

Curriculum Vitae

Name: Gaurav Deshpande

Degree and Date to be Conferred: Ph.D., 2013

Email: gauravdeshpande@gmail.com

Collegiate Institutions Attended:

2005-2013	Doctor of Philosophy Pharmaceutical Health Services Research University of Maryland Baltimore, Maryland
2006-2013	Master of Science Epidemiology University of Maryland Baltimore, Maryland
2002-2004	M.S., Pharmacy Administration St. John's University New York, New York
1997-2001	Bachelor of Science in Pharmacy University of Mumbai Mumbai, India

Major: Pharmacoepidemiology

Professional Publications:

Charneski L, **Deshpande G**, Weiss Smith S; The impact of an antimicrobial allergy label in the medical record on patient's clinical course; *Pharmacotherapy*; 31(8):742-7; August 2011

Weiss Smith S, **Deshpande G**, Chung S, Gogolak, V; FDA's Drug Safety Surveillance Program: Adverse Event Reporting Trends; *Arch Intern Med*; 171(6):591-593; March 28, 2011

Deshpande G, Gogolak V, Weiss S; Data Mining in Drug Safety: Review of published threshold criteria for defining signals of disproportionate reporting; *Pharmaceut Med*; 24(1): 37-43; February 1, 2010

Boyer R, McPherson, **Deshpande G**, Weiss S; Improving medication error reporting in hospice care; *Am J Hosp Palliat Care*; May 2009; Epub

Shaya F, **Deshpande G**; New Treatment Approaches to Diabetes; May 2006; *Managed Care*; 15(5):38-41

Posters and Presentation:

Wallace L, Phillips S, Zhao Y, **Deshpande G**, Yood M, Oliveria S; Use of opioids for pediatric pain treatment: A population study; 32nd Annual Scientific Meeting by American Pain Society. May 2013 (Poster)

Oliveria S, Wallace L, Phillips S, Wells KE, Alford SH, Zhao Y, **Deshpande G**, Yood M; Pediatric Use of Single-Entity Extended Release Oxycodone; 14th World Congress on pain by International Association for the Study of Pain. August 2012 (Poster)

Oliveria S, Wallace L, Phillips S, Wells KE, Alford SH, Zhao Y, **Deshpande G**, Yood M; Pediatric Use of Single-Entity Extended Release Oxycodone; 28th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Barcelona, Spain. August 2012 (Poster)

Deshpande G, Zheng X, Polli J, Weiss-Smith S; A pharmacoepidemiologic study design of drugside effects from in vitro cell culture; FDA OCP Science Day, Rockville, MD. October 2009 (Poster)

Deshpande G, Charneski L, Weiss S, Wilks A; Assessing the impact of an antimicrobial allergy label in the medical record on patient's clinical course; 2009 American College of Clinical Pharmacy (ACCP) Annual Meeting, Anaheim, CA; October 2009. (Poster)

Deshpande G, Weiss-Smith S; Thiazolidinediones and Bone Loss: A systematic review. *Pharmacoepidemiology and Drug Safety*, 2009; 18: S177. International Society of Pharmacoepidemiology Annual Meeting, Providence, RI. August 2009. (Poster)

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Deshpande G, Weiss S, Tommasello A, Simoni-Wastila L, Gogolak V; Characteristics of Adverse Event Reporting for Narcotic and Non-Narcotic Analgesics; ISPE 2007 Annual Meeting, Quebec City, Canada; August 2007 (Poster)

Deshpande G, Weiss S, Tommasello A, Simoni-Wastila L, Gogolak V; Characteristics of Adverse Event Reporting for Narcotic and Non-Narcotic Analgesics; DIA 43rd Annual Meeting, Atlanta, GA; June 2007 (Poster)

Shaya F, **Deshpande G**; Looking at Compliance at the Physician Level – Creating a Patient-Centered Focus for Addressing Adherence; Center for Business Intelligence’s 5th Annual Forum on “Patient Compliance, Adherence and Persistency”; Philadelphia, PA; April 2006

Deshpande G, Agrawal M; Analysis of Appeals used in Generic Prescription Drug Advertisements; “Association of Collegiate Marketing Educators”(ACME), 31st Annual Conference; Florida; March 2004 (*Winner of Best in Track Paper Award*)

Weiss S, **Deshpande G**. Cohort Studies in Epidemiology, Maryland General Hospital, Fall 2009

Deshpande G. Introduction on using QScan, an analysis tool for FDA-AERS. In: *Pharmacoepidemiology*, University of Maryland, Pharmaceutical Health Services Research Department, Fall 2008

Deshpande G. Introduction to Causal Inferences. In: *Study Design and Analysis*, University of Maryland, School of Pharmacy, Spring 2008

Deshpande G, Introduction on using QScan, an analysis tool for FDA-AERS. In: *Pharmacoepidemiology*, University of Maryland, Pharmaceutical Health Services Research Department, Fall 2007

Professional Positions Held:

2010-Present

Research Analyst

HealthCore, Inc. – A WellPoint Subsidiary
Wilmington, Delaware

2009-Present	Graduate Research Assistant National Cancer Institute (NCI) Veterans Administration (VA) University of Maryland Baltimore, Maryland
2006-2008	Graduate Research Assistant The Pharmaceutical Research and Manufacturers of America (PhRMA) Baltimore, Maryland
2005-2006	Teaching Assistant Department of Pharmaceutical Services University of Maryland Baltimore, Maryland
2004-2005	Pharmacy Intern Downtown Pharmacy Inc. New York, New York
2003-2004	Teaching Assistant Department of Pharmacy Administration & Allied Health Sciences St. John's University New York, New York

Committee Memberships:

	International Society of Pharmacoepidemiology (ISPE) University of Maryland International Society for Pharmacoepidemiology Student Chapter, Baltimore, Maryland
2008-2009	President
2008-2010	Co-founder
2008-2010	Member
	University of Maryland International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Student Chapter, Baltimore, Maryland
2006-2008	Public Relations Officer
2006-2010	Member
	University of Maryland, International Students Organization
2007-2008	Secretary

2006-2007 IT Secretary
2005-2010 Member

Special Awards:

2008-2009 Dr Arthur Schwartz Memorial Scholarship Award,
University of Maryland, School of Pharmacy, Baltimore,
Maryland

2009 Graduate Student Association Travel Fellowship,
University of Maryland Graduate Students Association,
University of Maryland, Baltimore, Maryland

2007 Student Travel Fellowship, Drug Information Association
43rd Annual Meeting, Atlanta, Georgia

2006-2010 Graduate Research Assistantship, Department of
Pharmaceutical Health Services Research, University of
Maryland, School of Pharmacy, Baltimore, Maryland

2005-2006 Teaching Assistantship, Department of Pharmaceutical
Health Services Research, University of Maryland, School
of Pharmacy, Baltimore, Maryland

2004 Winner of Best in Track Paper; Association of Collegiate
Marketing Educators Conference; Orlando, Florida

2003-2004 Teaching Assistantship, Department of Pharmacy
Administration and Allied Health Sciences, St John's
University, New York, New York

2005-2010 University of Maryland, Indian Students Organization
Member

Abstract

Title of Dissertation: Association between cardiovascular drugs and colon cancer

Gaurav Deshpande, Doctor of Philosophy, 2013

Dissertation Directed by: Sheila Weiss, Professor, Pharmaceutical Health Services

Research

Abstract:

The objective of the study was to determine (1) if cardiovascular drugs (CV) are associated with increased risk of colon cancer (CC), (2) if the risk for any individual agent differs from the risk of the therapeutically class overall, and (3) if the risk differs for patients with CC on right side based on inhibition properties of some CV drugs for bile acid uptake. A population-based case control study was conducted using the HealthCore Integrated Research Database (HIRDSM), a US commercial insurance claims database. Incident cases of CC were patients aged 18 years or older at diagnosis, with first CC diagnostic claim between Jan 1, 2001 to Jan 30, 2011. Each case was matched to one eligible control based on: no diagnosis of CC during study period, actively enrolled at index date of the case, and matched to cases by length of pre-index enrollment (same or greater), sex, and age. Exposure to a CV drug was defined as at least one claim during the risk period. Conditional logistic regression was used to calculate adjusted Odds Ratios (OR). 36,736 cases of CC were identified and successfully matched to controls. Sensitivity analysis were conducted by using alternate case definition, varying lag time between last prescription and CC diagnosis, and setting a

required minimum CV drug exposure (12 months). The mean age was 60 years (about 30% were 50-60 years old). Enalapril, labetalol, cholestyramin, diltiazem and furosemide (ORs range:1.07-2.05) were positively associated with CC while atorvastatin, pravastatin and simvastatin (ORs range:0.68-0.94) were negatively associated with CC. In the sensitivity analyses, positive associations remained for just cholestyramine and diltiazem, whereas the negative associations remained for atorvastatin and simvastatin. These results are consistent with beneficial impact of statins on CC risk. Drugs identified as inhibitors of bile acid uptake were not associated with CC on right side. However, the association of individual drugs was not consistent with that therapeutic class as a whole. This suggests that risk may vary by individual agent. Grouping drugs into therapeutic classes for studies of cancer risk may introduce a bias driven by the predominant agents used in a particular population.

Association between cardiovascular drugs and colon cancer

by
Gaurav Deshpande

Dissertation submitted to the faculty of the Graduate School
of the University of Maryland, Baltimore in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2013

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Dedication

To my parents Anant and Nita Deshpande.

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I. INTRODUCTION

About Colorectal Cancer

Colorectal Cancer is the cancer of the colon (large intestine) or rectum. These cancers are sometimes referred to separately as colon cancer or rectal cancer, depending on where they start. It is the second leading cause of cancer-related deaths of cancers that affect both men and women in the United States and the third most common cancer in men and in women.¹

In most people, colorectal cancers develop slowly over a period of several years. Before a cancer develops, a growth or tissue usually begins as a non-cancerous polyp on the inner lining of the colon or rectum. Only some polyps change into a cancer and that depends on the type of polyp²:

Adenomatous polyps (adenomas): These have a potential to change into a cancer.

Hyperplastic polyps and inflammatory polyps: These are generally non-cancerous but there is a debate about these becoming pre-cancerous or perceived as a sign of having a greater risk of adenomas and cancer.

Dysplasia: This is a pre-cancerous condition where the cells in an area in the lining of the colon look abnormal. These cells have potential to change into cancer over time. This is usually seen in people who have had diseases such as ulcerative colitis and crohn's disease. Both these diseases cause chronic inflammation of the colon.

Types of cancer in the colon and rectum

Adenocarcinomas: These are most common type and more than 95% of colorectal cancers are of this type.

There exist other less common types of tumors which include:

Carcinoid tumors: These tumors develop because of specialized hormone-producing cells of the intestine.

Gastrointestinal Stromal Tumors: These develop from a special group of cells in the wall of the colon called as “interstitial cells of Cajal”. These tumors although found anywhere in the intestinal tract are unusual in the colon.

Lymphomas: These are cancers of immune cells that typically develop in the lymph nodes. They may also start in colon or rectum or other organs.

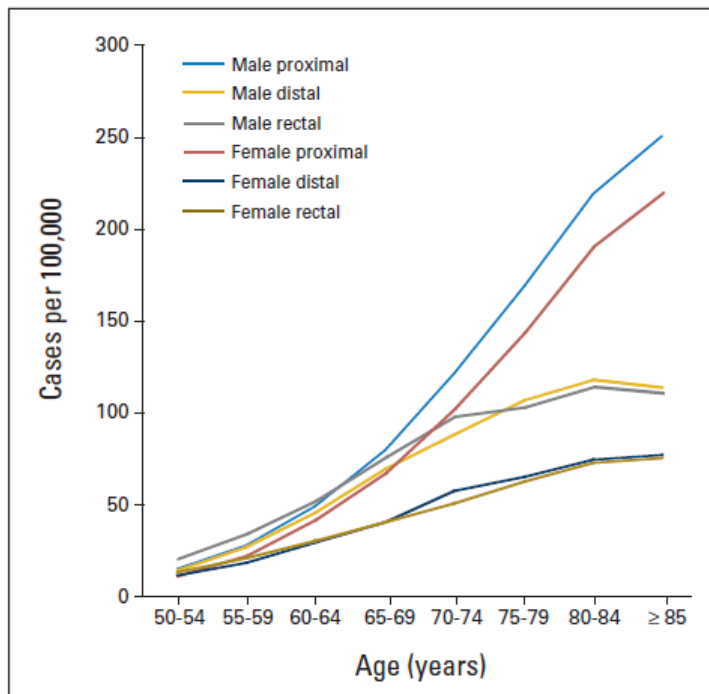
Risk Factors⁴

A variety of risk factors have been associated with colon or rectal cancer which includes age, history of CRC in first-degree relatives, history of sigmoidoscopy and/or colonoscopy; history of polyps; use of multivitamins; red meat, vegetable and fruit consumption; alcohol intake; elevated BMI (kg/m^2); cigarette smoking; use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs); current leisure-time vigorous activity; and estrogen status (assessed by menopausal status and hormone-replacement therapy (HRT) use. Some additional nutrient variables such as calcium dietary fiber and iron have been associated with CRC risk in some studies.³ Freedman et al developed a risk prediction tool for non-hispanic white men and women aged 50 years and above. The principal risk factors are discussed below.

