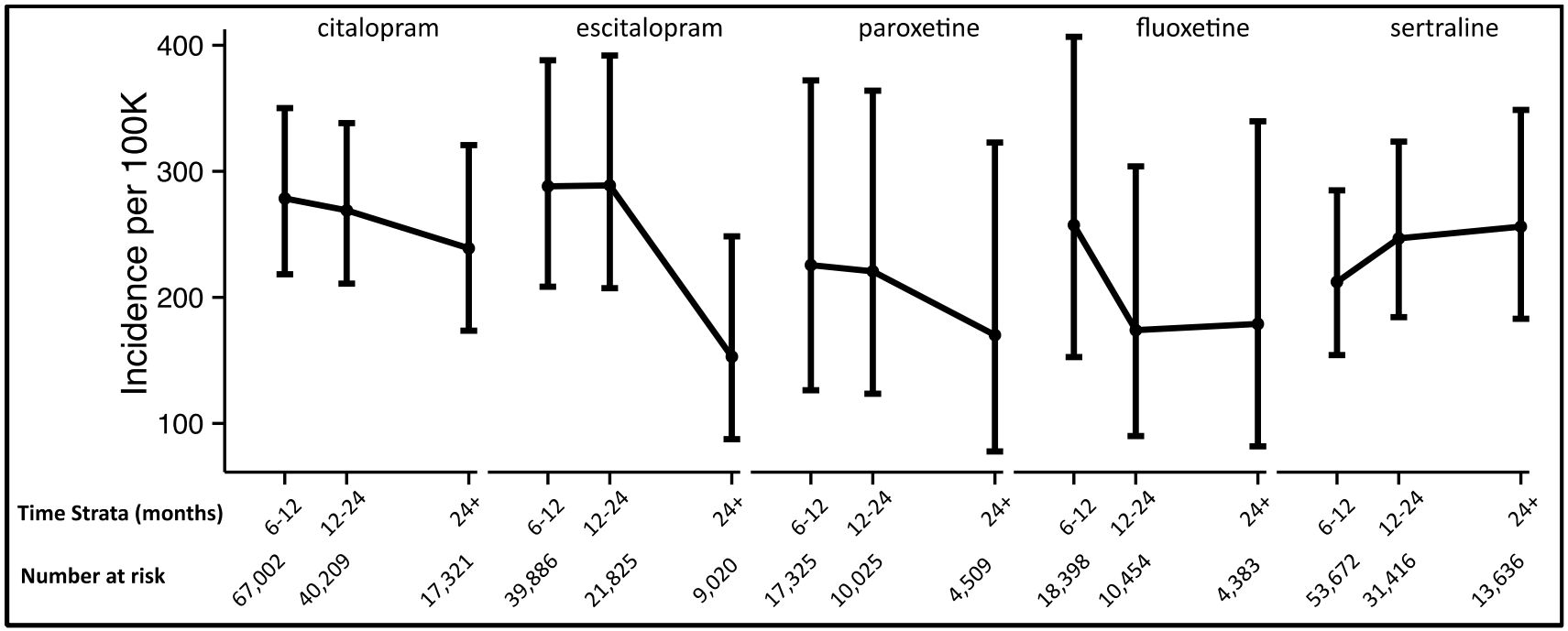

Figure 12: Incidence over time for each SSRI.

All sub-images show incidence per 100,000 persons and 95% CI for all drugs (y-axis). The x-axis contains a tick mark for each time strata (since the second prescription) and the corresponding number of cohort members below. The incidence was highest in the first 0-6 months after the second prescription (data not shown).

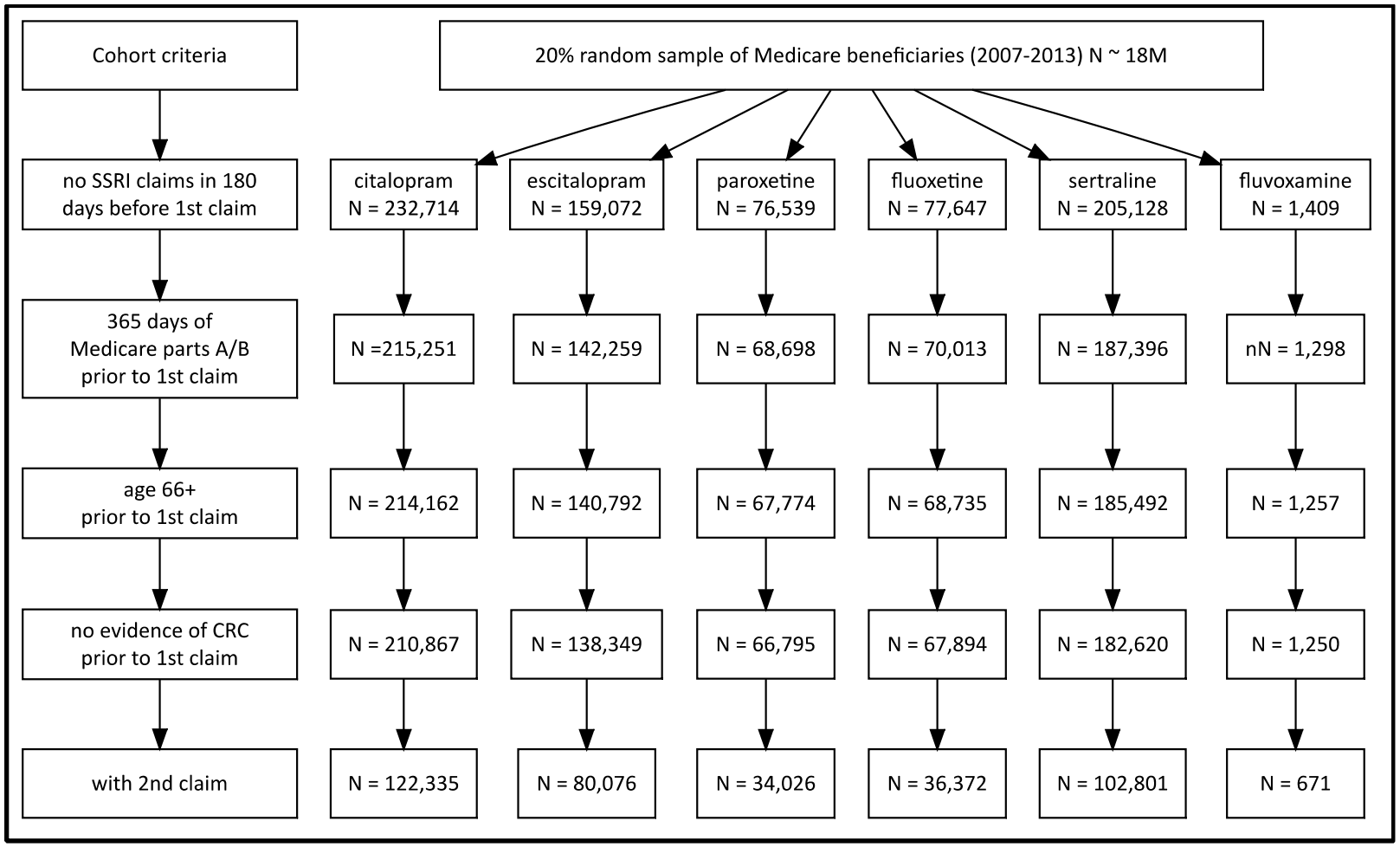

Figure 13: Flowchart of SSRI initiator loss

This image shows how the number of cohort members drops for each group as exclusion criteria are sequentially applied to each cohort.

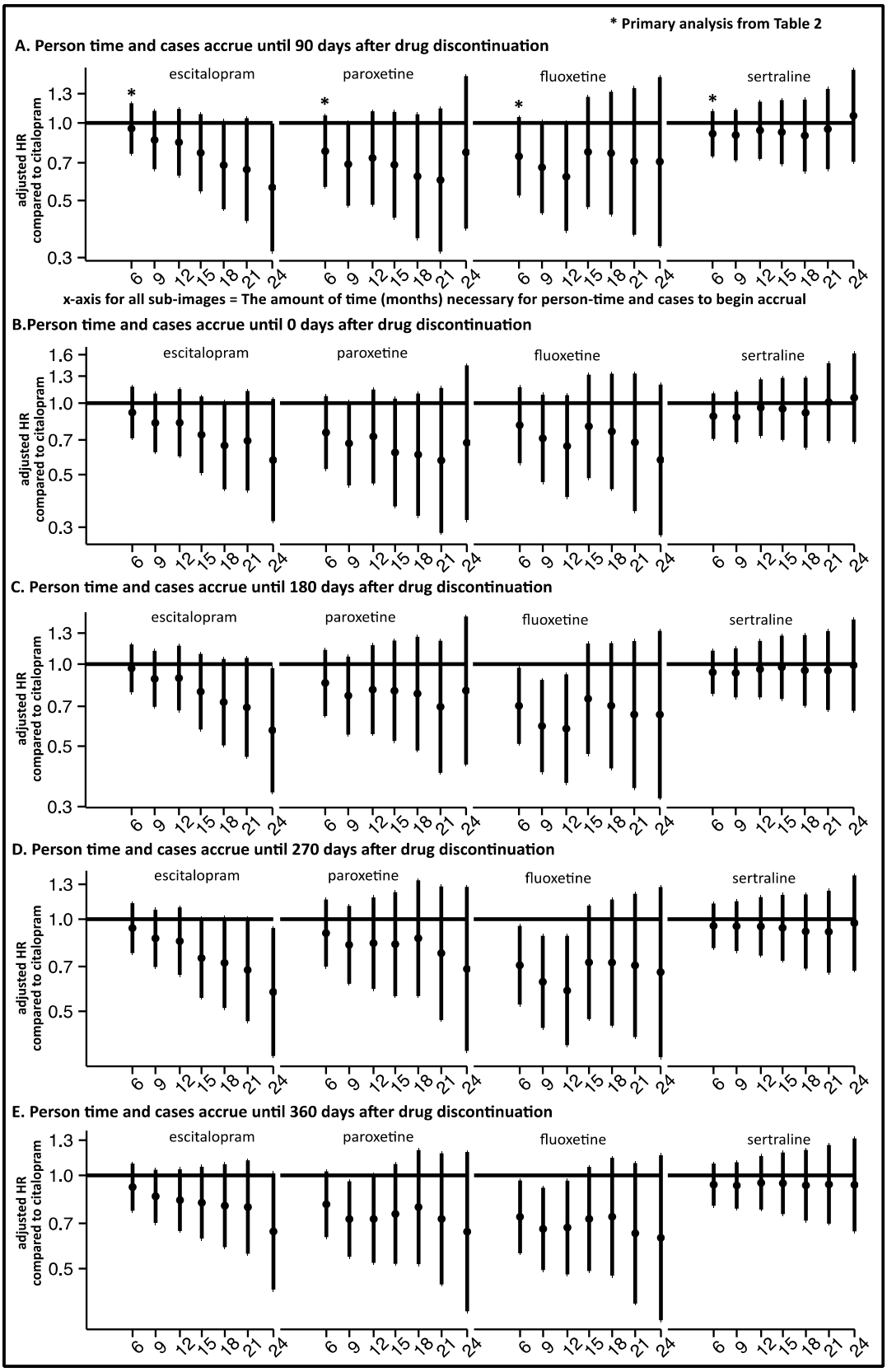

Figure 14: Sensitivity analyses with varying induction and latency assumptions.