Age

The risk of colorectal cancer increases with age. Younger adults may get colorectal cancer but the chances of developing increase markedly after age 50. More than 90% of the people diagnosed with colorectal cancer are 50 years or at the time of diagnosis.

Figure 1.1 Colorectal cancer incidence by tumor site for white non-Hispanic men and women [13 Surveillance, Epidemiology and End Results [SEER] sites 1992-2002]³



Family history

Individuals are more likely to get colorectal cancer if one of their parents and/or siblings have had this disease. Most of the colorectal cancers occur in people without a family history; about 20% of people diagnosed with CRC have one or more family members who have been affected previously.

Personal medical history

A history of (other types of) cancer, a history of colon polyps, and inflammatory diseases of the bowel can put an individual at increased risk.

Lifestyle

Cigarette smoking, heavy alcohol use, inactivity, obesity and a high-fat/low-fiber diet places an individual at an increased risk of colon cancer.

Screening

Regular screening or testing is one of the most powerful weapons in preventing colon cancer. From the time the first abnormal cells start to grow, it takes about 10 to 15 years to develop into colon cancer. Regular screening can prevent cancer altogether if polyps are found and removed before they turn into cancer.

Based on the recommendations from the American Cancer Society, U.S. Multisociety Task Force on Colorectal Cancer, and American College of Radiology; individuals who have no identified risk factors should begin screening at age 50.⁴ People with family history should consult their physician and begin screening at an early age.

The tests are grouped into two major categories^{4,5}:

Tests used primarily to detect cancer:

Fecal occult blood test (FOBT): Testing stool for small amounts of blood. Positive results are associated with an increased risk of colon cancer and advanced neoplasia; colonoscopy should be recommended if tests results are positive. If the results are negative, it should be repeated annually.

Fecal immunochemical tests

Stool DNA tests: Cancer cells that contain altered DNA are continuously shed into the colon and passed into the feces. Identification of this altered DNA in the feces is what the stool DNA tests target. Colonoscopy recommended on positive results. If the result is negative, the appropriate interval for a repeat test is uncertain (owing to the lack of longitudinal follow-up).

Tests with higher potential for cancer prevention

These tests help detect both precancerous polyps and early asymptomatic cancer. These tests include:

Sigmoidoscopy: Placement of a lighted tube into the rectum to examine the lower part of the colon. Positive findings at sigmoidoscopy result in a referral for colonoscopy.

Appropriate interval for repeat test is every 5 years.

Colonoscopy: A lighted tube with an attached camera is inserted through the rectum to view the large bowel and to take tissue samples. Appropriate interval for repeat test is every 10 years.

Barium enema: A type of X-ray procedure. Appropriate interval for repeat test is every 5 years.

CT colonography (virtual colonoscopy): This is one of the newly recommended screening tests. Recent data suggest that CT colonography is comparable to optical colonoscopy for the detection of cancer and polyps of significant size. Offers advantages over other tests such as minimally invasive, whole colon-structural examination with high sensitivity for detection of advanced neoplasia. The test time is efficient, no sedation, recovery time, or need for a scheduled driver after the procedure is required and patients have the capability to return to work the same day. Appropriate interval for repeat test is every 5 years.

Genetic Screening

This is considered essential for people with a strong family history of colorectal polyps. Genetic testing can determine if they carry the genes associated with a high risk of colon cancer.⁶

Prevalence of Cancer of the colon and rectum

Based on the data available on Jan 1, 2005, there were approximately 1,095,283 men and women alive who had a history of the cancer of colon and rectum. The lifetime risk of colorectal cancer is 1 in 19 men and women. It is estimated that 148,810 men and women (77,250 men and 71,560 women) will be diagnosed with cancer of the colon and rectum in 2008. The age adjusted incidence rate was 50.6 per 100,000 persons per year. These rates are based on cases diagnosed in the years 2001-2005.⁷

Cancer of the colon and rectum is the second leading cause of cancer-related deaths in the United States for men and women combined.⁸ It is expected to cause about 49,960 deaths (24,260 men and 25,700 women) during 2008.

The death rate from colorectal cancer has been dropping for more than 20 years.^{7;8} Based on the patients who died in 2001-2005 in the US; the age adjusted death-rate was 18.8 per 100,000 men and women per year. Considering the sex separately, the death rate is 22.7 per 100,000 men and 15.9 per 100,000 women.

Cardiovascular disease (CVD)

Diseases of disorders of the cardiovascular system are termed as cardiovascular diseases. Cardiovascular diseases include conditions such as hypertension, coronary heart disease, heart attack, chest pain, stroke, etc. An estimated 82,600,000 American adults (>1 in 3) have 1 or more types of cardiovascular disease.⁹ The total and direct and indirect cost of CVD and stroke in the United States for 2008 is estimated to be \$297.7 billion.⁹

Hypertension or high blood pressure is one of the most common chronic medical conditions. It is reported to have affected more than 65 million individuals in the United States. In 2005-2006, 29% of all US adults 18 years and older were hypertensive.

According to the statistics obtained from the National Center for Health Statistics, overall 68% of adults with hypertension were using anti-hypertensive medication.

Figure 1.2. Prevalence of cardiovascular disease in adults ≥ 20 years of age and sex (National Health and Nutrition Examination Survey; 2005-2008) Source: National Center for Health Statistics and National Heart, Lung and Blood Institute. These data include coronary heart disease, heart failure, stroke and hypertension⁹

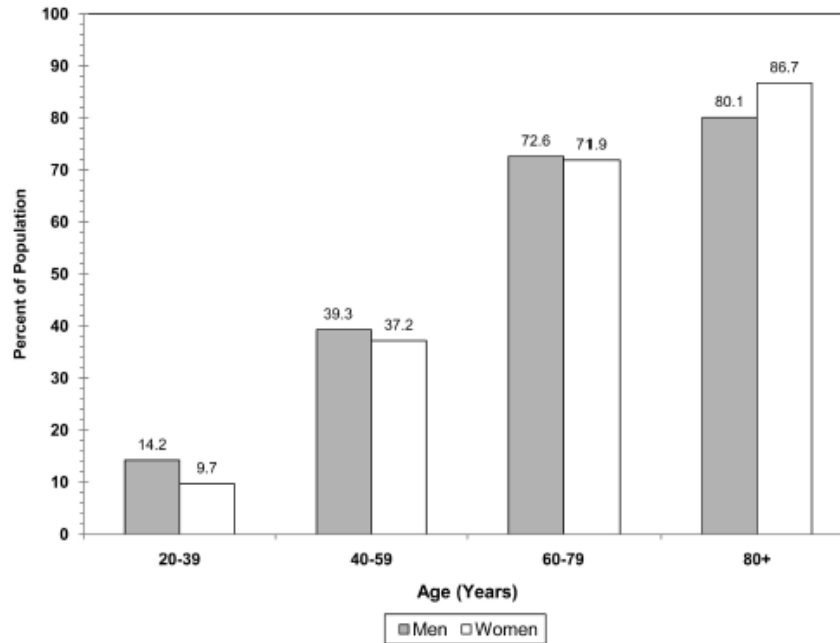
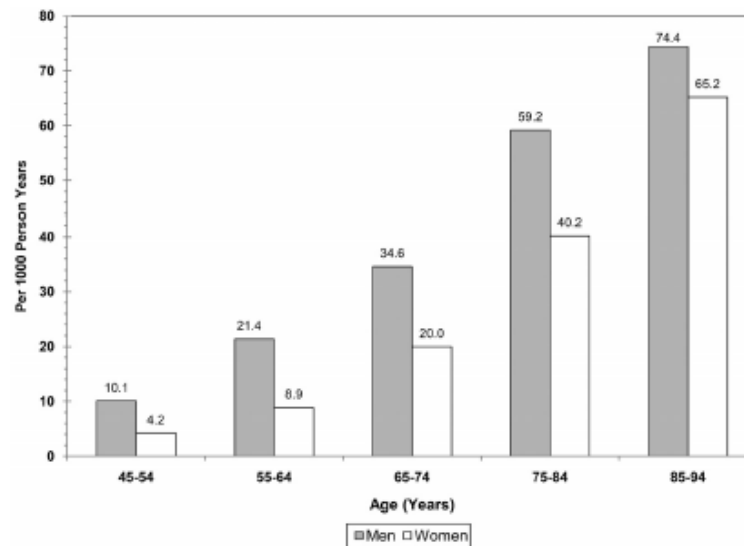


Figure 1.3. Incidence of cardiovascular disease by age and sex (Framingham Heart Study, 1980-2003) Source: National Heart, Lung and Blood Institute⁹



Cardiovascular Drugs

The drug classes used commonly in the treatment of cardiovascular conditions are as follows: Beta (β) blockers, Angiotensin converting enzyme (ACE) inhibitors, Angiotensin receptor blockers (ARB), Calcium channel blockers (CCB), Diuretics, Fibrates and Statins. Based on the estimates from the National Health and Nutrition Examination Survey (NHANES), the prevalence of use by different drug classes is given below.

Table 1.1: Prevalence of drug use by drug class in the United States^{10;11}

Drug class	Time frame	Prevalence % (SE [†])
Prevalence among hypertensive adults		
Diuretics	2009-2010	35.8 (1.2)
Beta blockers	2009-2010	31.9 (1.6)
ACE inhibitors	2009-2010	33.3 (1.1)
Calcium channel blockers	2009-2010	20.9 (1.4)
Angiotensin receptor blockers	2009-2010	22.2 (1.6)
Prevalence among patients diagnosed with hypercholesterolemia		
Statins	2003-2006	91.3 (0.9)
Fibrates	2003-2006	8.3 (1.0)

[†]SE: Standard error

Cardiovascular Drugs and the risk of cancer

Cardiovascular drugs have always been the subject of speculation regarding their carcinogenic potential. This associated has been disputed since the increased cancer risk first arose with *Rauwolfia* use in women with breast cancer.¹² Drug classes such as calcium channel blockers, diuretics, beta blockers, ACE inhibitors, angiotensin receptor blockers, statins and fibrates have been associated with cancer as protective or promotive. Several mechanisms have been hypothesized to link the association between use of the cardiovascular drugs with risk of cancer. Statins are known to inhibit the production of endogenous cholesterol and block protein prenylation.¹³⁻¹⁵ As a result statins may

influence cell proliferation (clinically seen as cancer growth and metastasis). Angiotensin receptor blockers are known to play a role in regulating angiogenesis, cell proliferation, and tumor progression providing a justification for concern regarding risk of cancer theoretically.^{16;17} Beta blockers weaken the norepinephrine signaling systematically thus reducing the risk of different types of cancer based on animal and cell studies.¹⁸⁻²⁰

Evidence on the use of cardiovascular drugs and risk of cancer from the available literature has been summarized in the Table 1.2 as follows:

Table 1.2: Summary of the literature for cardiovascular drugs and the risk of cancer by drug class

Study	Drug class	Sample	Odds ratio/Relative risk (CI)	Cancer type
Calcium channel blockers				
Pahor et al 1996 ²¹	Calcium channel blockers	750 participants (age 71 to 96 years) of an ongoing descriptive study living in the communities of East Boston, MA, Iowa and New Haven, CT	Calcium channel blockers compared to β -blockers, all CCBs had a significantly increased risk of cancer (RR 2.02; 95% CI 1.16-3.54)	Lung, urinary tract, colorectal, prostate, lymphoma and leukemia, breast, uterus, skin, liver, gallbladder, pancreas and stomach
Jick et al 1997 ²²	Calcium channel blockers and ACE inhibitors	446 cases and 1,750 controls	For CCBs compared to β -blockers, OR 1.27 (95% CI, 0.98-1.63). For ACE inhibitors OR 0.79 (95% CI, 0.58-1.06)	All cancers combined
Sorensen et al 2000 ²³	Calcium channel blockers	23,167 users	RR 1.04 (95% CI, 0.98-1.11) For colon cancer (RR 0.86, 95% CI 0.68-1.06) For cancer of the rectum (RR, 0.97 95% CI, 0.73-1.27)	All cancers combined and separately for each type of cancer

Table 1.2 Continued

Study	Drug class	Sample	Odds ratio/Relative risk (CI)	Cancer type
Boudreau et al 2008 ²⁴	Calcium channel blockers	665 cases and 665 controls	For colorectal cancer, OR 1.06 (95% CI, 0.72-1.55). For colon cancer, OR 1.08 (95% CI, 0.71-1.66)	Colorectal cancer
Bangalore et al 2011 ²⁵	Calcium channel blockers	6,839 cases	OR 1.05 (95% CI, 0.96-1.13)	Any cancer
Diuretics				
Tenenbaum et al 2001 ²⁶	Diuretics	14,166 patients	The higher incidence of colon cancer was observed only among non-users of aspirin (HR 1.96; 95% CI 1.21-3.17)	Colon cancer and all types of cancer
Boudreau et al 2008 ²⁴	Diuretics	665 cases and 665 controls	For colorectal cancer, OR 1.00 (95% CI, 0.70-1.44). For colon cancer, OR 1.00 (95% CI, 0.68-1.48)	Colorectal cancer
Bangalore et al ²⁵	Diuretics	6,548 cases	OR 1.00 (95% CI, 0.90-1.11)	Any cancer
Angiotensin-converting enzyme (ACE) inhibitors				
Lever et al 1998 ²⁷	ACE inhibitors	5,207 hypertensive patients	RR for incident and fatal cancers among patients receiving ACE inhibitors 0.72 (95% CI 0.5-0.92) and 0.65 (95% CI 0.44-0.93)	Incident cancer and fatal cancer
Friis et al 2001 ²⁸	ACE inhibitors	47,579 individuals	No risk reductions were observed. Colon (SIR 0.9, 95% CI 0.7-1.2) Rectum (SIR 0.8, 95% CI 0.6-1.2)	All cancers combined and separately for each type of cancer
Boudreau et al 2008 ²⁴	ACE inhibitors	665 cases and 665 controls	For colorectal cancer, OR 0.98 (95% CI, 0.67-1.43). For colon cancer, OR 1.00 (95% CI, 0.67-1.53)	Colorectal cancer

Table 1.2 Continued

Study	Drug class	Sample	Odds ratio/Relative risk (CI)	Cancer type
Kedika et al 2011 ²⁹	Lisinopril	4,660 patients	Use of lisinopril was associated with 41% reduction in the incidence of advanced adenomatous polyps	Adenomatous polyps
Bangalore et al 2011 ²⁵	ACE inhibitors	6,580 cases	OR 1.00 (95% CI, 0.92-1.09)	Any cancer
Angiotensin Receptor Blockers (ARB)				
Sipahi et al 2010 ³⁰	Meta-analysis of ARB users	61,590 patients with new cancer	RR 1.08 (95% CI, 1.01-1.15)	Any cancer
Bangalore et al 2011 ²⁵	ARB	6,613 cases	OR 1.01 (95% CI, 0.93-1.09)	Any cancer
Azoulay et al 2012 ³¹	ARB use relative to the use of diuretics or beta blockers	41,059 cases and 410,167 controls	RR 0.90(95% CI, 0.83-0.98)	Colorectal cancer
Bhaskaran et al 2012 ¹⁶	ARB compared with ACE inhibitors	377,649 users of ARB or ACE inhibitor	For colon cancer; HR 1.02 (95% CI, 0.91-1.16)	Any cancer, lung cancer, breast cancer, prostate cancer, colon cancer
Beta blockers				
Bangalore et al 2011 ²⁵	Beta blockers	6,386 cases	OR 0.97 (95% CI, 0.88-1.07)	Any cancer
Jansen et al 2012 ²⁰	Beta blockers	1,708 cases and 1,762 controls	OR 1.05 (95% CI, 0.86-1.29)	Colorectal cancer
Statins				

Table 1.2 Continued

Study	Drug class	Sample	Odds ratio/Relative risk (CI)	Cancer type
Coogan et al ³²	Statins	1,809 cases and 1,809 controls	Regular use of statins for at least 3 months was not associated with risk of colorectal cancer. Risk of stage IV cancer significantly lower among statin users (OR 0.49, 95% CI 0.26-0.91)	Colorectal cancer
Boudreau et al 2008 ²⁴	Statins	665 cases and 665 controls	For colorectal cancer, OR 1.02 (95% CI, 0.65-1.59). For colon cancer, OR 0.91 (95% CI, 0.55-1.50)	Colorectal cancer
Singh et al 2009 ³³	Statins	35,739 individuals	Risk among long-term use of statins similar to individuals never dispensed statins (IRR 0.89, 95% CI 0.70-1.13)	Colorectal cancer
Shadman et al 2009 ³⁴	Statins and/or NSAIDs	657 female cases and 1,342 female controls	Statin use was not associated with colorectal cancer risk. NSAID users had 30% reduction in risk of colorectal cancer (95% CI 0.56-0.88)	Colorectal cancer
Nielsen et al 2012 ¹⁵	Statins	18,721 statin users and 277,204 non-users of statins	For death from cancer, HR 0.85(95% CI, 0.82-0.87)	Any cancer related mortality
Fibrates				
Bonovas et al 2012 ³⁵	Meta-analysis of fibrate users compared with a placebo	780 fibrate users and 814 controls	For any cancer, RR 1.02 (95% CI, 0.92-1.12). For colorectal cancer RR 0.98(95% CI, 0.71-1.34)	Any cancers, respiratory cancer, breast cancer, genitourinary cancer, prostate cancer, gastrointestinal cancer, colorectal cancer

Biologic plausibility

Despite the conflicting evidence present in the literature, researchers continue to explore the relationship between certain classes of prescription drugs and cancer because of compelling hypothesized mechanisms as described earlier. The mechanism used in this research is explained in detail given below:

Bile Acid and colon cancer

Bile acids play a key role in the digestion and absorption of fats and lipophilic vitamins. Studies have shown that bile acids are important in the development of colorectal cancer. Fecal bile acids (secondary bile acids) play an important role in the genesis and progression of colon cancer. Increased levels of fecal bile acids augment the development of colorectal cancer.³⁶⁻⁴¹ Certain types of hydrophobic fecal bile acids such as deoxycholic acid (DCA), lithocolic acid (LCA) are thought to be contributors to the development and pathogenesis of colon cancer based on evidence from animal studies.⁴²⁻

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The mechanism behind this is explained by the inhibition of human apical sodium dependent transporter (hASBT) which is the primary mechanism for intestinal reabsorption of bile acids.^{45:46} Any factor that causes hASBT inhibition would result in an increased amount of bile acids passing in the colon with an increased exposure to the cytotoxic secondary bile acids either from the direct passage through the ileum-colon junction or from the increased bacterial transformation from primary bile acids. This may lead to more colorectal cancer development. Drug classes such as calcium channel blockers and thiazide diuretics have hASBT inhibition potency.

Rationale

Prescription drugs are used to reduce the morbidity of some of the common chronic medical conditions. These drugs are used in the long term management of the chronic conditions. There a body of literature, with conflicting results, regarding the risk of cancer associated with chronic disease medications. Almost all of the studies conducted have defined exposure by therapeutic class (e.g. to any drug within a single therapeutic class). However, the compelling biologic mechanism hypothesized here would suggest that the risk of developing colon cancer should differ by individual drug in the given class, and furthermore, the risk would be specific to the location of the tumor in the colon. If so, the results of class-based exposure studies would vary by the mix of individual drugs within the therapeutic class. As this would likely vary over time and across healthcare programs, so too would the magnitude of the association with CRC vary. Indeed, calculating risks as a class effect may obscure a true association with only one or a handful of agents, as models calculate an average effect based on the distribution of exposure in the population. Most studies in the published literature have not had sufficient statistical power to test for an association of an individual therapeutic agent with incident colon cancer.

The bile acid inhibition which can eventually lead to a higher risk of cancer is measured by inhibitory K_i value. Lower the K_i value higher is the inhibition. For example among the CCBs, Nifedipine has the lowest of the K_i value among the antihypertensive agents studied. Furthermore K_i values vary many-fold among drugs within the same therapeutic class. For example among the calcium channel blockers, the K_i value for nifedipine is 3.87 whereas the K_i value for verapamil in the same drug class is 266.⁴⁷ Given the

different inhibition properties of each drug, it is more likely that the cancer risk varies considerably by individual agents, with many agents having no discernable impact on colon cancer risk. A listing of the K_i values for prescription drugs is given in Appendix A.

This raises a need to determine if the risk of colorectal cancer is similar for the individual drugs as determined for the entire class. Since these drugs are used extensively and for extended periods of time even a small excess risk may have major public health implications.

II. RESEARCH METHODS AND ANALYTICAL PLAN

Objectives

The objective of this study is to:

- Determine which commonly used cardiovascular drugs are associated with risk of colon cancer and determine how a drug's ability to inhibit bile acid reuptake (as measured by K_i) impacts risk.

Research Questions

Based on the objectives mentioned this study plans to address the following research questions:

- Is there an association between the use of cardiovascular drugs (by each class) and colon cancer; and does the association of colon cancer differ by individual cardiovascular drug for the given class?
- Based on the study rationale, is the association between the individual cardiovascular drugs strongest among the patients with a diagnosis of colon cancer in the proximal location.
- Are the cardiovascular drugs identified as inhibitors of bile acid reuptake (as measured by K_i) associated with colon cancer?

Hypothesis

- Chronic use of the cardiovascular drug [*Name of the individual drug*] is associated with the risk of colon cancer.
- This association is strongest among patients with colon cancer in the proximal location.

- Drugs identified as inhibitors of bile acid reuptake (as measured by K_i) are associated with colon cancer.

Study Design

A population based case-control study was conducted nested within a cohort of presumed incident cases of colon cancer and carcinoma in situ of the colon. The HealthCore Integrated Research Database (HIRDSM) will be used for this study. The cases along with their cardiovascular drug history were identified from the research database.

A case control design was selected because colon cancer is a relatively rare disease, and even more so when a specific location is sought. Also, given the time-varying nature of cardiovascular drug therapy, the case-control methodology is a very efficient design in this situation.

Data Source

The HealthCore Integrated Research Database (HIRDSM) based on Blue Cross Blue Shield member data is a Health Insurance Portability Accountability Act (HIPAA) - compliant data source that contains fully adjudicated paid claims, from the largest commercially insured population in the US, with dates of service available from January 1, 2001 to December 30, 2010 for all non-capitated ambulatory, emergency department, inpatient, and outpatient encounters (including administrative claims for laboratory tests) for members with eligibility at the time of service. The HIRDSM contains claims information for approximately 31.2 million lives available for research. Diagnostic laboratory testing results are obtained from two large national reference laboratories. Health plans included in the HIRDSM include lines of business such as health maintenance, point of service, preferred provider organizations, and indemnity plans.

Patient enrollment data, medical care, cardiovascular drug use, and health care utilization are tracked for each patient in the database. Diagnoses and procedures are identified by International Classification of Diseases, 9th Edition/Revision, Clinical Modification (ICD-9-CM), Current Procedural Terminology (CPT), and Health Care Financing Administration Common Procedure Coding System (HCPCS) codes for both outpatient and inpatient stays. Drug claims are captured by National Drug Codes (NDCs), which can then be translated to broader, more meaningful classification systems such as Generic Product Identifier (GPI) codes. Physician specialist, and emergency room visits, as well as hospital stays, are captured in the database through CPT codes, UB-92 Revenue codes (e.g., room and board), and place of service codes. Information on physician specialty is also retained in the database.

Sample selection

The study population aged 18 years and older was identified during the study period, from January 1, 2001 to January 30, 2011. The cases, along with the pool of potential controls, were selected among patients enrolled in a healthcare plan that contributed patient-level claims data to HIRDSM during this time period.

Identification of Cases

Incident cases of colon cancer were identified from the database based on the diagnosis in the medical claims. Any patient that had a presence of at least one medical claim with an ICD-9 code for a colon cancer (153.xx) or carcinoma in situ of the colon (230.3 or 230.4) was identified as a case. The index date for the cases was defined as the earliest (first) service date for the first claim with an eligible code for colon cancer or carcinoma in situ of the colon. The cases were required to have at least one year of continuous eligibility in

the HIRDSM prior to the index date. The patients that had less than one year of continuous eligibility were excluded.

As per the hypothesis, in order to study if the association between a specific cardiovascular drug was strongest among patients with a diagnosis of colon cancer in the proximal location, the sub-group among the cases were identified that had a colon cancer diagnosis in the proximal location (or right side). Cases that had at least one medical claim with a diagnosis of ICD-9 codes: 153.0, 153.4 and 153.6 were included in the cohort with colon cancer on the right side.

The two different subgroups were selected to test if the association between cardiovascular drugs and colon cancer varied between the full cohort (patients with a diagnosis of colon cancer and carcinoma in situ) and cohort with colon cancer on the right side. The association between cardiovascular drugs and colon cancer, observed among colon cancer cases on the right side when compared to the association with the full cohort was used to test the hypothesis on the bile acid reuptake.

Alternate case definition

Along with the primary definition, an alternate definition was used to identify cases. The medical claims in the HIRDSM have information on physician specialty that assigned the diagnosis. The alternate case definition which was nested within the primary definition required evidence of a diagnosis by an oncologist. The alternate case definition was applied to both the full cohort (cases with a diagnosis of colon cancer or carcinoma in situ) and the cases with colon cancer on proximal location. The primary and the alternate case definition were used to estimate the different ranges of plausible values for the association.

Among the cases defined using primary and alternate case definition, any cases that had a prior history of other malignancies with evidence of a diagnosis by an oncologist in the pre-index period were excluded from the case set. Diagnoses of other malignancies were identified using at least one medical claim with a diagnosis of ICD-9 codes between 140.xx and 208.xx with an evidence of a diagnosis by an oncologist. Cases with other malignancies were excluded in order to include a cleaner sample with incident cases of colon cancer only.

Control selection

Controls were required to not have a diagnosis of colon cancer during their entire enrollment period. A random sample of eligible controls was drawn in the HIRDSM prior to matching. One control was selected for each case from the sample of eligible controls. A control was randomly selected from those eligible for healthcare at the same time (calendar date) as the case's index date. Each control was matched to the case on age (± 2 years) and sex. The control had to be insured under the same state's plan as the respective case and was required to have at least same number of days of eligibility prior to the index date as the matched case. The control was assigned the same index date as the case to which the control was matched. Any controls that had a prior history of other malignancies with evidence of a diagnosis by an oncologist in the pre-index period were excluded from the case set. Diagnoses of other malignancies were identified using at least one medical claim with a diagnosis of ICD-9 codes between 140.xx and 208.xx (except 153.xx) with an evidence of a diagnosis by an oncologist.