All sub-images show HR and 95% CI comparing non-referent SSRIs to citalopram. The x-axis for all images is the lag period in increments of ~ 3 months for a specific latent period. **Figure 14A:** Sensitivity analyses where the latent period = 90 days. The primary analyses occur at lag time = 180 days and are distinguished with a '*' **Figure 14B:** Sensitivity analyses with latent period = 0 days. Person time and cases accrue until the date of the last prescription plus the days supply plus the grace period (30 days). **Figure 14C:** Sensitivity analyses with latent period = 180 days. Person time and cases accrue until the date of the last prescription plus the days supply plus the grace period (30 days) plus 180 days. **Figure 14D:** Sensitivity analyses where latency = 270 days. Person time and cases accrue until the date of the last prescription plus the days supply plus the grace period (30 days) plus 270 days. **Figure 14E:** Sensitivity analyses where latency = 360 days. Person time and cases accrue until the date of the last prescription plus the days supply plus the grace period (30 days) plus 360 days.

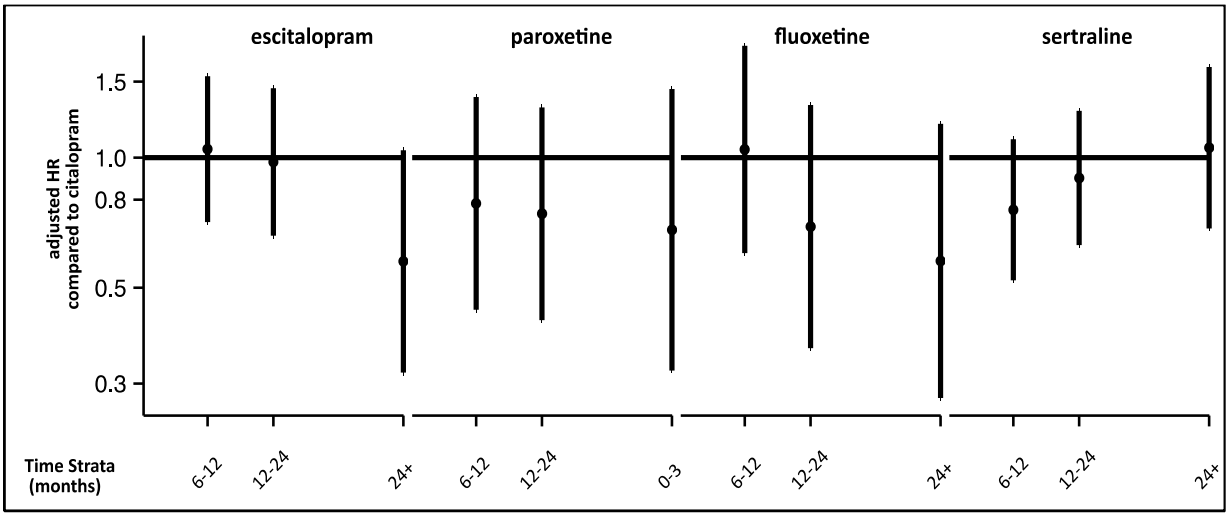

Figure 15: Adjusted hazard ratios stratified by time on SSRI.

All sub-images show adjusted hazard ratios and 95% confidence intervals for escitalopram, paroxetine, fluoxetine and sertraline compared citalopram during the following time: 6-12 months, 12-24 months, 24+ months. We used this to determine how well the proportional hazard assumption held over time.

CHAPTER 6: RE-EVALUATION OF COMMONLY USED DEFINITIONS TO IDENTIFY COLORECTAL CANCER IN A NORTH CAROLINA POPULATION (2006-2009)

6.1 Background

Administrative data are increasingly being used to investigate both the beneficial and harmful effects of drug exposures on health outcomes in large populations, with growing interest focused on the risk of cancer [188] . Although drug exposure information from claims is generally considered reliable relative to self-report, claims data do not as reliably capture incident cancer because they are used for reimbursement do not contain clinical or pathologic details. Therefore, algorithms are necessary to identify incident cancer cases when using administrative data, and very specific definitions are required to obtain unbiased hazard ratio estimates [105]. Claims data are critical to answering questions that could not be feasibly investigated within the context of a randomized clinical trial (RCT), because certain questions require a very large sample size or do not have enough evidence to warrant an RCT. An example is examining the association between specific selective serotonin reuptake inhibitors and colorectal cancer [177].

6.1.1 Current algorithm

One of the most commonly used claims-based algorithms to identify incident cancers was developed by Setoguchi and colleagues [28]. They generated four definitions (Figure 1) of varying sensitivity and specificity using a population of individuals who were continuously co-enrolled in both Medicare and the Pharmaceutical Contract for the Elderly (PACE) program between Jan 1,1997-Dec 31, 2000. The PACE program provides comprehensive drug coverage for low-income individuals. Of the four definitions developed, definitions #2 and #4 rely only upon *International Classification of Diseases, Clinical Modification, Ninth Revision*

(ICD-9) diagnosis codes, whereas definitions #1 and #3 incorporate diagnosis, procedure and treatment codes. Passing time, low-income status and continuous enrollment criteria contribute to the original population inadequately representing a more economically diverse and recent Medicare population. The algorithms require four years of continuous enrollment within the Medicare and PACE programs. By requiring extended continuous enrollment and ignoring changes in case status, we may overestimate the incidence or prevalence of cancer in the population. For example, a case diagnosed in late 2000 should ideally have been classified as a non-case for the earlier portion of the enrollment, because they are more similar to non-cases at that point in time. When we overestimate the prevalence of cancer, a relatively rare outcome, we are likely to overestimate the positive predictive value (PPV) in the population [189] . Therefore, PPV as calculated in the original population may be a large overestimation of the PPV in the population.

An additional limitation to these definitions is that they group colon and rectal cancers together. Although risk factors are similar for colon and rectal cancers, the effect estimates of risk factors vary qualitatively. For instance, a 2008 meta-analysis [106] reported that the association between smoking and cancer is stronger among rectal cancer cases than among colon cancer cases. Also, the median age at diagnosis is younger for rectal cancer [64 years] than for colon cancer [71 years] [1], suggestive of etiological heterogeneity. Thus, there may be instances where an investigator wants to separately evaluate the association between a particular drug exposure and colon cancer or rectal cancer, as opposed to the combined outcome of colorectal cancer (CRC).

6.1.2 Objectives

We will re-evaluate the validity of the algorithms defined by Setoguchi [28] for CRC cases in a more recent and economically diverse Medicare population for the years 2006-2009. We will assemble a cohort with less stringent continuous enrollment criteria. Additionally, we

will use information from true CRC cases about their pre-diagnosis non-case status, pre-diagnosis and diagnostic case status, and post-diagnosis prevalent case-status to validate the algorithms. Time-varying claims information is more informative than just case status in the development and validation of definitions to identify incident cases.

6.2 Methods

6.2.1 Data source

We used the Integrated Cancer Information and Surveillance System (ICISS), a resource at the University of North Carolina (UNC) Lineberger Comprehensive Cancer Center. ICISS houses several linked data sources with the goal of understanding cancer incidence, risk factors and patterns of care for NC residents [162]. ICISS contains a 100% sample of NC Medicare beneficiary enrollment and claims information, and can link a substantial proportion of NC Central Cancer Registry (NCCCR) cases to the NC Medicare beneficiary files.

6.2.1.1 Case selection and data linkage

We identified all individuals, aged ≥65 years with a first primary diagnosis of colon or rectal cancer in the NCCCR from Jul 1, 2006-Dec 31, 2009 that were linkable to NC Medicare enrollment and beneficiary files. We then further required that all cases had ≥13 months of continuous enrollment in Medicare parts A/B at any point during Jul 1, 2006-Dec 31, 2009, and at least one claim to ensure benefit utilization. The NCCCR has a gold star rating from the North American Association of Cancer Registries [163]. This rating is only given to those registries with ≥95% case ascertainment, and timely reporting [164].

6.2.1.2 Non-case selection criteria

We identified all NC Medicare beneficiaries not appearing in the cancer registry who were continuously enrolled for at least 13 months in Medicare parts A/B between Jul 1, 2006-Dec 31, 2009, were aged ≥65 at the start of a period of ≥13 months of continuous enrollment,

and had at least one in or outpatient claim in order to ensure benefit utilization. We then randomly selected 150,000 of these non-cases meeting cohort criteria.

6.2.2 Main validation cohort

We did not require individuals to have continuous enrollment during the entire study period (Jul 1, 2006-Dec 31, 2009), but instead created a series of continuous enrollment windows of a smaller size, thereby capturing a less select, and more representative, aged ≥65 Medicare beneficiary and allowing for the case status of beneficiaries to evolve over time

6.2.2.1 Rationale for dynamic enrollment periods

Individuals who are diagnosed with colorectal cancer are generally worked-up and treated according to screening and treatment guidelines. As a result, there is a minimum period of time that is necessary to follow an individual in claims data in order to identify whether the individual becomes a true incident case. Individuals in a claims dataset can move from pre-diagnosis non-case status to pre-diagnosis and diagnostic case status, and thus in and out of the cohort, depending where in time they are relative to the registry diagnosis date. In order to loosen the continuous enrollment criteria previously imposed by Setoguchi and colleagues and to more appropriately incorporate the pre-diagnosis non-case status, pre-diagnosis and diagnostic case status, and post-diagnosis prevalent case-status case state, we will create a series of cohorts that move over time

6.2.2.2 A complete window

The cohort will consist of a series of cohorts with a minimum enrollment criteria of 365 days that is bounded by a period of time before this window (pre-buffer) and after the window (post-buffer) whereby if a case is diagnosed within the pre-buffer or post-buffer, they would be excluded from the specific cohort, because they are potentially not contributing all critical information. Non-cases are eligible for all cohorts as long as they are continuously enrolled

during the entire period of observation (primary window + pre-buffer + post-buffer). Cases can move from non-case status to case status. After they have become a case, they can no longer enter future cohorts, because they are now prevalent cases (Figure 2).

6.2.2.3 Calculation of pre-buffer size

For each individual in the cohort, we calculated the mean amount number of days between the registry diagnosis date and the claim dates of all diagnostic-associated procedures (e.g. colonoscopy, APPENDIX C) occurring within 365 days of the registry diagnosis date. We then calculated the earliest 1% of the distribution, corresponding to the largest 99th percentile of the amount of time in days between the diagnostic procedures and registry diagnosis dates, and used this value as the pre-buffer size. For our analysis, we excluded all cases from the analysis whose registry diagnosis date fell within the pre-buffer window because the window would be too narrow to observe all of the diagnostic claims that might help to identify a true case.

6.2.2.4 Calculation of post-buffer size

We calculated for each individual the mean amount of time in days between the registry diagnosis date and all dates on which a treatment code was observed (e.g., chemotherapy, APPENDIX C) occurring within 365 days of the registry diagnosis date. We used the 99th percentile of this distribution as the post-buffer size. This corresponds to the largest 99th percentile of the mean amount of time in days between registry diagnosis dates and treatment events. We excluded all cases whose registry diagnosis date fell within this post-buffer window because the window would be too narrow to observe all of the treatment-related claims that might help to identify a true case.

6.2.3 Sensitivity analyses

6.2.3.1 Cohort replication of Setoguchi definitions

To mimic the continuous enrollment criteria imposed on the PA/PACE population, we required cohort-eligible individuals to maintain continuous part A/B enrollment for at least 36 months. This was to emulate the 48 months of continuous enrollment in Medicare and PACE in the PA/PACE validation, as we do not have 48 months of data. We also tested the Setoguchi definitions among all individuals continuously enrolled for only ≥13 months. We finally examined how incorporating new and updated treatment and procedure codes that did not exist in 1997-2000 impacts the performance of definitions #1 and #3. Definitions #1 and #3 use both diagnosis and treatment or procedure codes to identify a case.