Exposure

The primary exposure of interest for this study was the use of cardiovascular drugs.

Pharmacy claims for the cardiovascular medications between the start of the follow-up and the index date were used as a proxy for drug exposure. Exposure to a cardiovascular medication was defined as the presence of at least one claim in the pharmacy data for the drug(s) of interest, with a claim date that occurs at any point during the risk period (prior to index date).

Cardiovascular drug exposure was identified using the generic product identifier code.

Medi-Span's Generic Product Identifier (GPI) is a unique and proprietary therapeutic classification system for drugs and drug products. The GPI classifies drugs in hierarchical arrangement of seven 2-digit sub-fields. Each group of 2 digits more specifically identifies the drug product until the drug is defined at the level of dosage form and strength. Drug products with identical 14-digit GPI numbers are pharmaceutically equivalent, meaning that a brand name and generic product that are otherwise equivalent at all 7 levels of the GPI classification system will share an identical number. The drug use was identified using the fourth level of the GPI classification system which grouped the brand and generic products for a given drug along with the different dosage forms and strength.

The total number of days supply of the cardiovascular drug as dispensed was used as a proxy for calculating the duration of cardiovascular drug use. The days supply for a given cardiovascular drug during the pre-index look back period was summed to get the total duration of cardiovascular drug use in days.

The exposure for cardiovascular medications was defined as per the following categories:

1. Any use: Any use of the cardiovascular medication was defined as the presence of at least one pharmacy claim for a given drug with a claim date that occurred at any point during the pre-index risk period.
2. Use with a lag time of 6 months: Any use of the cardiovascular medication where the presence of pharmacy claim plus total number of days supply for the last episode occurred at least six months prior to the index date.
3. Duration of use greater than 1 year: Any use of cardiovascular medication where the duration of use for the given drug was at least 1 year (or 365 days).

All the categories of exposure definition were used for studying the impact of the association of the given drug with colon cancer. Impact of the different exposure definitions on the association with colon cancer was studied in the full cohort (primary and alternate case definition) and the subgroup of cases with colon cancer on the right side (primary and alternate case definition).

Covariates

Patients in the full cohort were characterized using the covariates described below. These characteristics were also used to present the subgroup of patients for full cohort that met the alternate case definitions and the subgroup of cases with colon cancer on right side (both primary and alternate case definition).

Demographic characteristics

- Age: Patient's age in years on index date. Age was characterized as a continuous variable and was also characterized using the following categories:
 - 18 to 20 years
 - 21 to 30 years

- 31 to 40 years
 - 41 to 50 years
 - 51 to 60 years
 - 61 to 70 years
 - 81 to 90 years
 - 91 to 100 years
 - Greater than 100 years
- Sex:
 - Male
 - Female
- Geographic region: Geographic region of the patient was determined based on the insurance plan of the state under which they were enrolled on the index date.
 - Northeast
 - South
 - Central
 - West

Comorbidities

It was evaluated whether the patients had the following conditions during the pre-index eligibility period (index date excluded) based on the presence of at least one medical claim with an ICD-9-CM diagnosis code of the listed condition.

- Myocardial infarction:
 - ICD-9-CM diagnosis code: 410, 412
- Congestive heart failure

- ICD-9-CM diagnosis code: 428
- Peripheral vascular disease
 - ICD-9-CM diagnosis code: 441,443.9, 785.4, V43.4
- Cerebrovascular disease
 - ICD-9-CM diagnosis code: 430, 431, 432, 433, 434, 435, 436, 437, 438
- Dementia
 - ICD-9-CM diagnosis code: 290
- Chronic obstructive pulmonary disease
 - ICD-9-CM diagnosis code: 490, 491, 492, 493, 494, 495, 496, 500, 501, 502, 503, 504, 505
- Rheumatological disease
 - ICD-9-CM diagnosis code:725, 714.81, 710.0, 710.1, 710.4, 714.0, 714.1, 714.2
- Peptic ulcer disease
 - ICD-9-CM diagnosis code: 531.4, 531.5, 531.6, 531.7, 532.4, 532.5, 532.6, 532.7, 533.4, 533.5, 533.6, 533.7, 534.4, 534.5, 534.6, 534.7, 531.0, 531.1, 531.2, 531.3, 532.0, 532.1, 532.2, 532.3, 533.0, 533.1, 533.2, 533.3, 534.0, 534.1, 534.2, 534.3, 531.9, 532.9, 533.9, 534.9
- Mild liver disease
 - ICD-9-CM diagnosis code: 571.2, 571.4, 571.5, 571.6
- Diabetes (mild to moderate)
 - ICD-9-CM diagnosis code: 250.0, 250.1, 250.2, 250.3, 250.7
- Hemiplegia or paraplegia

- ICD-9-CM diagnosis code: 342, 344.1
- Moderate to severe renal disease
 - ICD-9-CM diagnosis code: 585, 586, 582, 588, 583.0, 583.1, 583.2, 583.3, 583.4, 583.5, 583.6, 583.7
- Diabetes + complications
 - ICD-9-CM diagnosis code: 250.4, 250.5, 250.6
- Moderate to severe liver disease
 - ICD-9-CM diagnosis code: 572.2, 572.3, 572.4, 572.5, 572.6, 572.7, 572.8, 456.0, 456.1, 456.2
- Autoimmune disease (AIDS)
 - ICD-9-CM diagnosis code: 042
- Crohn's disease
 - ICD-9-CM diagnosis code: 555
- Ulcerative colitis
 - ICD-9-CM diagnosis code: 556

Descriptions for the ICD-9-CM diagnosis codes used to define comorbidities are detailed in the Appendix A.

Diagnostic Screening

Screening for colon cancer, particularly when screening includes the removal of precancerous polyps, can impact the potential to be diagnosed with colon cancer. If screening rates vary by use of cardiovascular medicines and/or particularly chronic conditions that they are being used for, diagnostic screening may be a confounder.

Patients with at least one medical claim for colonoscopy in the pre-index period were

identified as patients who had undergone screening for colon cancer. Colonoscopy was defined by the presence of any one of the following codes prior to the index date⁴⁸:

- ICD-9-CM diagnosis code: 45.22, 45.23, 45.25, 45.41, 45.42, 45.43
- CPT codes: 44388 to 44394, 45355, 45378 to 45385
- HCPCS codes: G0105, G0121

Descriptions for the ICD-9-CM diagnosis codes, CPT codes and HCPCS codes used to define screening are detailed in the Appendix B.

Statistical Analysis

Descriptive Analysis

The patient characteristics (as described in the section; *Covariates*) were compared among the cases and controls in the study population. Bivariate analysis of all the variables was performed to compare the distributions of the variables between cases and controls. Chi square tests were used to examine the difference of distributions and means between the two groups. The significance level was set at 0.05 for all analyses.

Hypothesis testing

Conditional logistic regression was used to investigate the relationship between an outcome and a set of prognostic factors in matched case-control studies. The outcome was whether the subject was a case or a control. For matched data (in case-control studies) or any data distributed into a large number of strata, estimates resulting from application of standard logistic regression techniques are biased⁴⁹. Conditional logistic regression is an approach that produces estimates of the important parameters of the logistic regression model but does not incur the bias associated with estimating a large number of strata parameters. A conditional analysis produces unbiased estimates of the

parameters that describe the relationships between risk factors and outcome, but does not produce estimates of the parameters necessary to identify the influences of the stratum variable.

The conditional logistic regression was performed with the PHREG procedure by using the discrete logistic model and by forming a stratum for each matched set. In addition, dummy survival times were created so that all the cases in a matched set have the same event time value, and the corresponding controls are censored at later times. First, the crude estimates were assessed then the multivariate conditional logistic regression adjusting for potential confounders was performed. All analysis was performed using SAS[®] Software version 9.1 or later.

The multivariate conditional logistic regression was conducted by including the following covariates: colonoscopy, crohn's disease and ulcerative colitis. Presence of crohn's disease and ulcerative colitis were included as covariates as inflammatory diseases of the bowel can put an individual at an increased risk. Screening is also believed to confound the association as screening can prevent cancer if the polyps are found and removed early.

The impact on the association was also studied by including interactions in the multivariate model. Interactions between colonoscopy and age group, colonoscopy and crohn's disease, colonoscopy and ulcerative colitis were included in the multivariate model with interactions. Interaction between colonoscopy and age group was included to see whether the age group modifies the effect of colonoscopy on the outcome. Similarly the interaction between crohn's disease and ulcerative colitis each with colonoscopy was included to see whether presence of crohn's disease or ulcerative colitis modified the

effect of colonoscopy on the outcome. The interactions terms were studied for significance where a p-value of 0.05 or less was considered as statistically significant. A significant interaction term would help infer on the impact of the interaction term on the outcome.

III. RESULTS

Study Population

There were a total of 44,200,000 patients in the HIRDSM during the period of January 2001 and January 2011. Searching claims for diagnostic codes of colon cancer or carcinoma in situ identified 67,511 patients. After applying the inclusion and exclusion criteria, we had a total of 67,220 eligible cases (See Figure 3.1). A total of 7,157 cases that had that diagnoses of other malignancies with a supporting claim for a diagnosis by an oncologist were excluded from the case set. A random sample of about 2 million patients without a colon cancer diagnosis was drawn as potential controls. Colon cancer cases were matched to these potential controls on a one-to-one ratio based on age (± 2 years), sex, and eligibility for healthcare at the same time (calendar date) as the case's index date. A total of 36,736 cases (54.6%) were matched to an eligible control.

The majority of cases were successfully matched to a control. Cases for whom a matched control could not be identified in the database were compared to cases for whom a matched control could be identified are compared in Table 3.1. Cases for which a matched control could be identified were slightly younger than the cases for which a matched control was not identified. The mean age of the cases with a matched control was 60.7 (± 13.2) and of the cases without a matched control was 67.4 (± 14.4). The cases with a matched control varied significantly with the cases without a matched control on mean age ($p < 0.0001$), age distribution ($p < 0.0001$) and the geographic region of the enrollment plan ($p < 0.0001$).

Table 3.1 Comparison between matched and unmatched cases

	Matched Cases		Unmatched Cases		p-value
	N	%	N	%	
Total	36,736	100.0	30,484	100.0	
Sex					
Male	18,007	49.0	15,157	49.7	0.0692
Female	18,729	51.0	15,327	50.3	
Age¹	60.7 (13.2), 60		67.4 (14.4), 69		<0.0001
Age group					
≥18 to ≤20	44	0.1	29	0.1	<0.0001
>20 to ≤30	381	1.0	247	0.8	
>30 to ≤40	1,547	4.2	829	2.7	
>40 to ≤50	5,676	15.5	2,811	9.2	
>50 to ≤60	11,755	32.0	5,863	19.2	
>60 to ≤70	8,849	24.1	6,837	22.4	
>70 to ≤80	5,302	14.4	7,629	25.0	
>80 to ≤90	2,723	7.4	5,282	17.3	
>90 to ≤100	453	1.2	948	3.1	
>100	6	0.0	9	0.0	
Geographic region					
Central	9,539	26.0	13,571	44.5	<0.0001
Northeast	8,547	23.3	5,232	17.2	
South	7,713	21.0	3,540	11.6	
West	10,937	29.8	8,141	26.7	

¹Mean (standard deviation), median

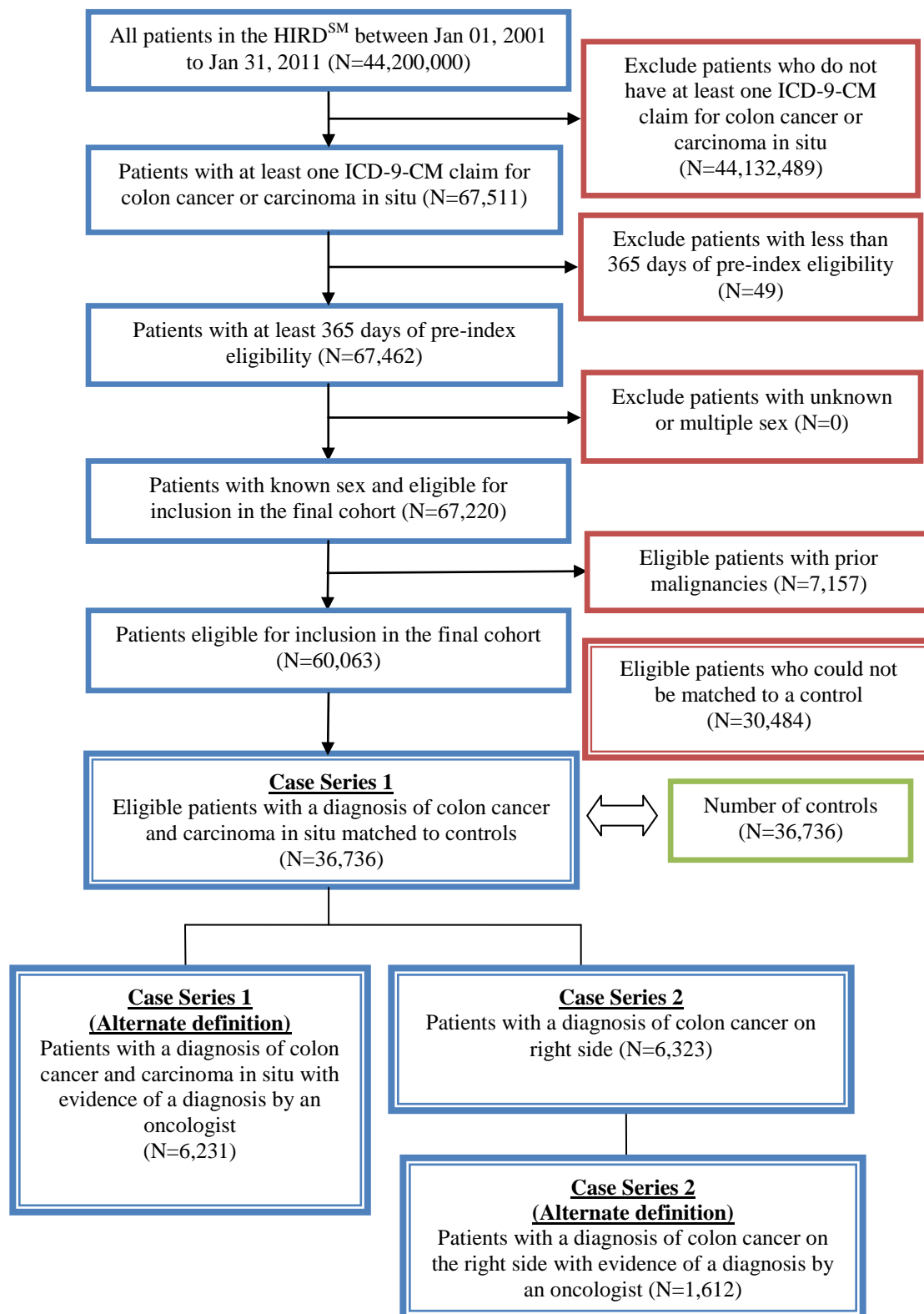


Figure 3.1 Case selection

Characteristics by patients with a diagnosis of colon cancer or carcinoma in situ

Table 3.2 describes the patient characteristics overall and among cases and controls.

There were 73,472 patients (36,736 cases and 36,736 controls) in the cohort of patients with a diagnosis of colon cancer and carcinoma in situ. The mean age of the patients was 60.7 (± 13.2) and ranged from 18 to 104 years. About one-third patients in the cohort (32%) were between 50 to 60 years and a quarter of the patients (24.5%) were between the ages 60 to 70 years. The cohort was equally divided between males (49.0%) and females (51.0%). Most of the patients were insured under a plan from the west (29.8%) and the central (26.0%) region. The most common comorbidities among the patients were the presence of chronic obstructive pulmonary disease (COPD) (16.9%) and mild to moderate diabetes (16.3%).

The cases and controls are well balanced with respect to the demographic characteristics (sex, age and geographic region). The presence of comorbidities varied significantly among the cases and controls. The cases were more likely than controls to have comorbidities especially diabetes, COPD and congestive heart failure.

Table 3.2 Demographic characteristics and comorbidities for all patients with a diagnosis of colon cancer or carcinoma in situ

	Total		Cases		Controls		p-value
	N	%	N	%	N	%	
Total							
Gender							
Female	36,014	49	18,007	49	18,007	49	1.0000
Male	37,458	51	18,729	51	18,729	51	
Age¹	60.7 (13.2), 59.8		60.7 (13.2), 60		60.6 (13.2), 59.6		0.2236
Age group							
≥18 to ≤20	75	0.1	44	0.1	31	0.1	
>20 to ≤30	728	1.0	381	1.0	347	0.9	
>30 to ≤40	3,003	4.1	1,547	4.2	1,456	4.0	
>40 to ≤50	11,055	15.0	5,676	15.5	5,379	14.6	
>50 to ≤60	23,473	31.9	11,755	32.0	11,718	31.9	0.0005
>60 to ≤70	18,034	24.5	8,849	24.1	9,185	25.0	
>70 to ≤80	10,544	14.4	5,302	14.4	5,242	14.3	
>80 to ≤90	5,571	7.6	2,723	7.4	2,848	7.8	
>90 to ≤100	979	1.3	453	1.2	526	1.4	
>100	10	0.0	6	0.0	4	0.0	
Geographic region							
Central	19,078	26.0	9,539	26.0	9,539	26.0	
Northeast	17,094	23.3	8,547	23.3	8,547	23.3	1.0000
South	15,426	21.0	7,713	21.0	7,713	21.0	
West	21,874	29.8	10,937	29.8	10,937	29.8	
Comorbidities							
Myocardial infarction	2,408	3.3	1,295	3.5	1,113	3.0	0.0347
Congestive Heart Failure	4,302	5.9	2,485	6.8	1,817	4.9	<0.0001
Peripheral vascular disease	3,547	4.8	1,882	5.1	1,665	4.5	0.0884
Cerebrovascular disease	6,791	9.2	3,597	9.8	3,194	8.7	0.0239
Dementia	542	0.7	263	0.7	279	0.8	0.1417
Chronic obstructive pulmonary disease	12,430	16.9	6,613	18.0	5,817	15.8	0.0002
Rheumatological disease	1,762	2.4	898	2.4	864	2.4	0.5507
Peptic ulcer disease	1,715	2.3	1,071	2.9	644	1.8	<0.0001
Mild liver disease	600	0.8	376	1.0	224	0.6	<0.0001
Diabetes (mild to moderate)	11,958	16.3	6,673	18.2	5,285	14.4	<0.0001

Table 3.2 Continued

	Total		Cases		Controls		p-value
	N	%	N	%	N	%	
Hemiplegia or Paraplegia	332	0.5	185	0.5	147	0.4	0.1381
Moderate or severe renal disease	2,286	3.1	1,379	3.8	907	2.5	<0.0001
Diabetes + complications	2,512	3.4	1,385	3.8	1,127	3.1	0.0004
Moderate to severe liver disease	248	0.3	162	0.4	86	0.2	<0.0001
AIDS	150	0.2	90	0.2	60	0.2	0.0409

¹Mean (standard deviation), median

Characteristics of patients with a diagnosis of colon cancer (primary definition and alternate definition), and with a diagnosis with colon cancer on the right side (primary definition and alternate definition)

Table 3.3 describes the patient characteristics among the four different case series (cases with colon cancer and carcinoma in situ both primary definition and alternate definition, cases with colon cancer on the right side, both primary definition and alternate definition). The distribution of demographic characteristics and comorbidities are compared using the cases with colon cancer and carcinoma in situ (primary definition) as the reference group.

There are no significant differences when comparing the different case series with the primary definition of cases with colon cancer and carcinoma in situ. The proportion of females is slightly higher for cases with colon cancer and carcinoma in situ for both the definitions (primary definition: 51.0% females; alternate definition: 51.7% females). The proportion of males is slightly higher than females for cases with colon cancer on the right side for both the definitions (primary definition: 48.1% females; alternate definition: 49.9% females).

The age distribution is similar among all the case series with about one-third of the patients (cases with colon cancer and carcinoma in situ: primary definition: 32.0%; alternate definition: 34.1%; cases with colon cancer on right side: primary definition: 28.5%; alternate definition: 32.2%) in between 50 to 60 years of age and about a quarter of the patients (cases with colon cancer and carcinoma in situ: primary definition: 24.1%; alternate definition: 24.8%; cases with colon cancer on right side: primary definition: 25.1%; alternate definition: 27.7%) between 60 to 70 years of age.

There are significant differences when comparing certain comorbidities between the primary and alternate definition of cases with colon cancer and carcinoma in situ such as myocardial infarction ($p=0.0258$), congestive heart failure ($p<0.0001$), peripheral vascular disease ($p=0.0041$), cerebrovascular disease ($p<0.0001$), dementia ($p=0.0013$), COPD ($p=0.0021$), rheumatological disease ($p=0.0020$), mild liver disease ($p=0.0406$), mild to moderate diabetes ($p=0.0320$), renal disease ($p=0.0003$), diabetes with complications ($p=0.0259$), and liver disease ($p=0.0086$). When comparing comorbidities among primary definitions of cases with colon cancer on the right side ; and cases with colon cancer and carcinoma in situ significant differences across certain comorbidities were observed such as myocardial infarction ($p=0.0107$), congestive heart failure ($p<0.0001$), peripheral vascular disease ($p=0.0006$), cerebrovascular disease ($p<0.0001$), dementia ($p=0.0322$), COPD ($p=0.0006$), mild to moderate diabetes ($p=0.0039$), renal disease ($p=0.0311$), diabetes with complications ($p=0.0042$), and AIDS ($p=0.0385$). No significant differences were observed when comparing comorbidities between cases with colon cancer on right side (alternate definition) with the cases with colon cancer and carcinoma in situ (primary definition).

Table 3.3 Comparison of characteristics between the different case series

	Cases with colon cancer and carcinoma insitu			Cases with colon cancer and carcinoma insitu with evidence of a diagnosis by an oncologist			Cases with colon cancer on the right side			Cases with colon cancer on the right side with evidence of a diagnosis by an oncologist		
	N	%	p-value	N	%	p-value	N	%	p-value	N	%	p-value
Total	36,736			6,231			6,323			1,612		
Gender												
Male	18,007	49.0	<i>Ref.</i>	3,009	48.3	0.2888	3,283	51.9	<0.0001	808	50.1	0.3843
Female	18,729	51.0		3,222	51.7		3,040	48.1		804	49.9	
Age¹	61 (13), 60			59 (12), 58			63 (13), 62			61 (12), 60		
			<i>Ref.</i>			<0.0001			<0.0001			0.6775
Age group												
≥18 to ≤20	44	0.1	<i>Ref.</i>	4	0.1	<0.0001	7	0.1	<0.0001	0	0.0	0.0070
>20 to ≤30	381	1.0		58	0.9		41	0.6		11	0.7	
>30 to ≤40	1,547	4.2		310	5.0		202	3.2		65	4.0	
>40 to ≤50	5,676	15.5		1,083	17.4		782	12.4		220	13.6	
>50 to ≤60	11,755	32.0		2,127	34.1		1,799	28.5		519	32.2	
>60 to ≤70	8,849	24.1		1,547	24.8		1,588	25.1		447	27.7	
>70 to ≤80	5,302	14.4		760	12.2		1,134	17.9		232	14.4	
>80 to ≤90	2,723	7.4		316	5.1		666	10.5		109	6.8	
>90 to ≤100	453	1.2		26	0.4		104	1.6		9	0.6	
>100	6	0.0		0	0.0		0	0.0		0	0.0	
Geographic region												
Central	9,539	26	<i>Ref.</i>	2,450	39.3	<0.0001	1,846	29.2	<0.0001	703	43.6	<0.0001
Northeast	8,547	23.3		1,026	16.5		1,429	22.6		257	15.9	
South	7,713	21		877	14.1		1,332	21.1		208	12.9	
West	10,937	29.8		1,878	30.1		1,716	27.1		444	27.5	
Comorbidities												
Myocardial infarction	1,295	3.61	<i>Ref.</i>	183	3.0	0.0258	263	4.3	0.0107	54	3.5	0.7305
Congestive Heart Failure	2,485	6.9	<i>Ref.</i>	307	5.1	<0.0001	535	8.7	<0.0001	100	6.4	0.4015
Peripheral vascular disease	1,882	5.3	<i>Ref.</i>	263	4.4	0.0041	389	6.3	0.0006	78	5.0	0.6371
Cerebrovascular disease	3,597	10.0	<i>Ref.</i>	440	7.3	<0.0001	723	11.8	<0.0001	135	8.6	0.0669
Dementia	263	0.7	<i>Ref.</i>	22	0.4	0.0013	61	1.0	0.0322	7	0.5	0.1892
Chronic obstructive pulmonary disease	6,613	18.5	<i>Ref.</i>	1,011	16.8	0.0021	1,248	20.3	0.0006	292	18.7	0.8490
Rheumatological disease	898	2.5	<i>Ref.</i>	111	1.8	0.002	153	2.5	0.9412	34	2.2	0.4052
Peptic ulcer disease	1,071	3.0	<i>Ref.</i>	159	2.6	0.1404	192	3.1	0.5641	48	3.1	0.8625
Mild liver disease	376	1.1	<i>Ref.</i>	46	0.8	0.0406	57	0.9	0.3834	9	0.6	0.0685
Diabetes (mild to moderate)	6,673	18.6	<i>Ref.</i>	1,051	17.5	0.032	1,240	20.2	0.0039	308	19.7	0.2989

Table 3.3 Continued

	Cases with colon cancer and carcinoma insitu			Cases with colon cancer and carcinoma insitu with evidence of a diagnosis by an oncologist			Cases with colon cancer on the right side			Cases with colon cancer on the right side with evidence of a diagnosis by an oncologist		
	N	%	p-value	N	%	p-value	N	%	p-value	N	%	p-value
Hemiplegia or Paraplegia	185	0.5	<i>Ref.</i>	21	0.4	0.0861	43	0.7	0.0705	7	0.5	0.7072
Moderate or severe renal disease	1,379	3.9	<i>Ref.</i>	174	2.9	0.0003	272	4.4	0.0311	60	3.8	0.9725
Diabetes + complications	1,385	3.9	<i>Ref.</i>	197	3.3	0.0259	285	4.6	0.0042	67	4.3	0.4074
Moderate to severe liver disease	162	0.5	<i>Ref.</i>	13	0.2	0.0086	27	0.4	0.8911	3	0.2	0.1278
AIDS	90	0.3	<i>Ref.</i>	14	0.2	0.7893	7	0.1	0.0385	1	0.1	0.1408

¹Mean (standard deviation), median

Frequency of use and Duration of use of cardiovascular drugs

Table 3.4 describes the frequency of drug use and the duration of use (in days) for each drug among the four case series. Among the angiotensin II receptor antagonists, losartan followed by valsartan was the most frequently used drug among all the four case series. Among the drug class, ACE inhibitors, the most frequently used drugs were ramipril followed by a combination drug – trandolapril and verapamil among all the four case series. The drug atenolol (beta blockers), cholestyramine (bile acid sequestrants), diltiazem (calcium channel blockers), hydrochlorothiazide (diuretics), fenofibrate (fibrates) and atorvastatin (statins) were the most frequently used drugs in their respective drug classes among all four case series. Among the most commonly used drugs in all the drug classes, the duration of use exceeded one year except for cholestyramine (bile acid sequestrants).