6.2.3.2 Low-income status (LIS)

The PA/PACE population was highly select with respect to both continuous enrollment criteria and income, with cohort members having a very low maximum income. Thus, their patterns of cancer diagnosis and treatment may differ from a more typical and economically diverse Medicare population. They may not have the same level of geographic mobility as a more economically diverse population. We attempted to capture a lower income population by using a flag ("Cost Share Group Code"; CST_SHR_GRP_CD_1-CST_SHR_GRP_CD_12 variables) representing LIS-eligibility in the beneficiary summary file; this flag is present for each month of Medicare enrollment. Specifically, we classified individuals as ever LIS if they had a code of 01-03 (fully-subsidized part D), or 04-08 (LIS eligible, but not receiving full part D subsidy) in any month of the period of continuous enrollment.

6.2.3.3 Modification of algorithms to identify colon and rectal cancer cases

We further evaluated modifications of definition #2 (2+ ICD-9 diagnoses within 60 days) to identify cancer sites not originally validated. Because colon and rectal cancers may have distinct etiology, we were specifically interested in evaluating modifications of the existing

algorithms to identify each cancer site separately. Because our cancer cases are distinct primaries, we are able to test our hypothesis of overlap.

6.2.4 Statistical analyses

We identified all claims-defined cases captured by all the four definitions in our primary analysis and in all sensitivity analyses. We calculated sensitivity (Se) (the proportion of true CRC cases captured by the algorithm); specificity (Sp) (the proportion of true non-CRC cases classified as a non-case); positive predictive value (PPV) (the probability that an individual is a CRC case given the algorithm identifies the individual as a CRC case); negative predictive value (NPV) (the probability that an individual is non-CRC case given the algorithm identifies the individual as a non-case), and corresponding 95% confidence intervals using the exact binomial distribution as implemented in the epiR package [175] for sensitivity cohorts. We adjusted both NPV and PPV for the sampling fraction of non-cases (17%). Because individuals in the primary cohort may appear in multiple windows, we used generalized estimating equations (GEE) with a binomial distribution and a logit link to calculate Se, Sp, PPV, NPV and associated standard errors to account for individuals appearing in multiple windows. Specifically, we needed to use a resampling (N=300) approach of 40,000 persons to estimate these values, because running the calculation on the full population was too computationally intensive. The confidence intervals were calculated as the mean of the 300 estimates +/- 1.96*standard error of the mean. Bootstrapping was performed in R. Other major analyses and cohort generation were performed in SAS V9.4. Post hoc calculations and images were completed using R 3.3.1 [181].

6.3 Results

Our full analytic validation cohort consisted of 149,568 non-cases and 2,951 individuals (colon=2,316; rectum=635) who were diagnosed from 7/1/2006-12/31/2009 (Table 13). CRC cases were slightly older than non-cases (75.0 versus 74.0) when they entered the cohort, included a larger proportion of men (47.2% versus 39.7%), and were more likely to be LIS-

eligible during their Medicare enrollment (24.9% versus 21.6%). On average, cases were continuously enrolled for slightly less time than non-cases (34.1 months versus 38.1 months) and included a smaller proportion of white individuals (81.3% versus 84.6%).

6.3.1 Creation of primary (dynamic) cohorts.

We calculated the pre-buffer size to be 155 (5% = 44, 10% = 18, 50% = 0) days and the post-buffer size to be 218 (95%=168, 90%=129, 50% =12) days. As a result of these estimated window sizes, we were able to construct four cohorts (Table 14) with close to two years of continuous Medicare parts A/B enrollment. Sensitivity varied over the four windows and definitions from 90.5%-95.7%, Specificity from 98.2%-99.4%, PPV from 17.6%-39.6%, and NPV >99.99% (Table 16) with global summary estimates shown in Table 17, Figure 16. Compared with the original population, sensitivity was higher, specificity was lower and PPV was markedly lower in our population for all definitions. Sensitivity was much less variable in our population compared with the PA/PACE population (Figure 16A), and notably, in contrast to the PA/PACE population, definition #1 was more sensitive than definition #2 (Figure 16A). When we used the original (outdated) treatment and procedure codes from the original validation, definition #2 was less sensitive than definition #1, (Figure 17A). We captured several more cases when we incorporated 2006-2009 procedure and treatment codes, such that definition #1 has higher sensitivity and lower specificity than definition #2 with more timely codes.

6.3.2 Sensitivity analyses

We re-evaluated the performance of the algorithms in a number of sensitivity analyses. In cohort constructed similar to Setoguchi et al (i.e., requiring longer continuous enrollment of 3 years), sensitivity was higher, specificity was lower and PPV was significantly lower for all definitions (Table 19, Figure 17); however, when we stratified by low-income status among individuals who were continuously enrolled for 13+ months we found that the PPV was lower

among LIS-eligible persons (Table 19, analyses 6/7; Figure 17D). Thus, definition performance among LIS-eligible persons was more similar to that in the original PA/PACE population.

6.3.3 Evaluation of modification of algorithms

We evaluated how well the modifications of definitions #2 (2+ ICD-9 codes within 60 days) and definition #4 (1+ ICD-9 code) for both colon (153.x) and rectal (154.0, 154.1, 154.8) cancer performed among cases continuously enrolled for ≥36 months. There was almost complete overlap between colon and rectal cases identified using definition 4 (Figure 18A) and substantial overlap between colon and rectal cases identified with definition 2 (Figure 18B), indicating that primary cancers of the two site were largely indistinguishable using claims data alone.

6.4 Discussion

We re-evaluated a commonly used set of claims-based algorithms to identify incident CRC in a contemporary and economically diverse North Carolina population for the years 2006-2009. We created a dynamic cohort design such that individuals could contribute both as a non-case and a case. We also employed a series of sensitivity analyses to evaluate the definitions among individuals continuously enrolled for ≥36 months with identical codes to the original PA/PACE population, with treatment and procedure codes that did not exist in 1997-2000, but existed in 2006-2009, among LIS-eligible individuals, and among colon or rectum only cases using modified definitions.

In our primary cohort and in all sensitivity cohorts, sensitivity generally increased, whereas specificity and PPV generally decreased, with PPV decreasing substantially. We captured many more cases when we incorporated 2006-2009 treatment and procedural codes that definition #1 became more sensitive and less specific than definition #2. Our colon-only and rectal-only algorithm modifications performed poorly, especially for rectal cases, and could

not adequately distinguish between colon and rectal cancer cases. These modifications should not be used and colon-only and rectal-only definitions should be developed, given potential interest in the studying associations between a specific exposure and colon cancer alone or rectal cancer alone.

6.4.1 Features driving poor PPV and high false positive (FP) rate

We attempted to identify features associated with being a FP, under the assumption that FP cases were not true cases. We examined claims-based differences among true positive (TP) cases and FP cases in the 90 days prior to the first observed ICD-9 CRC code among individuals flagged by definition #2 (2 ICD-9 codes within 60 days) as case. The codes statistically associated with being FPs are suggestive of prevalent—or recently diagnosed—as opposed to incident cases (i.e. history of colon cancer, rectal cancer, on-going surveillance).

We are concerned that many of these FP cases may be true cases, but not newly diagnosed cases. This could be due to individuals obtaining treatment in a different state. State cancer registries are incentivized to accurately ascertain case status of residents in their state and low case count, and thus if a case is not truly a NC resident, they would be removed from the registry once this information was known. This may also be due to individuals undergoing routine surveillance for a prevalent cancer. This may be more common now than in the 1997-2000 population, because of the increase in the types of treatments since the algorithms were originally evaluated

We hypothesized that individuals with higher income would have the financial means to travel outside of their home state for treatment, and conversely that very poor individuals would not have the means to receive care outside their home state. This could contribute to a higher proportion of FP cases appearing in individuals with higher income. We tested this hypothesis by comparing the proportion of LIS-eligible individuals in cases versus non-cases, by examining

algorithm performance stratified by LIS-status and by comparing the proportion of TP versus FP LIS-eligible individuals. For all three metrics we found support for this hypothesis. The PA/PACE population was comprised of individuals with very low income and potentially limited ability to seek care outside of PA. This suggests that income differences between the two populations may in part be driving differences in the performance between the PA/PACE population and our NC population.

There are a few other reasons that may be contributing to the poor PPV performance compared to the original population. First, we believe the original population overestimated the incidence of CRC in their population. If the incidence were overestimated, then the PPV would also be overestimated, because of the prevalence-PPV relationship that occurs with rare events. The original validation reported a CRC incidence that was substantially higher than SEER age and sex adjusted estimates. Additionally, by conditioning on having four years of continuous enrollment, cases will never appear as a non-case, pre incident-case. This should falsely inflate the incidence of CRC. We have shown in our analyses, that PPV drops substantially when we properly account for individuals have case and non-case status. A final reason for marked differences between Sensitivity and PPV performance in the PA/PACE performance compared with the NC population could simply be time driven. There were a number of new treatment, screening and surveillance modalities, as well as screening guidelines that changed between 1997-2000 and 2006-2009.

6.4.2 Conclusions and future directions

Identifying truly incident cases is critical when evaluating associations between drug exposures and cancer, as prevalent cases mixed with incident cases may bias or dilute any observable associations, and would be especially problematic if prevalent cases were included differentially across treatment arms. We have, in part, mitigated this problem in the past by excluding individuals with evidence of CRC treatment or with a V-code indicative of “history of

colon/rectal cancer" during a baseline covariate assessment period, but there may still be prevalent cases entering the cohort. Therefore, we need to develop algorithms to more specifically identify incident cancer cases. Information specific to TP and FP individuals will likely be key in identifying true incident cancer cases. We should also examine how the proportion of probable CRC cases varies as a function of time since drug initiation in a new user study design. If the bulk of CRC cases occurs within the first few months after initiation, then 1) this may in part explain previously observed high CRC incidence shortly after initiation and 2) provides more justification for excluding cases that occur within the first few months after initiation (Aim 1)

In summary, although these algorithms are required to perform studies of cancer incidence using administrative data (Aim1, Aim 2), some caution is warranted. We have shown that claims-based CRC-identification algorithm performance can vary drastically between populations. Because we found some evidence that FP cases were prevalent cases, we suggest excluding individuals with an obvious history of colon or rectal cancer as indicated by the presence of V10.05/V10.06 diagnosis codes when using algorithms to identify incident CRC. We have also provided evidence that by requiring a long period of continuous enrollment, there is an overestimation of incidence, and hence PPV, and we have herein provided a template of a cohort design to more accurately ascertain algorithm performance in a given population. This cohort design is transferrable to other populations and cancer sites.

6.5 Tables

Table 13: Characteristics of cases and non-cases.