When studying the individual drug use in the entire study population (irrespective of drug class), atorvastatin (drug class: statins) was the most frequently used drug in the study

sample (cases with colon cancer and carcinoma in situ: primary definition: 15.9%; alternate definition: 14.9%; cases with colon cancer on right side: primary definition: 17.3%; alternate definition: 16.8%). Among all the different case series, the mean duration of use of atorvastatin was around 855 days (2.3 years). After atorvastatin, the most frequently used drugs were hydrochlorothiazide (~8.5% among all the four case series), simvastatin (~7.9% among the four case series), furosemide (~6.9% among the four case series) and atenolol (~6.4% among the four case series). Among the most frequently used drugs as described above, the mean duration of use exceeded one year (>365 days) whereas the mean duration of use for atenolol and atorvastatin exceeded two years (>730 days).

Table 3.4 Frequency of use and duration of use of cardiovascular drugs in the study sample

Drug	Patients with Colon Cancer and Carcinoma in situ			Patients with colon cancer and carcinoma insitu with evidence of a diagnosis by an oncologist			Patients with Colon Cancer on the right side			Patients with colon cancer on the right side with evidence of a diagnosis by an oncologist		
	Frequency of use			Frequency of use			Frequency of use			Frequency of use		
	N	%	Mean (SD), Median	N	%	Mean (SD), Median	N	%	Mean (SD), Median	N	%	Mean (SD), Median
Total	73,472	100.0		12,462	100.0		12,646	100.0		3,224	100.0	
<i>Angiotensin II Receptor Antagonist</i>												
Candesartan	3886	5.3	612 (665.5), 360	562	4.5	627 (678.3), 360	692	5.5	615 (677.4), 330	152	4.7	619 (675.3), 285
Eprosartan	2617	3.6	695 (689.1), 430	416	3.3	687 (715.3), 420	467	3.7	697 (667.6), 503	121	3.8	710 (722.4), 510
Irbesartan	962	1.3	631 (635.3), 430	131	1.1	532 (578.7), 315	183	1.4	635 (637.1), 450	38	1.2	517 (507.8), 360
Losartan	720	1.0	460 (523.7), 244	107	0.9	459 (481.8), 270	146	1.2	472 (527.2), 300	33	1.0	523 (525.7), 345
Olmesartan	419	0.6	651 (657.7), 430	64	0.5	631 (652.6), 480	75	0.6	582 (637.6), 360	13	0.4	422 (367), 435
Telmisartan	257	0.3	468 (395), 210	39	0.3	454 (506.5), 240	47	0.4	392 (434.6), 251	7	0.2	472 (461.8), 338
Valsartan	33	0.0	434 (473.7), 313	3	0.0	276 (263.9), 208	8	0.1	501 (394.3), 433	1	0.0	325 (-), 325
<i>ACE Inhibitors</i>												
Benazepril	2,036	2.8	747 (745.2), 510	304	2.4	761 (778.6), 465	391	3.1	784 (756.4), 540	91	2.8	896 (815.7), 645
Captopril	1,695	2.3	816 (738.2), 600	255	2.0	802 (751.9), 540	290	2.3	817 (790.5), 540	70	2.2	793 (740.9), 508
Enalapril	1,600	2.2	780 (767.4), 540	217	1.7	768 (770.4), 495	310	2.5	795 (757.7), 570	62	1.9	771 (740.7), 540
Fosinopril	1,177	1.6	911 (858.9), 630	168	1.3	820 (778.1), 570	224	1.8	949 (861.7), 690	48	1.5	846 (788.6), 600
Moexipril	1,131	1.5	756 (817.2), 430	187	1.5	688 (760.7), 390	202	1.6	747 (803.9), 450	55	1.7	682 (751), 405
Perindopril	381	0.5	878 (818.6), 630	55	0.4	1029 (976.4), 570	71	0.6	835 (774.6), 525	18	0.6	687 (688.9), 420
Quinapril	285	0.4	559 (592.8), 360	46	0.4	629 (589.6), 540	62	0.5	659 (598), 540	17	0.5	700 (597.4), 660
Ramipril	124	0.2	689 (797.9), 417	34	0.3	633 (682.9), 390	24	0.2	566 (643.9), 330	12	0.4	546 (668), 300
Trandolapril	124	0.2	673 (721.3), 430	17	0.1	567 (595), 378	23	0.2	635 (651.2), 435	5	0.2	730 (671.8), 525
Trandolapril_Verapamil	88	0.1	621 (653.6), 360	16	0.1	647 (588.3), 510	23	0.2	835 (760.9), 630	5	0.2	721 (792.3), 390

Table 3.4 Continued

Drug	Patients with Colon Cancer and Carcinoma in situ			Patients with colon cancer and carcinoma insitu with evidence of a diagnosis by an oncologist			Patients with Colon Cancer on the right side			Patients with colon cancer on the right side with evidence of a diagnosis by an oncologist		
	Frequency of use		Duration of use	Frequency of use		Duration of use	Frequency of use		Duration of use	Frequency of use		Duration of use
	N	%	Mean (SD), Median	N	%	Mean (SD), Median	N	%	Mean (SD), Median	N	%	Mean (SD), Median
Total	73,472	100.0		12,462	100.0		12,646	100.0		3,224	100.0	
Beta Blockers												
Acebutolol	4,966	6.8	852 (810.1), 630	705	5.7	804 (794.9), 570	907	7.2	860 (795.9), 630	199	6.2	830 (816.1), 570
Atenolol	1,398	1.9	596 (602.5), 390	189	1.5	567 (605.2), 360	295	2.3	651 (647.8), 450	68	2.1	545 (560.7), 360
Betaxolol	932	1.3	609 (786.2), 240	136	1.1	536 (746.6), 120	158	1.2	698 (816.6), 330	40	1.2	603 (795), 200
Bisoprolol	309	0.4	712 (727.5), 422	31	0.2	619 (665.3), 390	66	0.5	777 (747), 510	8	0.2	1055 (860.4), 1125
Carvedilol	298	0.4	669 (740.3), 390	35	0.3	624 (783.7), 276	55	0.4	767 (829), 364	10	0.3	638 (848.3), 240
Labetalol	262	0.4	924 (870.5), 630	41	0.3	787 (788.5), 390	56	0.4	996 (910), 715	10	0.3	707 (713.2), 480
Metoprolol	134	0.2	678 (751.1), 435	24	0.2	605 (715.3), 330	24	0.2	807 (829.2), 510	4	0.1	431 (698.8), 225
Nadolol	95	0.1	260 (236.6), 180	12	0.1	250 (228.8), 180	15	0.1	269 (239.1), 240	1	0.0	196 (165.1), 180
Nebivolol	78	0.1	724 (718.3), 480	17	0.1	697 (716.6), 450	77	0.6	753 (741.2), 510	17	0.5	751 (790.6), 480
Penbutolol	54	0.1	1089 (722.6), 990	8	0.1	1151 (612.3), 1140	10	0.1	1130 (539.5), 1125	3	0.1	813 (607), 885
Pindolol	28	0.0	682 (752.5), 450	7	0.1	577 (646.5), 203	6	0.0	526 (580.5), 270	3	0.1	886 (758.6), 900
Propranolol	19	0.0	1011 (683.1), 831	2	0.0	1917 (80.6), 1917	2	0.0	720 (339.4), 720	0	0.0	
Sotalol	16	0.0	726 (696.2), 615	0	0.0	150 (0), 150	3	0.0	593 (225), 630	0	0.0	
Timolol	1	0.0	1470 (0), 1470	0	0.0		1	0.0	1470 (0), 1470	0	0.0	
Bile Acid Sequestrants												
Cholestyramine	553	0.8	118 (260), 30	81	0.6	102 (238.8), 30	90	0.7	107 (222.1), 30	20	0.6	82 (169), 30
Colesevelam	326	0.4	259 (410.7), 90	48	0.4	267 (436.4), 84	62	0.5	313 (523), 90	16	0.5	365 (535.9), 120
Colestipol	108	0.1	227 (427.3), 60	11	0.1	225 (421.2), 60	23	0.2	221 (363.4), 105	1	0.0	197 (346), 51

Table 3.4 Continued

Drug	Patients with Colon Cancer and Carcinoma in situ			Patients with colon cancer and carcinoma insitu with evidence of a diagnosis by an oncologist			Patients with Colon Cancer on the right side			Patients with colon cancer on the right side with evidence of a diagnosis by an oncologist		
	Frequency of use		Duration of use	Frequency of use		Duration of use	Frequency of use		Duration of use	Frequency of use		Duration of use
	N	%	Mean (SD), Median	N	%	Mean (SD), Median	N	%	Mean (SD), Median	N	%	Mean (SD), Median
Total	73,472	100.0		12,462	100.0		12,646	100.0		3,224	100.0	
Calcium channel blockers												
Amlodipine_Atorvastatin	2386	3.2	770 (799), 510	324	2.6	729 (781.3), 450	465	3.7	739 (736.3), 480	90	2.8	732 (810.2), 450
Amlodipine_Valsartan_Hydrochlorothiazide	1329	1.8	876 (849.7), 630	185	1.5	850 (854.8), 570	261	2.1	817 (777.5), 600	57	1.8	983 (911.5), 720
Amlodipine	1,138	1.5	815 (874), 480	160	1.3	781 (847.4), 450	223	1.8	837 (845.8), 564	46	1.4	863 (872.1), 511
Bepidil	359	0.5	737 (777.2), 480	54	0.4	757 (774.7), 540	66	0.5	684 (726.1), 450	18	0.6	749 (820.7), 450
Diltiazem	285	0.4	592 (566), 390	41	0.3	594 (549.1), 420	52	0.4	564 (524.9), 360	14	0.4	461 (406.5), 330
Felodipine	173	0.2	666 (696.5), 420	21	0.2	617 (679.9), 360	75	0.6	661 (690.5), 450	10	0.3	621 (659.2), 375
Isradipine	153	0.2	484 (534.2), 270	16	0.1	404 (429.6), 210	31	0.2	559 (596.6), 315	5	0.2	380 (440.7), 210
Nicardipine	138	0.2	505 (601.4), 270	14	0.1	447 (580.8), 284	24	0.2	489 (680.8), 210	5	0.2	279 (341.6), 150
Nifedipine	12	0.0	758 (812), 555	2	0.0	453 (241.9), 540	3	0.0	698 (465.6), 660	1	0.0	360 (254.6), 360
Nimodipine	6	0.0	64 (144), 12	0	0.0		1	0.0	110, 11	0	0.0	
Nisoldipine	4	0.0	222 (169.8), 180	0	0.0	1800, 180	0	0.0	212 (208.6), 135	0	0.0	
Verapamil	1	0.0	80 (-), 80	0	0.0		1	0.0	800, 80	0	0.0	
Diuretics												
Acetazolamide	6,310	8.6	567 (642.3), 300	913	7.3	527 (627.7), 270	1,190	9.4	576 (656.3), 316	275	8.5	556 (664.3), 300
Amiloride	5,279	7.2	433 (567.1), 180	709	5.7	369 (544.6), 120	1,082	8.6	458 (575.8), 200	203	6.3	411 (576.5), 130
Amlodipine_Valsartan_Hydrochlorothiazide												
rothiazide	3,679	5.0	383 (522.1), 150	575	4.6	297 (467.7), 90	664	5.3	413 (540.2), 180	153	4.7	335 (530), 120
Bumetanide	394	0.5	471 (605.4), 240	59	0.5	509 (599.7), 270	85	0.7	443 (587.8), 210	15	0.5	350 (383), 233
Chlorothiazide	383	0.5	255 (368.7), 90	45	0.4	209 (269.7), 90	83	0.7	294 (390.1), 132	16	0.5	207 (250.9), 90
Chlorthalidone	273	0.4	71 (246.8), 10	37	0.3	77 (290.8), 14	50	0.4	66 (229.6), 10	8	0.2	108 (395.9), 14
Ethacrynic	271	0.4	399 (540.5), 150	34	0.3	484 (635.3), 150	55	0.4	404 (506.3), 186	5	0.2	689 (763.6), 245
Furosemide	248	0.3	856 (839.2), 571	39	0.3	1089 (914), 870	45	0.4	771 (845.3), 390	12	0.4	913 (990.2), 300
Hydrochlorothiazide	141	0.2	521 (652.8), 240	20	0.2	519 (681.1), 246	19	0.2	642 (620.7), 450	3	0.1	733 (569.7), 810
Indapamide	27	0.0	474 (574.5), 225	3	0.0	384 (414.6), 210	5	0.0	356 (461.9), 210	2	0.1	290 (307.5), 210
Mannitol	25	0.0	133 (295.1), 30	3	0.0	181 (88.3), 17	6	0.0	57 (88.4), 30	1	0.0	17 (19.1), 17
Methazolamide	20	0.0	540 (523.8), 255	4	0.0	457 (532.3), 435	4	0.0	456 (535.5), 270	3	0.1	487 (376.6), 510
Methyclothiazide	16	0.0	562 (645.5), 264	1	0.0	270 (254.6), 270	3	0.0	370 (555.6), 30	1	0.0	450 (-), 450
Metolazone	10	0.0	820 (801.7), 510	3	0.0	1052 (888.3), 600	2	0.0	390 (127.3), 390	1	0.0	480 (-), 480
Spirinolactone	9	0.0	298 (534.4), 90	2	0.0	1308 (1460.2), 1308	3	0.0	800 (1333.7), 30	1	0.0	2340 (-), 2340
Torsemide	4	0.0	222 (169.8), 180	0	0.0		0	0.0		0	0.0	
Triamterene	4	0.0	6 (14.5), 1	0	0.0		0	0.0		0	0.0	