	Cases N (%)*	Non-cases N
	2,951	149,568
Mean age (sd) when first eligible for cohort	75.0 (7.8)	74.0 (7.6)
Mean months (sd) of continuous enrollment	34.1 (11.7)	38.1 (7.5)
% With break in enrollment	72 (2.4)	3100 (2.1)
% Ever eligible for LIS	735 (24.9)	32,282 (21.6)
Sex		
Male	1393 (47.2)	59,365 (39.7)
Female	1558 (52.8)	90,203 (60.3)
Race		
White (non-Hispanic)	2399 (81.3)	126,507 (84.6)
Black (non-Hispanic)	508 (17.2)	20,421 (13.7)
Other	44 (1.5)	2,640 (1.8)
Tumor Characteristics		
Colon	2316 (78.5)	NA
Rectum	635 (21.5)	NA
TNM Stage		NA
0	113 (5.0)	NA
1	417 (18.6)	NA
2	485 (21.6)	NA
3	467 (20.8)	NA
4	223 (9.9)	NA
8 (B cell origin); 88(NA, co code assigned); 99 (unknown, un-staged), X	539 (22.8)	NA
Missing	707	NA
Grade		
1	268 (9.1)	NA
2	1605 (54.4)	NA
3	421 (14.3)	NA
4	35 (1.2)	NA
6	18 (0.6)	NA
9	604 (20.5)	NA
Age at Diagnosis	76.6 (7.8)	NA

All individuals in this table had 13+ months of continuous enrollment in Medicare parts A/B at some point between Jul 1,2006-Dec 31, 2009. Three cases and 432 non-cases had demographic information that changed over time, (sex, race and date of birth) within the

Table 14: Window characteristics stratified by case status (Group)

Window	Window Start	Window End date	Cases (N)	Non-cases (N)	Excluded cases	Included in window (N)	Enrolled during interval (N)	Group
1	1-Jul-06	8-Jul-08	476	1118	530	1594	2124	case
2	3-Dec-06	10-Dec-	452	588	987	1040	2027	case
3	7-May-07	14-May-	469	542	892	1011	1903	case
4	9-Oct-07	16-Oct-09	469	219	1145	688	1833	case
1	1-Jul-06	8-Jul-08	0	118824	0	118824	118824	control
2	3-Dec-06	10-Dec-	0	118179	0	118179	118179	control
3	7-May-07	14-May-	0	115542	0	115542	115542	control
4	9-Oct-07	16-Oct-09	0	115394	0	115394	115394	control

Table 15: Identified case characteristics by window

Window	Definition	Total N	True Positives	False Positives	True Negative	False Negative
1	4	120948	453	2117	117825	23
1	2	120948	431	1156	118786	45
1	3	120948	449	1324	118618	27
1	1	120948	441	802	119140	35
2	4	120206	429	2014	116753	23
2	2	120206	409	1040	118033	43
2	3	120206	426	1194	117573	26
2	1	120206	415	736	118031	37
3	4	117445	447	1973	114111	22
3	2	117445	426	1020	115064	43
3	3	117445	442	1168	114916	27
3	1	117445	433	725	115359	36
4	4	117227	449	1909	113704	20
4	2	117227	429	1001	114612	40
4	3	117227	444	1138	114475	25
4	1	117227	440	664	114949	29

Table 16: Algorithm performance stratified by window

Window	Definition	Se	Se Lo	Se Hi	Sp	Sp Lo	Sp Hi	PPV	PPV Lo	PPV Hi
1	4	0.952	0.928	0.969	0.982	0.982	0.983	0.176	0.162	0.192
1	2	0.905	0.876	0.930	0.990	0.990	0.991	0.272	0.250	0.294
1	3	0.943	0.919	0.962	0.989	0.988	0.990	0.253	0.233	0.274
1	1	0.926	0.899	0.948	0.993	0.993	0.994	0.355	0.328	0.382
2	4	0.949	0.925	0.967	0.983	0.982	0.984	0.176	0.161	0.191
2	2	0.905	0.874	0.930	0.991	0.991	0.992	0.282	0.259	0.306
2	3	0.942	0.917	0.962	0.990	0.989	0.991	0.263	0.242	0.285
2	1	0.918	0.889	0.942	0.994	0.993	0.994	0.361	0.333	0.389
3	4	0.953	0.930	0.970	0.983	0.982	0.984	0.185	0.169	0.201
3	2	0.908	0.878	0.933	0.991	0.991	0.992	0.295	0.271	0.319
3	3	0.942	0.917	0.962	0.990	0.989	0.991	0.275	0.253	0.297
3	1	0.923	0.895	0.946	0.994	0.993	0.994	0.374	0.346	0.403
4	4	0.957	0.935	0.974	0.983	0.983	0.984	0.190	0.175	0.207
4	2	0.915	0.886	0.938	0.991	0.991	0.992	0.300	0.276	0.324
4	3	0.947	0.922	0.965	0.990	0.990	0.991	0.281	0.259	0.304
4	1	0.938	0.912	0.958	0.994	0.994	0.995	0.399	0.370	0.428

Table 17: Aggregated algorithm performance

Definition	Sensitivity (95% CI)			Specificity (95% CI)			Positive Predictive Value (95% CI)			Negative Predictive Value (95% CI)		
Def 1	0.929	0.927	0.932	0.994	0.994	0.994	0.371	0.369	0.374	1.000	1.000	1.000
Def 2	0.909	0.906	0.911	0.991	0.991	0.991	0.288	0.285	0.290	1.000	1.000	1.000
Def 3	0.944	0.942	0.945	0.991	0.990	0.992	0.294	0.292	0.296	1.000	1.000	1.000
Def 4	0.954	0.953	0.956	0.983	0.981	0.985	0.182	0.180	0.183	1.000	1.000	1.000

* Standard error calculated using 300 bootstrapped samples (N=40,000) generalized estimating equations in R.

Table 18: Sensitivity analyses

Sensitivity Analysis	Definition	True Positives	False Positives	True Negative	False Negative
1	1	1666	681	229	114771
1	2	1693	1372	202	114080
1	3	1722	1433	173	114019
1	4	1795	2522	100	112930
2	1	2275	952	370	145931
2	2	2370	1898	275	144985
2	3	2409	1974	236	144909
2	4	2511	3332	134	143551
3	1	2385	1396	260	145487
3	3	2465	2142	180	144741
4	2	1839	1910	239	145540
4	4	1970	3361	108	144089
5	2	476	1221	91	147740
5	4	519	2354	48	146607
6	1	516	186	106	30539
6	2	549	394	73	30331
6	3	558	407	64	30318
6	4	588	678	34	30047
7	1	1759	766	264	115393
7	2	2023	1504	202	114654
7	3	1851	1567	172	114951
7	4	1923	2654	100	113504

1: Individuals continuously enrolled for 36+ months, original treatment and procedure codes
2: Individuals continuously enrolled for 13+ months, original treatment and procedure codes
3: Individuals continuously enrolled for 13+ months, 2006-2009 treatment and procedure codes
4: Individuals continuously enrolled for 13+ months, identify colon cancer with 153.x codes
5: Individuals continuously enrolled for 13+ months, identify rectal cancer with 154.x codes
6: Individuals continuously enrolled for 13+ months, among LIS eligible persons
7: Individuals continuously enrolled for 13+ months, among not LIS eligible persons

Table 19: Sensitivity analyses for algorithm performance for each definition

Sensitivity Analysis	Definition	Se	Se Lo	Se Hi	Sp	Sp Lo	Sp Hi	PPV	PPV Lo	PPV Hi	NPV	NPV Lo	NPV Hi
1	1	0.879	0.864	0.893	0.994	0.994	0.995	0.710	0.691	0.728	0.998	0.998	0.998
1	2	0.893	0.879	0.907	0.988	0.987	0.989	0.552	0.535	0.570	0.998	0.998	0.998
1	3	0.909	0.895	0.921	0.988	0.987	0.988	0.546	0.528	0.563	0.998	0.998	0.999
1	4	0.947	0.936	0.957	0.978	0.977	0.979	0.416	0.401	0.431	0.999	0.999	0.999
2	1	0.860	0.846	0.873	0.994	0.993	0.994	0.705	0.689	0.721	0.997	0.997	0.998
2	2	0.896	0.884	0.907	0.987	0.986	0.988	0.555	0.540	0.570	0.998	0.998	0.998
2	3	0.911	0.899	0.921	0.987	0.986	0.987	0.550	0.535	0.564	0.998	0.998	0.999
2	4	0.949	0.940	0.957	0.977	0.977	0.978	0.430	0.417	0.443	0.999	0.999	0.999
3	1	0.902	0.890	0.913	0.990	0.990	0.991	0.631	0.615	0.646	0.998	0.998	0.998
3	3	0.932	0.922	0.941	0.985	0.985	0.986	0.535	0.521	0.550	0.999	0.999	0.999
4	2	0.885	0.870	0.898	0.987	0.986	0.988	0.491	0.474	0.507	0.998	0.998	0.999
4	4	0.948	0.938	0.957	0.977	0.976	0.978	0.370	0.357	0.383	0.999	0.999	0.999
5	2	0.840	0.807	0.869	0.992	0.991	0.992	0.280	0.259	0.303	0.999	0.999	1.000
5	4	0.915	0.889	0.937	0.984	0.984	0.985	0.181	0.167	0.195	1.000	1.000	1.000
6	1	0.830	0.798	0.858	0.994	0.993	0.995	0.735	0.701	0.767	0.997	0.996	0.997
6	2	0.883	0.855	0.907	0.987	0.986	0.988	0.582	0.550	0.614	0.998	0.997	0.998
6	3	0.897	0.871	0.920	0.987	0.985	0.988	0.578	0.546	0.610	0.998	0.997	0.998
6	4	0.945	0.924	0.962	0.978	0.976	0.980	0.464	0.437	0.492	0.999	0.998	0.999
7	1	0.870	0.854	0.884	0.993	0.993	0.994	0.697	0.678	0.715	0.998	0.997	0.998
7	2	0.909	0.897	0.921	0.987	0.986	0.988	0.574	0.557	0.590	0.998	0.998	0.998
7	3	0.915	0.902	0.927	0.987	0.986	0.987	0.542	0.525	0.558	0.999	0.998	0.999
7	4	0.951	0.940	0.960	0.977	0.976	0.978	0.420	0.406	0.435	0.999	0.999	0.999

6.6 Figures

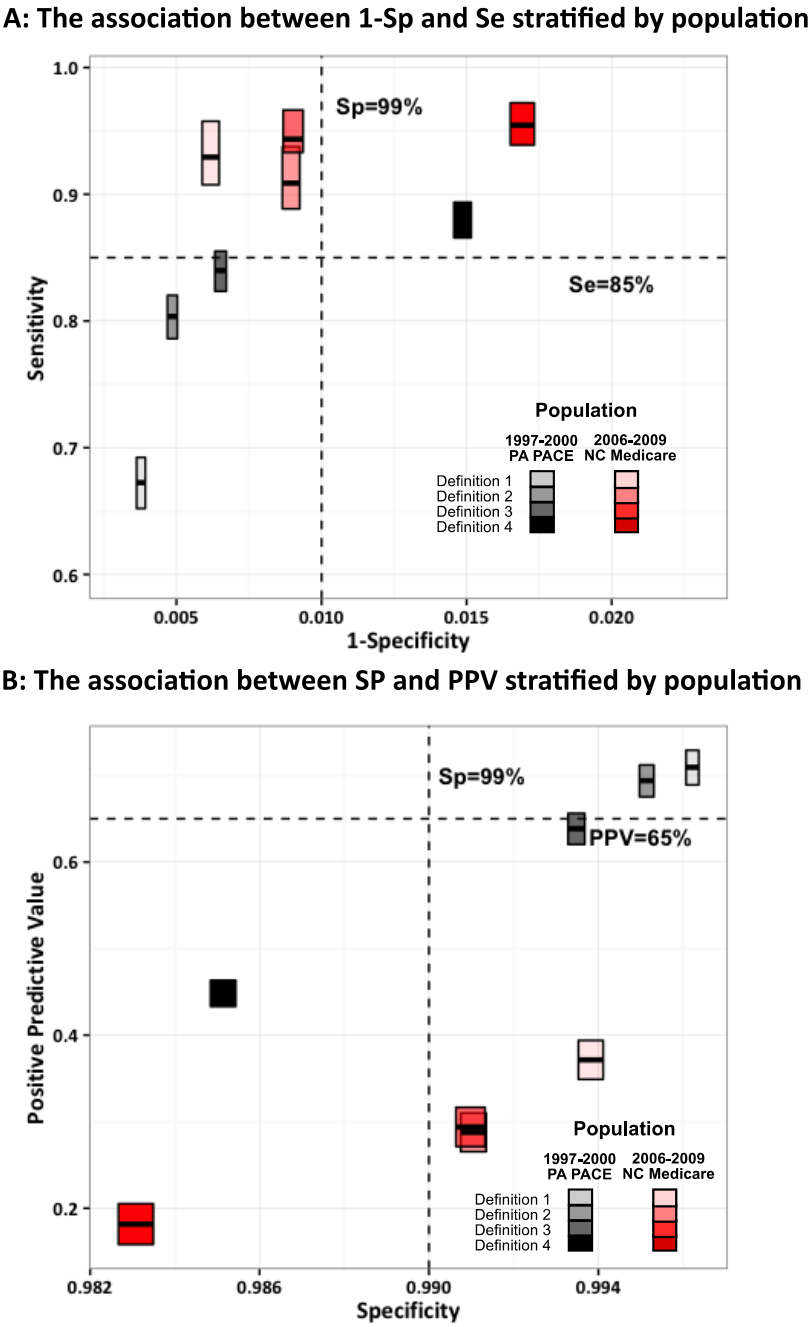

Figure 16: Algorithm performance in original and current population

A: Se/1-Sp stratified by population. **B**: Sp/PPV stratified by population. NC population metrics and confidence intervals are calculated by bootstrapped generalized estimating equations (Actual values listed in Table 16). Images use 2.5% and 97.5% CI for visualization purposes for NC GEE estimates.

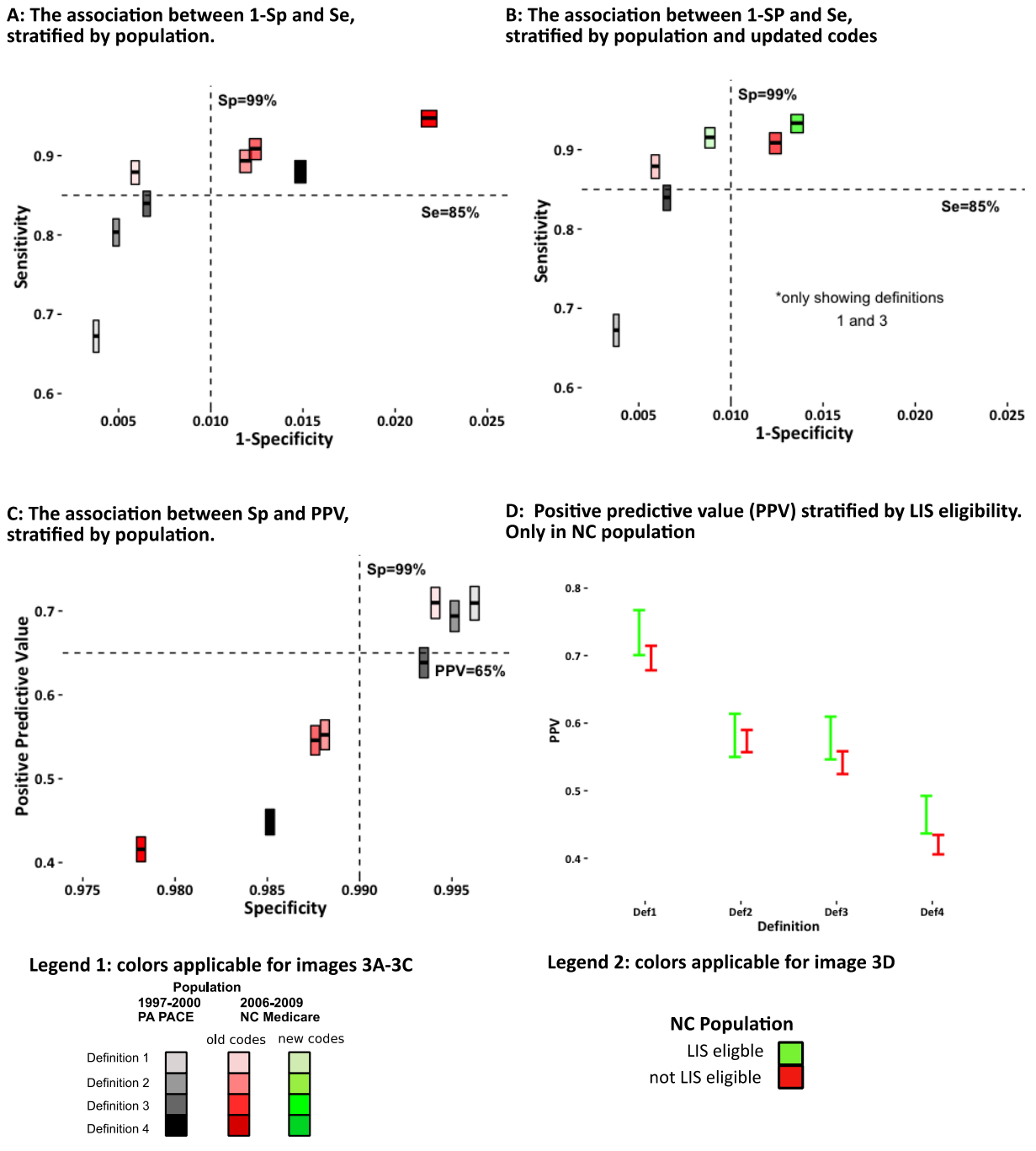

Figure 17: Visualization of various sensitivity analyses of algorithm performance

A: Se and 1-Sp stratified by NC population with 36+ months continuous enrollment and PA/PACE population **B:** Se and 1-Sp by NC population with 36+ months continuous enrollment and PA/PACE population for definitions 1, 3. **C:** PPV and 1-Sp calculated by NC population with 36+ months continuous enrollment and PA/PACE population **D:** PPV stratified by low-income eligible (LIS) status. **A, C** and are based on individuals who were continuously enrolled for 36+ months and with the original treatment and procedural codes. **D** PPV calculated among individuals continuously enrolled for 13+ months and uses updated treatment codes for definitions 1 and 3

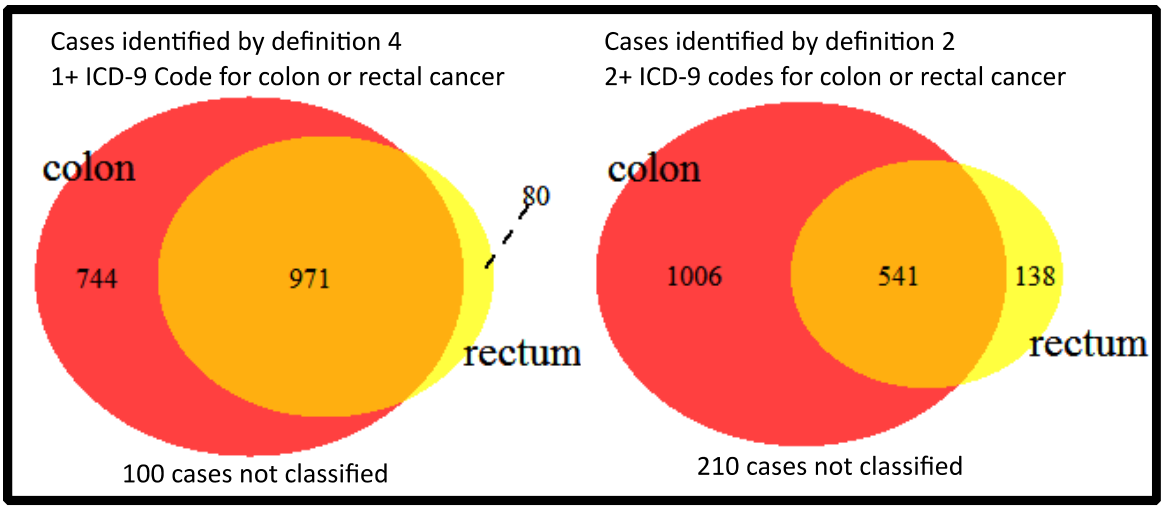

Figure 18: Overlap of colon/rectal cancer cases identified with definition 2 and 4.

These images are based on individuals who were continuously enrolled for 36+ months in Medicare parts A/B. Colon cancer and rectal cancer cases were identified using modified definitions of either 153.x for colon cancer or 154.x for rectal cancer. There is substantial overlap between algorithm-identified cases.

CHAPTER 7: CONCLUSIONS

7.1 Main findings

We had three primary goals in this study: 1) to illustrate the usage of a negative exposure control and examine the associations between AD classes (SSRIs, TCAs, SNRIs) compared with a negative exposure control, AHT, and CRC, 2) to examine specific drug effects within the SSRI class with respect to CRC risk and 3) to re-evaluate how well the set of definitions we used to identify CRC cases in the first two aims worked in a more contemporary and economically diverse NC population. We also used the first goal as an opportunity to explore reasons for relatively high cancer incidence rates occurring shortly after drug initiation, by examining patterns of healthcare utilization in the period of time proximal to the first prescription.

We used a 20% random sample of Medicare beneficiaries for the years 2007-2013 to answer the first two goals. We found that SSRI initiators had lower rates of CRC compared with AHT initiators (aHR=0.85, 95% CI: 0.70-1.02) and this estimate was fairly constant over sensitivity analyses. For most analyses there was a small, relative reduction in the rate (5%-20%) of CRC among SSRI users compared with AHT initiators, with estimates falling between previously reported estimates [21-26]. There was little we could conclude about the SNRI-AHT and TCA-AHT association, because precision was poor, resulting from the small numbers of SNRI and TCA initiators and events. We also provided some evidence for the “medicalization” phenomena by showing that, on average, initiators of both AD and AHT had a surge in physician encounters in the time proximal to the first prescription when compared to their

physician encounters in the time before the first prescription. This phenomenon may contribute to high cancer rates shortly after medication initiation.

The relative rate of CRC was lower among paroxetine and fluoxetine initiators compared with citalopram uses (aHR: 0.78, 95% CI: 0.56-1.06; aHR: 0.74, 95% CI: 0.52-1.05, respectively) in our primary analysis, and these estimates were consistent in numerous sensitivity analyses. In contrast, we found that a relative protective effect emerged as we increased the amount of time between the second prescription and when cases began accrual, such that after 2 years of use, there was almost a 50% reduction in CRC rates among escitalopram users compared with citalopram initiators.

We re-evaluated a commonly used set of CRC identification definitions in a more contemporary and economically diverse North Carolina population for the years 2006-2009, using a dynamic cohort approach such that individuals could move in and out of the cohort and in and out of case status. We employed a series of sensitivity analyses to evaluate the definitions among individuals continuously enrolled for 36+ months with identical codes to the original PA/PACE population, with updated treatment and procedure codes, among LIS-eligible or Medicaid dual-eligible individuals, and among colon or rectum only cases using modified definitions.

In our primary cohort and in all sensitivity cohorts, including that which was most similar to the original population with respect to continuous enrollment, sensitivity generally increased, whereas specificity and PPV generally decreased, with PPV decreasing substantially. Our colon-only and rectal-only algorithm modifications performed poorly, especially for rectal cancer identification, and could not adequately distinguish between colon and rectal cancer cases.

We found that we captured a substantial number of FP CRC cases, and that these individuals seemed qualitatively different from TP cases, such they had diagnoses (e.g. ICD-

9=153.9, CRC NOS; V10.05, history of colon cancer) and procedures (surveillance tests) suggestive of non-specific and prevalent CRC. Therefore high CRC rates shortly after initiation may also be attributable to individuals with prevalent CRC who had not visited the physician in the period of time before the first prescription. For example, individuals who are prevalent cases, and who are also new users, may have also undergone a period of relatively reduced healthcare seeking behavior. Therefore, when these individuals return to the physician for a routine checkup, they may undergo procedures related CRC surveillance, such as a CEA test. At this point, they may also receive a CRC diagnosis on their claim, and may therefore appear as an incident case.