Table 3.4 Continued

Drug	Patients with Colon Cancer and Carcinoma in situ			Patients with colon cancer and carcinoma insitu with evidence of a diagnosis by an oncologist			Patients with Colon Cancer on the right side			Patients with colon cancer on the right side with evidence of a diagnosis by an oncologist		
	Frequency of use		Duration of use	Frequency of use		Duration of use	Frequency of use		Duration of use	Frequency of use		Duration of use
	N	%	Mean (SD), Median	N	%	Mean (SD), Median	N	%	Mean (SD), Median	N	%	Mean (SD), Median
Total	73,472	100.0		12,462	100.0		12,646	100.0		3,224	100.0	
Fibrates												
Choline	1,752	2.4	626 (653), 390	314	2.5	641 (659.3), 420	298	2.4	619 (651.2), 390	78	2.4	625 (634.2), 375
Fenofibrate	951	1.3	573 (661.2), 300	135	1.1	510 (613.7), 270	180	1.4	601 (705.8), 293	31	1.0	497 (660.4), 240
Gemfibrozil	41	0.1	240 (185.9), 180	7	0.1	262 (187.4), 210	6	0.0	233 (177.8), 180	1	0.0	293 (187.9), 330
Statins												
Amlodipine_Atorvastatin	11,701	15.9	845 (778.3), 630	1,839	14.9	834 (779.2), 600	2,182	17.3	877 (780.3), 660	541	16.8	867 (781.1), 630
Atorvastatin	5,772	7.9	552 (569), 360	851	6.8	547 (548.6), 360	1,116	8.8	570 (570.3), 390	264	8.2	565 (567.9), 360
Genvastatin	2,529	3.4	560 (652.2), 300	405	3.2	530 (637.6), 270	460	3.6	590 (651.7), 330	117	3.6	483 (587.5), 225
Ezetimibe_Simvastatin	1,796	2.4	657 (673.4), 427	276	2.2	582 (625.5), 390	349	2.8	704 (682.5), 510	85	2.6	635 (630.7), 420
Fluvastatin	1,530	2.1	452 (503.3), 270	239	1.9	399 (472.8), 210	292	2.3	462 (542.5), 241	72	2.2	452 (549.2), 240
Lovastatin	1,432	1.9	558 (512.6), 390	200	1.6	542 (500.8), 360	264	2.1	599 (521.4), 473	66	2.0	632 (532.3), 480
Niacin_Lovastatin	568	0.8	522 (592.8), 300	78	0.6	485 (559.9), 300	106	0.8	534 (598.6), 315	30	0.9	556 (584.9), 405
Pravastatin	285	0.4	592 (566), 390	41	0.3	594 (549.1), 420	52	0.4	564 (524.9), 360	14	0.4	461 (406.5), 330
Rosuvastatin	225	0.3	429 (534.1), 180	35	0.3	474 (522.7), 300	41	0.3	451 (524.2), 210	10	0.3	563 (589.4), 255
Simvastatin	137	0.2	120 (69.2), 120	17	0.1	132 (73.6), 150	30	0.2	110 (66.9), 105	5	0.2	120 (69.3), 120

Conditional logistic regression results for patients with colon cancer and carcinoma in situ (primary definition)

Conditional logistic regression was used to investigate the unadjusted and multivariate-adjusted relationship between the drug class (and the respective drug included in the drug class) with the outcome. The relationship was studied in an unadjusted model followed by controlling for confounders such as colonoscopy, crohn's disease and ulcerative colitis. A potential interaction between colonoscopy and age group; colonoscopy and crohn's disease; and colonoscopy and ulcerative colitis was also evaluated in a third model. Where the parameter estimates of the interaction terms were found to be statistically significant an interaction term was included in the model. Odds ratios were further calculated for the drug classes and the individual drugs. This relationship was studied in the full cohort (primary and alternate definition) and the cases with colon cancer on the right side (primary and alternate definition).

Table 3.5a depicts the regression results for association between the drug class; and the individual drugs with colon cancer or carcinoma in situ (primary definition). In the unadjusted model, angiotensin II receptor antagonists were associated with the outcome (OR=1.13; 95% CI=1.08, 1.19). When the model was adjusted for presence of other malignancy and colonoscopy, the association changed (OR=1.07; 95% CI=1.02, 1.12). When the model was further adjusted for interactions, the association remained the same. Among the angiotensin II receptor antagonists, the drugs olmesartan and telmisartan showed association in the unadjusted model. But the associations were not significant after adjusting for confounders and confounders with interactions.

The association between the drug class ACE inhibitors and colon cancer or carcinoma in situ showed an association in all three models. The drug enalapril showed an association in all three models (Adjusted model: OR=1.25, 95% CI= 1.13, 1.39).

The drug class beta blockers showed an association in the unadjusted model but the association was not significant after adjusting for confounders and interactions. When studying the association with individual drugs, the drug carvedilol and labetalol showed an association with colon cancer or carcinoma in situ in the unadjusted model (OR=1.67; 95% CI=1.32, 2.11), model with confounders (OR=1.65; 95% CI=1.30, 2.09) and with interactions (OR=1.65; 95% CI=1.30, 2.09).

The drug class bile acid sequestrants were associated with colon cancer and carcinoma in situ. The drug cholestyramine was associated with colon cancer and carcinoma in situ in all three models (Adjusted model: OR=2.04, 95% CI= 1.69, 2.46)

The drug class calcium channel blockers were associated with colon cancer or carcinoma in situ in all three models. Among the individual drugs, the drugs diltiazem, nifedipine and verapamil showed association in all three models.

The drug class diuretics were associated in all three models. Among the individual drugs, furosemide (Adjusted model: OR=1.29, 95% CI= 1.21, 1.37) was associated in all three models.

The drug class statins did not show an association with colon cancer and carcinoma in situ. Among the individual drugs, atorvastatin, fluvastatin, pravastatin and simvastatin showed a negative association after adjusting for confounders and interactions.

Table 3.5a Conditional Logistic Regression to test the association of the drug classes and individual drugs with colon cancer and carcinoma in situ (primary definition)

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
<i>Angiotensin II Receptor Antagonist</i>	1.13	1.08	1.19	1.07	1.02	1.12	1.07	1.02	1.13
Candesartan	1.08	0.89	1.31	1.01	0.83	1.23	1.01	0.83	1.23
Eprosartan	1.66	0.81	3.41	1.55	0.75	3.22	1.56	0.75	3.23
Irbesartan	1.10	0.97	1.25	1.05	0.92	1.20	1.05	0.92	1.20
Losartan	1.13	1.06	1.21	1.08	1.01	1.15	1.08	1.01	1.15
Olmesartan	1.20	1.03	1.39	1.11	0.95	1.29	1.11	0.96	1.29
Telmisartan	1.22	0.95	1.56	1.15	0.90	1.48	1.16	0.90	1.49
Valsartan	1.06	0.98	1.15	0.99	0.91	1.07	0.99	0.92	1.08
<i>ACE Inhibitors</i>	1.10	1.05	1.15	1.07	1.02	1.12	1.07	1.02	1.12
Benazepril	1.01	0.90	1.14	1.00	0.89	1.13	1.00	0.89	1.13
Captopril	0.96	0.76	1.21	0.95	0.75	1.21	0.95	0.75	1.21
Enalapril	1.28	1.16	1.42	1.25	1.13	1.39	1.26	1.13	1.39
Fosinopril	1.00	0.81	1.22	0.99	0.81	1.22	0.99	0.81	1.22
Moexipril	1.14	0.80	1.63	1.13	0.79	1.61	1.13	0.79	1.61
Perindopril	1.12	0.74	1.71	1.12	0.73	1.71	1.11	0.73	1.71
Quinapril	1.00	0.89	1.12	0.96	0.85	1.08	0.96	0.85	1.08
Ramipril	1.08	0.99	1.18	1.03	0.95	1.13	1.03	0.95	1.13
Trandolapril	0.88	0.61	1.25	0.83	0.58	1.20	0.83	0.58	1.20
Trandolapril_Verapami l	1.11	1.01	1.23	1.08	0.97	1.19	1.07	0.97	1.19
<i>Beta Blockers</i>	1.09	1.04	1.14	1.04	0.99	1.09	1.04	1.00	1.10
Acebutolol	1.41	0.81	2.43	1.31	0.75	2.28	1.32	0.76	2.30
Atenolol	1.04	0.98	1.11	1.01	0.95	1.07	1.01	0.95	1.07
Bisoprolol	0.90	0.64	1.27	0.82	0.58	1.17	0.82	0.58	1.17
Carvedilol	1.18	1.06	1.32	1.15	1.03	1.28	1.15	1.03	1.28
Labetalol	1.67	1.32	2.11	1.65	1.30	2.09	1.65	1.30	2.09
Nadolol	0.91	0.71	1.16	0.85	0.66	1.09	0.85	0.66	1.09
Nebivolol	1.00	0.67	1.50	0.86	0.57	1.30	0.88	0.58	1.32
Pindolol	1.54	0.72	3.28	1.41	0.65	3.06	1.45	0.67	3.13
Propranolol	1.03	0.90	1.17	0.97	0.85	1.11	0.97	0.85	1.11
Sotalol	1.08	0.86	1.35	1.04	0.83	1.31	1.04	0.83	1.31
<i>Bile Acid Sequestrants</i>	1.77	1.55	2.03	1.52	1.33	1.75	1.53	1.33	1.75
Cholestyramine	2.42	2.01	2.91	2.04	1.69	2.46	2.05	1.70	2.48
Colesevelam	1.13	0.91	1.40	1.00	0.80	1.25	1.00	0.80	1.25
Colestipol	1.37	0.93	2.02	1.18	0.79	1.76	1.15	0.77	1.72

Table 3.5a Continued

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
<i>Calcium channel blockers</i>	1.22	1.15	1.29	1.17	1.11	1.24	1.17	1.11	1.24
Amlodipine_Atorvastatin	1.09	0.86	1.38	1.04	0.82	1.32	1.04	0.82	1.32
Amlodipine	1.04	0.73	1.48	0.92	0.64	1.32	0.93	0.65	1.34
Diltiazem	1.29	1.18	1.40	1.24	1.13	1.34	1.24	1.14	1.35
Felodipine	1.05	0.86	1.30	1.02	0.82	1.26	1.03	0.83	1.27
Isradipine	1.09	0.78	1.53	1.04	0.74	1.46	1.03	0.73	1.46
Nifedipine	1.23	1.09	1.38	1.19	1.05	1.34	1.19	1.05	1.34
Nisoldipine	0.75	0.54	1.03	0.70	0.50	0.97	0.68	0.49	0.95
Verapamil	1.20	1.08	1.34	1.16	1.04	1.30	1.16	1.04	1.30
<i>Diuretics</i>	1.19	1.14	1.23	1.14	1.10	1.19	1.14	1.10	1.19
Acetazolamide	0.93	0.73	1.18	0.89	0.70	1.14	0.90	0.70	1.14
Amiloride	1.70	0.78	3.72	1.43	0.64	3.16	1.43	0.65	3.17
Bumetanide	1.32	1.04	1.68	1.28	1.00	1.64	1.28	1.00	1.64
Chlorthalidone	0.88	0.63	1.23	0.89	0.63	1.24	0.88	0.63	1.24
Furosemide	1.33	1.25	1.41	1.29	1.21	1.37	1.29	1.21	1.37
Hydrochlorothiazide	1.13	1.07	1.19	1.08	1.02	1.14	1.08	1.02	1.14
Indapamide	0.92	0.71	1.18	0.89	0.69	1.14	0.89	0.69	1.15
Methazolamide	3.01	1.19	7.57	2.74	1.08	6.98	2.74	1.08	6.96
Metolazone	1.25	1.02	1.54	1.21	0.98	1.48	1.20	0.98	1.48
Spirolactone	1.08	1.01	1.15	1.04	0.97	1.11	1.04	0.97	1.11
Torseamide	1.17	0.96	1.43	1.10	0.89	1.34	1.10	0.90	1.35
<i>Fibrates</i>	1.02	0.95	1.11	0.96	0.89	1.05	0.96	0.89	1.05
Choline	0.79	0.42	1.46	0.78	0.42	1.47	0.77	0.41	1.45
Fenofibrate	1.06	0.96	1.17	0.98	0.89	1.08	0.98	0.89	1.08
Gemfibrozil	0.99	0.87	1.13	0.96	0.84	1.09	0.96	0.84	1.09
<i>Statins</i>	1.02	0.94	1.11	0.96	0.89	1.04	0.96	0.89	1.05
Atorvastatin									
Amlodipine_Atorvastatin	1.09	0.86	1.38	1.04	0.82	1.32	1.04	0.82	1.32
Cerivastatin	1.05	0.75	1.47	1.05	0.75	1.48	1.05	0.75	1.48
Ezetimibe_Simvastatin	1.05	0.95	1.17	0.97	0.87	1.08	0.97	0.87	1.08
Fluvastatin	0.87	0.73	1.03	0.84	0.71	0.99	0.84	0.71	0.99
Lovastatin	1.08	0.98	1.19	1.04	0.94	1.14	1.04	0.94	1.14
Niacin_Lovastatin	1.08	0.83	1.40	1.03	0.79	1.35	1.03	0.79	1.35
Pravastatin	0.97	0.89	1.05	0.91	0.84	0.99	0.91	0.84	0.99
Rosuvastatin	1.06	0.96	1.18	0.97	0.87	1.07	0.97	0.87	1.08
Simvastatin	1.00	0.95	1.06	0.93	0.88	0.99	0.94	0.89	0.99