7.2 Significance

Despite declines in incidence and mortality over the past 30 years, colorectal cancer (CRC) remains the second leading cause of cancer mortality in the United States [1] with almost 50,000 deaths expected in 2015 [2]. CRC treatment is expensive, with the average cost per colon cancer Medicare beneficiary in the first year after diagnosis estimated at $30,000 in 2010 [3]. High costs of cancer treatment have generated interest in identifying existing drugs and supplements with the potential to prevent cancer [4]. In these two large cohort studies among older adults, we presented evidence that SSRIs, as a class, may reduce the risk of CRC compared to a negative control, and that SSRIs may vary in their chemopreventive efficacy against CRC. SSRIs are commonly used, inexpensive and generally well tolerated.

We used an algorithm to identify probable CRC cases in the first goals; however, we provided evidence in the third part of this study that the definition does not work quite as well as expected, with both specificity and PPV having markedly worse performance in a more recent and economically diverse population, and in a cohort specifically designed to capture the essence of a very rare event. We hypothesize one of the reasons performance was so poor in our dynamic cohort compared to a static cohort is that failure to consider a case in its non-case,

pre-diagnostic state will falsely inflate the prevalence or incidence of this very rare event. The longer the continuous enrollment criteria, the more inflated the incidence of the cancer, and therefore the more inflated the PPV. Because our modifications of the colon-only or rectal-only cases performed so poorly, we strongly suggest that they should not be used, and that colon-only and rectal-only definitions should be developed.

Although these algorithms are necessary when identifying cancer incidence in administrative data, they should be used with caution, as their performance appear to be population- and time-specific.

7.3 Future directions

Our results from the first two goals warrant further investigation (including mechanistic studies) into the association between SSRIs and CRC. Incorporating more part D data as it becomes available will help to clarify the signal, but it will not elucidate the mechanisms. We believe this methodological approach could serve as a cost-effective and timely framework for identifying other potential chemopreventive drugs.

We recommend that future pharmacoepidemiologic studies evaluating the effects of prescribed medications on cancer risk should examine cancer incidence rates after follow-up begins, and exclude all person-time and cancer events preceding the sharp incidence decline and flattening (e.g., 180 days in our study). Cancers diagnosed shortly after initiation, within a period of increased healthcare utilization following a new prescription, may not be attributable to the new use of a medication, but instead to reduced physician encounters in the time leading up to the first prescription. Had these individuals visited a physician prior to the first prescription, they may have been diagnosed with CRC, making them ineligible for the study. These cases may have also been known or prevalent CRC cases that appear incident because of visit to a physician following a period of relatively low healthcare system interaction. We will attempt to

reclassify individuals called as cases in Aim 1 as probable FP (potential known CRC or prevalent case) or TP cases, and examine if the proportion of cases occurring in the first few months after the new prescription is dominated by probable FP or prevalent cases. If a substantial proportion of probable FP cases occur shortly after medication initiation, then this provides more justification for excluding cases and person time immediately after drug initiation.

We suggest that studies using a negative exposure control should compare patterns of healthcare utilization between the primary exposure groups and the control. Marked differences in utilization patterns may put the study at risk for outcome detection bias. Medicalization patterns, and their potential for assessing bias in pharmacoepidemiologic studies, should be further examined in other drug exposure and disease outcome settings.

In the third aim of this dissertation, we found that sensitivity of a claims-based algorithm to identify incidence colorectal cancer generally increased, whereas specificity and PPV generally decreased, with PPV decreasing substantially. Because colon-only and rectal-only cancer identification algorithms performed so poorly, these modifications should not be used, and new colon-only and rectal-only claims-based algorithms should be developed.

We found evidence from examining the differences between TP and FP CRC cases that a substantial proportion of the FP cases may be prevalent CRC cases. It is important to be able to distinguish between incident and prevalent cancer cases in a drug-cancer new user study, because falsely identifying incident cases may bias any apparent association. We believe that we will be able to use the information specific to that of a FP or TPs cases to develop new and more discriminating claims-based algorithms to identify incident colon, rectal and CRC cancer.

Finally, we believe that currently used algorithms for other cancer sites that have not been recently re-evaluated should be examined in more contemporary populations. These validation studies should carefully consider the creation of the cohort, and the impact that

conditioning on continuous enrollment may have on algorithm validity. We have shown that by conditioning on continuous enrollment, and failing to consider cases in both their case and non-case status, we inflate incidence and therefore PPV, because of the relationship between PPV and prevalence in rare events. Cancer is generally a very rare event. Administrative data are an increasingly used and vital resource for the timely evaluation of drug-cancer associations, but algorithms are generally necessary. Algorithm performance can greatly influence the validity of a study.

APPENDIX A – DRUG TABLES

Antihypertensives (AHT) not including beta-blockers

Generic Name
Aliskiren/Amlodipine Besylate
Aliskiren/Valsartan
Amlodipine Besylate
Amlodipine Besylate/Atorvastatin Calcium
Amlodipine Besylate/Benazepril Hydrochloride
Amlodipine Besylate/HCTZ/Olmesartan Medoxomil
Amlodipine Besylate/Olmesartan Medoxomil
Amlodipine Besylate/Telmisartan
Amlodipine Besylate/Valsartan
Azilsartan Medoxomil
Benazepril Hydrochloride
Candesartan Cilexetil
Captopril
Clevidipine Butyrate
Dextrose/Nicardipine Hydrochloride
Diltiazem Malate/Enalapril Maleate
Doxazosin Mesylate
Enalapril Maleate
Enalapril Maleate/Felodipine
Enalaprilat
Epinephrine Bitartrate/Prilocaine Hydrochloride
Eprosartan Mesylate
Felodipine
Fosinopril Sodium
Irbesartan
Isradipine
Lidocaine/Prilocaine
Lisinopril
Losartan Potassium
Moexipril Hydrochloride
Nicardipine Hydrochloride
Nicardipine Hydrochloride/Sodium Chloride
Nifedipine
Nimodipine
Nisoldipine
Olmesartan Medoxomil
Perindopril Erbumine
Phenoxybenzamine Hydrochloride

Phentolamine Mesylate
Prazosin Hydrochloride
Prilocaine
Prilocaine Hydrochloride
Quinapril Hydrochloride
Ramipril
Telmisartan
Terazosin Hydrochloride
Tolazoline Hydrochloride
Trandolapril
Trandolapril/Verapamil Hydrochloride
Valsartan

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

Generic Name
DESVENLAFAXINE
DULOXETINE
MILNACIPRAN
VENLAFAXINE

Selective Serotonin Reuptake Inhibitors (SNRIs)

Generic Name
CITALOPRAM
ESCITALOPRAM
FLUOXETINE
FLUVOXAMINE
PAROXETINE
SERTRALINE

Tricyclic Antidepressants (TCAs)

Generic Name
AMITRIPTYLINE
AMOXAPINE
BUTRIPTYLINE
CLOMIPRAMINE
DESIPRAMINE
DOXEPIN
IMIPRAMINE
MAPROTILINE
NORTRIPTYLINE
PROTRIPTYLINE
TRIMIPRAMINE

Estrogen based medications

Generic Name of estrogen-based medications
ethinyl estradiol-norgestrel
ethinyl estradiol-levonorgestrel
Intramuscular
estradiol-medroxyPROGESTERone
ethinyl estradiol-ethynodiol
ethinyl estradiol-norethindrone
esterified estrogens
Oral
conjugated estrogens
conjugated estrogens topical
desogestrel-ethinyl estradiol
ethinyl estradiol-etonogestrel
ethinyl estradiol-norgestimate
ethinyl estradiol-norelgestromin
drospirenone-ethinyl estradiol
drospirenone/ethinyl estradiol/levomefolate
dienogest-estradiol

NSAID generic formulations

ATC_LABEL
PHENYLBUTAZONE
ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES
INDOMETACIN

SULINDAC
TOLMETIN
DICLOFENAC
ETODOLAC
KETOROLAC
DICLOFENAC, COMBINATIONS
PIROXICAM
MELOXICAM
IBUPROFEN
NAPROXEN
KETOPROFEN
FENOPROFEN
FLURBIPROFEN
OXAPROZIN
IBUPROFEN, COMBINATIONS
NAPROXEN AND ESOMEPRAZOLE
MEFENAMIC ACID
MECLOFENAMIC ACID
CELECOXIB
ROFECOXIB
VALDECOXIB
OTHER ANTIINFLAM & ANTIRHEUMATIC AGNTS,NON-STEROID
NABUMETONE
GLUCOSAMINE
CHONDROITIN SULFATE

APPENDIX B – SETOGUCHI CODES

ICD-9-CM Diagnoses Codes for Cancer	
Colorectal Cancer	153.XX, 230.3X, 154.XX (except 154.2, 154.3 and 154.4), 230.4

ICD-9 and CPT codes for complications of cancers	
Hypercalcaemia for any cancer	275.40, 275.42, 275.49
Spinal cord compression for breast, prostate, lung,	198.3, 336.9
Ileus/obstruction for colorectal cancer	560.8, 560.9
Pain management or palliative care for any cancer	99551, 99552

CPT codes for diagnostic procedures with biopsy	
Colorectal cancer	45305, 45308, 45309, 45315, 45317, 45320, 45331, 45333, 45383, 45384, 45385, 45338, 45339, 45341, 45342, 45355, 45380, 44100

CPT codes for surgery	
Colorectal cancer	44110, 44111, 44130, 44139, 44140, 44141, 44143, 44144, 44145, 44146, 44147, 44150, 44151, 44152, 44153, 44155, 44156, 44160, 45110, 45111, 45112, 45113, 45114, 45116, 45119, 45120, 45121, 45123, 45126, 45130, 45135, 45160, 45170, 45190, 44202, 44203, 44204, 44205, 44206, 44207, 44208, 44210, 44211, 44212, 44238, 44239

CPT codes for chemotherapies
36640, 51720, 96400, 96405, 96406, 96408, 96410, 96412, 96414, 96420, 96422, 96423, 96425, 96440, 96445, 96450, 96500, 96501, 96504, 96505, 96508, 96510, 96511, 96512, 96520, 96524, 96530, 96538, 96540, 96542, 96545, 96549, 96450, 99555

CPT codes for radiations
77261, 77262, 77263, 77280, 77285, 77290, 77295, 77299, 77300, 77305, 77310, 77315, 77321, 77326, 77327, 77328, 77331, 77332, 77333, 77334, 77336, 77370, 77399, 77401, 77402, 77403, 77404, 77406, 77407, 77408, 77409, 77411, 77412, 77413, 77414, 77416, 77417, 77419, 77420, 77425, 77430, 77431, 77432, 77470, 77499, 76960, 55859, 55860, 55862, 55865, 77750, 77761, 77762, 77763, 77776, 77777, 77778, 77781, 77782, 77783, 77784, 77789, 77790, 77799, 79200, 79300, 79400, 79420, 79440, 79900, 79999

Generic names for specific oral chemotherapies: Capecitabine

APPENDIX C – CURRENT COLONOSCOPY/SCREENING AND TREATMENT CODES

CODETYPE	CODE	DESCRIPTION
Proc CPT	45330	Diagnostic sigmoidoscopy
Proc CPT	45331	Sigmoidoscopy and biopsy
Proc CPT	45332	Sigmoidoscopy w/FB removal
Proc CPT	45333	Sigmoidoscopy & polypectomy
Proc CPT	45334	Sigmoidoscopy for bleeding
Proc CPT	45335	Sigmoidoscopy w/submuc inj
Proc CPT	45336	Flexible fibroptc sigmdscpy
Proc CPT	45337	Sigmoidoscopy & decompress
Proc CPT	45338	Sigmoidoscopy w/tumr remove
Proc CPT	45339	Sigmoidoscopy w/ablate tumr
Proc CPT	45340	Sig w/balloon dilation
Proc CPT	45341	Sigmoidoscopy w/ultrasound
Proc CPT	45342	Sigmoidoscopy w/US guide bx
Proc CPT	45345	Sigmoidoscopy w/stent
Proc HCPCS	G0104	CA screen;flexi sigmoidscope
Proc HCPCS	G0106	Colon CA screen;barium enema
Proc CPT	0066T	CT colonography;screen
Proc CPT	0067T	CT colonography;dx
Proc CPT	0528F	Rcmnd flw-up 10 yrs docd
Proc CPT	0529F	Intrvl 3+yrs pts clnscp docd
Proc CPT	3018F	Colonoscopy assess doc'd
Proc CPT	44388	Colonoscopy
Proc CPT	44389	Colonoscopy with biopsy
Proc CPT	44390	Colonoscopy for foreign body
Proc CPT	44391	Colonoscopy for bleeding
Proc CPT	44392	Colonoscopy & polypectomy
Proc CPT	44393	Colonoscopy, lesion removal
Proc CPT	44394	Colonoscopy w/snare
Proc CPT	44397	Colonoscopy w/stent
Proc CPT	45355	Surgical colonoscopy
Proc CPT	45378	Diagnostic colonoscopy
Proc CPT	45379	Colonoscopy w/FB removal
Proc CPT	45380	Colonoscopy and biopsy
Proc CPT	45381	Colonoscopy, submucous inj
Proc CPT	45382	Colonoscopy/control bleeding
Proc CPT	45383	Lesion removal colonoscopy
Proc CPT	45384	Lesion remove colonoscopy
Proc CPT	45385	Lesion removal colonoscopy
Proc CPT	45386	Colonoscopy dilate stricture
Proc CPT	45387	Colonoscopy w/stent
Proc CPT	45391	Colonoscopy w/endoscope US
Proc CPT	45392	Colonoscopy w/endoscopic FNB
Proc HCPCS	G0105	Colorectal scrn; hi risk ind
Proc HCPCS	G0120	Colon ca scrn; barium enema
Proc HCPCS	G0121	Colon ca scrn not hi rsk ind

Proc ICD9	45.21	Transabdominal endoscopy of large intestine
Proc ICD9	45.22	Endoscopy of large intestine through artificial stoma
Proc ICD9	45.23	Colonoscopy
Proc ICD9	45.25	Closed [endoscopic] biopsy of large intestine
Proc ICD9	45.41	Excision of lesion or tissue of large intestine
Proc ICD9	45.42	Endoscopic polypectomy of large intestine
Proc ICD9	45.43	Endoscopic destruction of other lesion or tissue of large intestine
Proc ICD9	48.36	[Endoscopic] polypectomy of rectum
Proc ICD9	45.24	Flexible sigmoidoscopy
Proc ICD9	48.21	Transabdominal proctosigmoidoscopy
Proc ICD9	48.22	Proctosigmoidoscopy through artificial stoma
Proc ICD9	48.23	Rigid proctosigmoidoscopy
Proc ICD9	48.24	Closed [endoscopic] biopsy of rectum
Proc CPT	45300	Proctosigmoidoscopy dx
Proc CPT	45302	Prctsgmdscpy w coll spec brs
Proc CPT	45303	Proctosigmoidoscopy dilate
Proc CPT	45305	Proctosigmoidoscopy w/bx
Proc CPT	45307	Proctosigmoidoscopy FB
Proc CPT	45308	Proctosigmoidoscopy removal
Proc CPT	45309	Proctosigmoidoscopy removal
Proc CPT	45315	Proctosigmoidoscopy removal
Proc CPT	45317	Proctosigmoidoscopy bleed
Proc CPT	45320	Proctosigmoidoscopy ablate
Proc CPT	45321	Proctosigmoidoscopy volvul
Proc CPT	45327	Proctosigmoidoscopy w/stent

Current Treatment codes

CODETYPE	CODE	DESCRIPTION	TRT Type
Proc CPT	44110	Excise intestine lesion(s)	Surgery
Proc CPT	44111	Excision of bowel lesion(s)	Surgery
Proc CPT	44139	Mobilization of colon	Surgery
Proc CPT	44140	Partial removal of colon	Surgery
Proc CPT	44141	Partial removal of colon	Surgery
Proc CPT	44143	Partial removal of colon	Surgery
Proc CPT	44144	Partial removal of colon	Surgery
Proc CPT	44145	Partial removal of colon	Surgery
Proc CPT	44146	Partial removal of colon	Surgery
Proc CPT	44147	Partial removal of colon	Surgery
Proc CPT	44150	Removal of colon	Surgery
Proc CPT	44151	Removal of colon/ileostomy	Surgery
Proc CPT	44152	Removal of colon/ileostomy	Surgery
Proc CPT	44153	Removal of colon/ileostomy	Surgery
Proc CPT	44155	Removal of colon/ileostomy	Surgery
Proc CPT	44156	Removal of colon/ileostomy	Surgery
Proc CPT	44157	Colectomy w/ileoanal anast	Surgery
Proc CPT	44158	Colectomy w/neo-rectum pouch	Surgery

Proc CPT	44160	Removal of colon	Surgery
Proc CPT	44204	Laparo partial colectomy	Surgery
Proc CPT	44205	Lap colectomy part w/ileum	Surgery
Proc CPT	44206	Lap part colectomy w/stoma	Surgery
Proc CPT	44207	L colectomy/coloproctostomy	Surgery
Proc CPT	44208	L colectomy/coloproctostomy	Surgery
Proc CPT	44209	Unlisted laparoscopy procedu	Surgery
Proc CPT	44210	Laparo total proctocolectomy	Surgery
Proc CPT	44211	Lap colectomy w/proctectomy	Surgery
Proc CPT	44212	Laparo total proctocolectomy	Surgery
Proc CPT	44238	Laparoscope proc, intestine	Surgery
Proc CPT	44239	Laparoscope proc, rectum	Surgery
Proc CPT	45110	Removal of rectum	Surgery
Proc CPT	45111	Partial removal of rectum	Surgery
Proc CPT	45112	Removal of rectum	Surgery
Proc CPT	45113	Partial proctectomy	Surgery
Proc CPT	45114	Partial removal of rectum	Surgery
Proc CPT	45116	Partial removal of rectum	Surgery
Proc CPT	45119	Remove rectum w/reservoir	Surgery
Proc CPT	45120	Removal of rectum	Surgery
Proc CPT	45121	Removal of rectum and colon	Surgery
Proc CPT	45123	Partial proctectomy	Surgery
Proc CPT	45126	Pelvic exenteration	Surgery
Proc CPT	45160	Excision of rectal lesion	Surgery
Proc CPT	45170	Excision of rectal lesion	Surgery
Proc CPT	45190	Destruction, rectal tumor	Surgery
Proc CPT	45300	Proctosigmoidoscopy dx	Surgery
Proc CPT	45302	Prctsgmdscpy w coll spec brs	Surgery
Proc CPT	45303	Proctosigmoidoscopy dilate	Surgery
Proc CPT	45305	Proctosigmoidoscopy w/bx	Surgery
Proc CPT	45307	Proctosigmoidoscopy FB	Surgery
Proc CPT	45308	Proctosigmoidoscopy removal	Surgery
Proc CPT	45309	Proctosigmoidoscopy removal	Surgery
Proc CPT	45315	Proctosigmoidoscopy removal	Surgery
Proc CPT	45320	Proctosigmoidoscopy ablate	surgery
Proc CPT	45321	Proctosigmoidoscopy volvul	surgery
Proc CPT	45327	Proctosigmoidoscopy w/stent	surgery
Proc CPT	45330	Diagnostic sigmoidoscopy	surgery
Proc CPT	45331	Sigmoidoscopy and biopsy	surgery
Proc CPT	45332	Sigmoidoscopy w/FB removal	surgery
Proc CPT	45333	Sigmoidoscopy & polypectomy	surgery
Proc CPT	45334	Sigmoidoscopy for bleeding	surgery
Proc CPT	45335	Sigmoidoscopy w/submuc inj	surgery
Proc CPT	45336	Flexible fibroptc sigmdscpy	surgery
Proc CPT	45337	Sigmoidoscopy & decompress	surgery
Proc CPT	45338	Sigmoidoscopy w/tumr remove	surgery
Proc CPT	45339	Sigmoidoscopy w/ablate tumr	surgery

Proc CPT	45378	Diagnostic colonoscopy	surgery
Proc CPT	45379	Colonoscopy w/FB removal	surgery
Proc CPT	45380	Colonoscopy and biopsy	surgery
Proc CPT	45381	Colonoscopy, submucous inj	surgery
Proc CPT	45382	Colonoscopy/control bleeding	surgery
Proc CPT	45383	Lesion removal colonoscopy	surgery
Proc CPT	45384	Lesion remove colonoscopy	surgery
Proc CPT	45385	Lesion removal colonoscopy	surgery
Proc CPT	45386	Colonoscopy dilate stricture	surgery
Proc CPT	45387	Colonoscopy w/stent	surgery
Proc CPT	74270	Contrast X-ray exam of colon	surgery
Proc CPT	74280	Contrast X-ray exam of colon	surgery
Proc CPT	82270	Occult blood, feces	surgery
Proc CPT	82271	Occult blood, other sources	surgery
Proc CPT	82272	Occult bld feces, 1-3 tests	surgery
Proc CPT	82274	Assay test for blood, fecal	surgery
ICISS Med	IC0068	Colon Cancer - Proctosigmoidoscopy	surgery
Proc CPT	81400	Mopath procedure Level 1	chemotherapy
Proc HCPCS	C9205	Oxaliplatin	chemotherapy
Proc HCPCS	C9214	Injection, bevacizumab	chemotherapy
Proc HCPCS	C9215	Injection, cetuximab	chemotherapy
Proc HCPCS	C9235	Injection, panitumumab	chemotherapy
Proc HCPCS	C9257	Bevacizumab injection	chemotherapy
Proc HCPCS	C9415	Doxorubic HCl chemo, brand	chemotherapy
Proc HCPCS	J0640	Leucovorin calcium injection	chemotherapy
Proc HCPCS	J8520	Capecitabine, oral, 150 mg	chemotherapy
Proc HCPCS	J8521	Capecitabine, oral, 500 mg	chemotherapy
Proc HCPCS	J9000	Doxorubicin HCl injection	chemotherapy
Proc HCPCS	J9001	Doxorubicin HCl liposome inj	chemotherapy
Proc HCPCS	J9035	Bevacizumab injection	chemotherapy
Proc HCPCS	J9055	Cetuximab injection	chemotherapy
Proc HCPCS	J9190	Fluorouracil injection	chemotherapy
Proc HCPCS	J9206	Irinotecan injection	chemotherapy
Proc HCPCS	J9263	Oxaliplatin	chemotherapy
Proc HCPCS	J9303	Panitumumab injection	chemotherapy
Proc HCPCS	Q2024	Bevacizumab injection	chemotherapy
Proc HCPCS	Q2048	Doxil injection	chemotherapy
Proc HCPCS	Q2049	Imported Lipodox inj	chemotherapy
Proc HCPCS	S0116	Bevacizumab 100 mg	chemotherapy
Proc HCPCS	S3722	Dose optimization AUC - 5FU	chemotherapy
Proc CPT	36260	Insertion of infusion pump	chemotherapy
Proc CPT	36640	Insertion catheter, artery	chemotherapy
Proc CPT	36823	Insertion of cannula(s)	chemotherapy
Proc CPT	4180F	Adj thxpy rx'd Stg3 colon ca	chemotherapy
Proc CPT	49418	Insert tun ip cath perc	chemotherapy
Proc CPT	61517	Implt brain chemotx add-on	chemotherapy
Proc CPT	96401	Chemo, anti-neopl, sq/im	chemotherapy

Proc CPT	96402	Chemo hormon antineopl sq/im	chemotherapy
Proc CPT	96405	Chemo intralesional, up to 7	chemotherapy
Proc CPT	96406	Chemo intralesional over 7	chemotherapy
Proc CPT	96409	Chemo, IV push, sngl drug	chemotherapy
Proc CPT	96411	Chemo, IV push, addl drug	chemotherapy
Proc CPT	96413	Chemo, IV infusion, 1 hr	chemotherapy
Proc CPT	96415	Chemo, IV infusion, addl hr	chemotherapy
Proc CPT	96416	Chemo prolong infuse w/pump	chemotherapy
Proc CPT	96417	Chemo IV infus each addl seq	chemotherapy
Proc CPT	96420	Chemo, ia, push technique	chemotherapy
Proc CPT	96422	Chemo ia infusion up to 1 hr	chemotherapy
Proc CPT	96423	Chemo ia infuse each addl hr	chemotherapy
Proc CPT	96425	Chemotherapy,infusion method	chemotherapy
Proc CPT	96440	Chemotherapy, intracavitary	chemotherapy
Proc CPT	96445	Chemotherapy, intracavitary	chemotherapy
Proc CPT	96446	Chemotx admn prtl cavity	chemotherapy
Proc CPT	96450	Chemotherapy, into CNS	chemotherapy
Proc CPT	96542	Chemotherapy injection	chemotherapy
Proc CPT	96549	Chemotherapy, unspecified	chemotherapy
Proc HCPCS	J9190	Fluorouracil injection	chemotherapy
Proc HCPCS	C8953	Chemotx adm, IV push	chemotherapy
Proc HCPCS	C8954	Chemotx adm, IV inf up to 1h	chemotherapy
Proc HCPCS	C8955	Chemotx adm, IV inf, addl hr	chemotherapy
Proc HCPCS	G0292	Adm exp drugs,clinical trial	chemotherapy
Proc HCPCS	G0355	Chemo administrate subcut/IM	chemotherapy
Proc HCPCS	G0359	Chemotherapy IV 1 hr initi	chemotherapy
Proc HCPCS	G0360	Each additional hr 1-8 hrs	chemotherapy
Proc HCPCS	G0361	Prolong chemo infuse>8hrs pu	chemotherapy
Proc HCPCS	G8371	Chemother not rec stg3 colon	chemotherapy
Proc HCPCS	G8372	Chemother rec stg 3 colon ca	chemotherapy
Proc HCPCS	G8373	Chemo plan docum prior chemo	chemotherapy
Proc HCPCS	G8374	Chemo plan not doc prior che	chemotherapy
Proc HCPCS	G8377	MD doc colon ca pt inelig ch	chemotherapy
Proc HCPCS	G9021	Chemo assess nausea vomit L1	chemotherapy
Proc HCPCS	G9022	Chemo assess nausea vomit L2	chemotherapy
Proc HCPCS	G9023	Chemo assess nausea vomit L3	chemotherapy
Proc HCPCS	G9024	Chemo assess nausea vomit L4	chemotherapy
Proc HCPCS	G9025	Chemo assessment pain level1	chemotherapy
Proc HCPCS	G9026	Chemo assessment pain level2	chemotherapy
Proc HCPCS	G9027	Chemo assessment pain level3	chemotherapy
Proc HCPCS	G9028	Chemo assessment pain level4	chemotherapy
Proc HCPCS	G9029	Chemo assess for fatigue L1	chemotherapy
Proc HCPCS	G9030	Chemo assess for fatigue L2	chemotherapy
Proc HCPCS	G9031	Chemo assess for fatigue L3	chemotherapy
Proc HCPCS	G9032	Chemo assess for fatigue L4	chemotherapy
Proc HCPCS	J7150	Prescription drug, oral chem	chemotherapy
Proc HCPCS	J9999	Chemotherapy drug	chemotherapy

Proc HCPCS	Q0083	Chemo by other than infusion	chemotherapy
Proc HCPCS	Q0084	Chemotherapy by infusion	chemotherapy
Proc HCPCS	Q0085	Chemo by both infusion and o	chemotherapy
Proc HCPCS	Q0162	Ondansetron oral	chemotherapy
Proc HCPCS	Q0163	Diphenhydramine HCl 50mg	chemotherapy
Proc HCPCS	Q0164	Prochlorperazine maleate 5mg	chemotherapy
Proc HCPCS	Q0165	Prochlorperazine maleate10mg	chemotherapy
Proc HCPCS	Q0166	Granisetron HCl 1 mg oral	chemotherapy
Proc HCPCS	Q0167	Dronabinol 2.5mg oral	chemotherapy
Proc HCPCS	Q0168	Dronabinol 5mg oral	chemotherapy
Proc HCPCS	Q0169	Promethazine HCl 12.5mg oral	chemotherapy
Proc HCPCS	Q0170	Promethazine HCl 25 mg oral	chemotherapy
Proc HCPCS	Q0171	Chlorpromazine HCl 10mg oral	chemotherapy
Proc HCPCS	Q0172	Chlorpromazine HCl 25mg oral	chemotherapy
Proc HCPCS	Q0173	Trimethobenzamide HCl 250mg	chemotherapy
Proc HCPCS	Q0174	Thiethylperazine maleate10mg	chemotherapy
Proc HCPCS	Q0175	Perphenazine 4mg oral	chemotherapy
Proc HCPCS	Q0176	Perphenazine 8mg oral	chemotherapy
Proc HCPCS	Q0177	Hydroxyzine pamoate 25mg	chemotherapy
Proc HCPCS	Q0178	Hydroxyzine pamoate 50mg	chemotherapy
Proc HCPCS	Q0179	Ondansetron HCl 8 mg oral	chemotherapy
Proc HCPCS	Q0180	Dolasetron mesylate oral	chemotherapy
Proc HCPCS	Q0181	Unspecified oral anti-emetic	chemotherapy
Proc HCPCS	S5019	Chemotherapy admin supplies	chemotherapy
Proc HCPCS	S5020	Chemotherapy admin supplies	chemotherapy
Proc HCPCS	S9329	HIT chemo per diem	chemotherapy
Proc HCPCS	S9330	HIT cont chem diem	chemotherapy
Proc HCPCS	S9331	HIT intermit chemo diem	chemotherapy
Proc HCPCS	S9425	Nursing services and all nec	chemotherapy
Proc CPT	0190T	Place intraoc radiation src	radiation
Proc CPT	01922	Anesth, CAT or MRI scan	radiation
Proc CPT	0197T	Intrafraction track motion	radiation
Proc CPT	0520F	Rad dos limts prior 3D rad	radiation
Proc CPT	32553	Ins mark thor for rt perq	radiation
Proc CPT	4165F	3D-CRT/IMRT received	radiation
Proc CPT	49327	Lap ins device for rt	radiation
Proc CPT	49411	Ins mark abd/pel for rt perq	radiation
Proc CPT	49412	Ins device for rt guide open	radiation
Proc CPT	55876	Place rt device/marker, pros	radiation
Proc CPT	6045F	Rad expos in end rprt fluro	radiation
Proc CPT	76950	Echo guidance radiotherapy	radiation
Proc CPT	76965	Echo guidance radiotherapy	radiation
Proc CPT	77014	CT scan for therapy guide	radiation
Proc CPT	77261	Radiation therapy planning	radiation
Proc CPT	77262	Radiation therapy planning	radiation
Proc CPT	77263	Radiation therapy planning	radiation
Proc CPT	77280	Set radiation therapy field	radiation

Proc CPT	77285	Set radiation therapy field	radiation
Proc CPT	77290	Set radiation therapy field	radiation
Proc CPT	77295	Set radiation therapy field	radiation
Proc CPT	77299	Radiation therapy planning	radiation
Proc CPT	77300	Radiation therapy dose plan	radiation
Proc CPT	77331	Special radiation dosimetry	radiation
Proc CPT	77332	Radiation treatment aid(s)	radiation
Proc CPT	77333	Radiation treatment aid(s)	radiation
Proc CPT	77334	Radiation treatment aid(s)	radiation
Proc CPT	77336	Radiation physics consult	radiation
Proc CPT	77338	Design mlc device for imrt	radiation
Proc CPT	77370	Radiation physics consult	radiation
Proc CPT	77371	SRS, multisource	radiation
Proc CPT	77372	SRS, linear based	radiation
Proc CPT	77373	SBRT delivery	radiation
Proc CPT	77399	External radiation dosimetry	radiation
Proc CPT	77401	Radiation treatment delivery	radiation
Proc CPT	77402	Radiation treatment delivery	radiation
Proc CPT	77403	Radiation treatment delivery	radiation
Proc CPT	77404	Radiation treatment delivery	radiation
Proc CPT	77406	Radiation treatment delivery	radiation
Proc CPT	77407	Radiation treatment delivery	radiation
Proc CPT	77408	Radiation treatment delivery	radiation
Proc CPT	77409	Radiation treatment delivery	radiation
Proc CPT	77411	Radiation treatment delivery	radiation
Proc CPT	77412	Radiation treatment delivery	radiation
Proc CPT	77413	Radiation treatment delivery	radiation
Proc CPT	77414	Radiation treatment delivery	radiation
Proc CPT	77416	Radiation treatment delivery	radiation
Proc CPT	77418	Radiation tx delivery, IMRT	radiation
Proc CPT	77421	Stereoscopic X-ray guidance	radiation
Proc CPT	77422	Neutron beam tx, simple	radiation
Proc CPT	77423	Neutron beam tx, complex	radiation
Proc CPT	77427	Radiation tx management, x5	radiation
Proc CPT	77431	Radiation therapy management	radiation
Proc CPT	77432	Stereotactic radiation trmt	radiation
Proc CPT	77435	SBRT management	radiation
Proc CPT	77469	Io radiation tx management	radiation
Proc CPT	77470	Special radiation treatment	radiation
Proc CPT	77499	Radiation therapy management	radiation
Proc CPT	77761	Apply intrcav radiat simple	radiation
Proc CPT	77762	Apply intrcav radiat interm	radiation
Proc CPT	77763	Apply intrcav radiat compl	radiation
Proc CPT	77776	Apply interstit radiat simpl	radiation
Proc CPT	77777	Apply interstit radiat inter	radiation
Proc CPT	77778	Apply interstit radiat compl	radiation
Proc CPT	77789	Apply surface radiation	radiation

Proc CPT	77790	Radiation handling	radiation
Proc CPT	92974	Cath place, cardio brachytx	radiation
Proc ICD9	92	Nuclear medicine	radiation
Proc ICD9	92.2	Therapeutic radiology and nuclear medicine	radiation
Proc ICD9	92.20	Infusion of liquid brachytherapy radioisotope	radiation
Proc ICD9	92.21	Superficial radiation	radiation
Proc ICD9	92.22	Orthovoltage radiation	radiation
Proc ICD9	92.23	Radioisotopic teleradiotherapy	radiation
Proc ICD9	92.24	Teleradiotherapy using photons	radiation
Proc ICD9	92.25	Teleradiotherapy using electrons	radiation
Proc ICD9	92.26	Teleradiotherapy of other particulate radiation	radiation
Proc ICD9	92.27	Implantation or insertion of radioactive elements	radiation
Proc ICD9	92.28	Injection or instillation of radioisotopes	radiation
Proc ICD9	92.29	Other radiotherapeutic procedure	radiation

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