Table 3.5a Continued

Drug	Unadjusted Model		Adjusted Model [†]		Fully-adjusted Model with Interactions [‡]	
	Odds ratio	95% Confidence Interval	Odds ratio	95% Confidence Interval	Odds ratio	95% Confidence Interval

[†] This model was adjusted using the covariates such as colonoscopy, crohn's disease and ulcerative colitis

[‡] This model was adjusted using covariates such as colonoscopy, crohn's disease and ulcerative colitis; and interactions between colonoscopy and age group, colonoscopy and crohn's disease, colonoscopy and ulcerative colitis

Table 3.5b depicts the regression results for association between the drug class; and the individual drugs with colon cancer and carcinoma in situ with a lag time of 6 months between last date of prescription drug use and index date.

There was no association between patients using drugs from the class angiotensin II receptor antagonists; and colon cancer and carcinoma in situ. None of the individual drugs from this drug class showed a significant association with colon cancer.

Patients using drugs from the drug class ACE inhibitors were not significantly associated with colon cancer. When comparing the association between individual drugs and colon cancer, enalapril was associated with colon cancer and carcinoma in situ in the unadjusted model (OR=1.25; 95% CI=1.13, 1.38); adjusted model with confounders (OR=1.22; 95% CI=1.10, 1.35) and the fully-adjusted model with interactions (OR=1.22; 95% CI=1.10, 1.36).

Patients using drugs from the drug class beta blockers did not show a significant association with colon cancer. When studying the association between use of individual drugs with colon cancer and carcinoma in situ, use of labetalol was significantly associated with colon cancer in all three models [Unadjusted (OR=1.73; 95% CI=1.36,

2.21); Adjusted (OR=1.71; 95% CI=1.34, 2.19); Adjusted with interactions (OR=1.71; 95% CI=1.33, 2.19)].

Use of drugs from the drug class bile acid sequestrants was associated with colon cancer and carcinoma in situ in the unadjusted model but the association was not significant in the adjusted model and the adjusted model with interactions.

Patients using drugs from the drug class calcium channel blockers showed were associated with colon cancer and carcinoma in situ. Patients using the drug diltiazem were associated with colon cancer and carcinoma in situ.

Use of drugs from the drug class diuretics was not associated with colon cancer. Among the individual drugs, use of furosemide was significantly associated with colon cancer [Unadjusted (OR=1.24; 95% CI=1.17, 1.32); Adjusted (OR=1.20; 95% CI=1.13, 1.28); Adjusted with interactions (OR=1.08; 95% CI=1.01, 1.15)].

Use of the drugs from the drug class fibrates showed a negative association in the adjusted model and the model with interactions. None of the individual drugs were associated with colon cancer and carcinoma in situ .

Use of drugs from the drug class statins showed a negative association with colon cancer and carcinoma in situ in the adjusted model and with interactions. Among the individual drugs from the drug class statins, atorvastatin, fluvastatin, pravastatin and simvastatin showed a negative association.

Table 3.5b Conditional Logistic Regression to test the association of the drug classes and individual drugs with colon cancer and carcinoma in situ with a lag time of 6 months between the last date of prescription drug use and index date

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
<i>Angiotensin II Receptor Antagonist</i>									
Candesartan	1.03	0.97	1.09	0.96	0.90	1.01	0.96	0.91	1.02
Eprosartan	1.05	0.86	1.28	0.97	0.79	1.18	0.97	0.79	1.19
Irbesartan	1.66	0.81	3.41	1.55	0.75	3.22	1.56	0.75	3.23
Losartan	1.09	0.95	1.24	1.04	0.91	1.19	1.04	0.91	1.19
Olmesartan	1.12	1.05	1.20	1.07	0.99	1.14	1.07	1.00	1.14
Telmisartan	1.23	1.05	1.43	1.12	0.96	1.32	1.13	0.96	1.32
Valsartan	1.25	0.97	1.61	1.18	0.91	1.53	1.19	0.92	1.54
Valsartan	1.05	0.97	1.14	0.98	0.90	1.06	0.98	0.90	1.06
<i>ACE Inhibitors</i>	0.99	0.95	1.04	0.96	0.91	1.01	0.96	0.92	1.01
Benazepril	1.02	0.90	1.15	1.01	0.89	1.15	1.01	0.89	1.14
Captopril	0.95	0.75	1.20	0.94	0.74	1.20	0.94	0.74	1.19
Enalapril	1.25	1.13	1.38	1.22	1.10	1.35	1.22	1.10	1.36
Fosinopril	0.95	0.77	1.17	0.94	0.76	1.17	0.94	0.76	1.16
Moexipril	1.13	0.79	1.61	1.11	0.77	1.60	1.11	0.77	1.60
Perindopril	1.08	0.70	1.66	1.06	0.68	1.64	1.05	0.68	1.63
Quinapril	1.01	0.90	1.14	0.97	0.86	1.10	0.97	0.86	1.09
Ramipril	1.06	0.97	1.17	1.02	0.93	1.12	1.02	0.93	1.12
Trandolapril	0.87	0.60	1.26	0.82	0.57	1.20	0.83	0.57	1.20
Trandolapril_Verapamil	1.11	1.01	1.23	1.07	0.97	1.19	1.07	0.97	1.19
<i>Beta Blockers</i>	1.02	0.98	1.06	0.97	0.93	1.01	0.97	0.93	1.01
Acebutolol	1.36	0.79	2.36	1.26	0.72	2.20	1.27	0.72	2.22
Atenolol	1.02	0.96	1.08	0.98	0.92	1.04	0.98	0.92	1.04
Bisoprolol	0.89	0.63	1.28	0.82	0.57	1.18	0.82	0.57	1.18
Carvedilol	1.14	1.02	1.27	1.11	0.99	1.24	1.11	0.99	1.24
Labetalol	1.73	1.36	2.21	1.71	1.34	2.19	1.71	1.33	2.19
Nadolol	0.90	0.71	1.16	0.84	0.65	1.09	0.84	0.66	1.09
Nebivolol	0.89	0.54	1.45	0.75	0.46	1.25	0.78	0.47	1.28
Pindolol	1.54	0.72	3.28	1.41	0.65	3.06	1.45	0.67	3.13
Propranolol	0.96	0.84	1.10	0.90	0.78	1.03	0.90	0.78	1.03
Sotalol	1.10	0.88	1.38	1.06	0.84	1.34			
<i>Bile Acid Sequestrants</i>	1.36	1.18	1.57	1.15	0.99	1.34	1.16	1.00	1.35
Cholestyramine	2.08	1.71	2.53	1.73	1.41	2.11			
Colesevelam	1.12	0.89	1.41	0.98	0.78	1.24	0.98	0.78	1.24
Colestipol	1.22	0.81	1.85	1.06	0.70	1.62	1.03	0.68	1.58

Table 3.5b Continued

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
<i>Calcium channel blockers</i>	1.11	1.06	1.16	1.06	1.01	1.11	1.06	1.01	1.11
Amlodipine_Atorvastatin	1.07	0.84	1.37	1.03	0.81	1.32	1.00	0.77	1.29
Amlodipine	1.00	0.68	1.47	0.89	0.60	1.32	1.04	0.98	1.11
Diltiazem	1.28	1.17	1.39	1.22	1.12	1.34	1.16	1.06	1.27
Felodipine	1.05	0.85	1.30	1.02	0.82	1.27	0.92	0.74	1.14
Isradipine	1.17	0.83	1.66	1.10	0.77	1.57	0.99	0.69	1.42
Nifedipine	1.22	1.08	1.38	1.18	1.04	1.33	1.05	0.93	1.19
Nisoldipine	0.80	0.57	1.11	0.74	0.53	1.04	0.63	0.45	0.89
Verapamil	1.19	1.07	1.33	1.15	1.02	1.28	1.02	0.91	1.14
<i>Diuretics</i>	1.04	1.00	1.09	0.99	0.95	1.04	1.00	0.95	1.04
Acetazolamide	0.98	0.76	1.26	0.94	0.73	1.22	0.72	0.56	0.92
Amiloride	1.49	0.67	3.33	1.28	0.57	2.91	1.04	0.47	2.33
Bumetanide	1.20	0.94	1.54	1.16	0.90	1.50	1.17	0.90	1.52
Chlorthalidone	0.87	0.62	1.23	0.87	0.61	1.23	0.89	0.62	1.26
Furosemide	1.24	1.17	1.32	1.20	1.13	1.28	1.08	1.01	1.15
Hydrochlorothiazide	1.10	1.04	1.16	1.05	0.99	1.11	0.93	0.88	0.98
Indapamide	0.91	0.71	1.18	0.88	0.68	1.14	0.81	0.63	1.05
Methazolamide	4.22	1.43	12.49	3.73	1.24	11.22	2.48	0.97	6.35
Metolazone	1.27	1.03	1.57	1.21	0.97	1.50	1.10	0.88	1.38
Spirolactone	1.06	0.99	1.13	1.02	0.95	1.09	0.95	0.83	1.08
Torseamide	1.14	0.93	1.41	1.06	0.86	1.31	1.09	0.88	1.36
<i>Fibrates</i>	0.93	0.86	1.01	0.87	0.80	0.94	0.87	0.80	0.95
Choline	0.72	0.37	1.40	0.70	0.36	1.38	0.69	0.35	1.36
Fenofibrate	1.06	0.96	1.17	0.98	0.88	1.08	0.98	0.88	1.08
Gemfibrozil	0.98	0.86	1.12	0.94	0.82	1.08	0.94	0.82	1.08
<i>Statins</i>	1.01	0.98	1.04	0.94	0.91	0.97	0.94	0.91	0.97
Atorvastatin	0.99	0.95	1.03	0.92	0.88	0.95	0.92	0.88	0.95
Amlodipine_Atorvastatin	1.07	0.84	1.37	1.03	0.81	1.32	0.96	0.75	1.24
Cerivastatin	1.05	0.75	1.47	1.05	0.75	1.48	1.05	0.75	1.48
Ezetimibe_Simvastatin	1.08	0.97	1.20	0.98	0.88	1.10	0.99	0.88	1.10
Fluvastatin	0.87	0.73	1.03	0.84	0.71	1.00	0.84	0.71	1.00
Lovastatin	1.06	0.96	1.17	1.01	0.92	1.12	1.02	0.92	1.12
Niacin_Lovastatin	1.06	0.81	1.40	1.01	0.76	1.34	1.01	0.76	1.33
Pravastatin	0.95	0.87	1.03	0.89	0.82	0.97	0.89	0.82	0.97
Rosuvastatin	1.06	0.95	1.18	0.96	0.86	1.07	0.96	0.86	1.07
Simvastatin	0.98	0.93	1.04	0.91	0.86	0.96	0.91	0.86	0.97

Table 3.5b Continued

Drug	Unadjusted Model		Adjusted Model [†]		Fully-adjusted Model with Interactions [‡]	
	Odds ratio	95% Confidence Interval	Odds ratio	95% Confidence Interval	Odds ratio	95% Confidence Interval

[†] This model was adjusted using the covariates such as colonoscopy, crohn's disease and ulcerative colitis

[‡] This model was adjusted using covariates such as colonoscopy, crohn's disease and ulcerative colitis; and interactions between colonoscopy and age group, colonoscopy and crohn's disease, colonoscopy and ulcerative colitis

Table 3.5c depicts the regression results for association between the drug classes; the individual drugs (minimum use of 12 months) with colon cancer and carcinoma in situ. Patients with a use of drugs from the drug class beta blockers for a minimum of 12 months were associated with colon cancer and carcinoma in situ. Among the beta blockers, use of individual drugs such as labetalol and metaprolol for a minimum of 12 months were associated with colon cancer and carcinoma in situ. Patients with a use of drugs from the class bile acid sequestrants; and the use of individual drug cholestyramine for a minimum of 12 months were associated with colon cancer and carcinoma in situ. Use of drugs from the drug classes, calcium channel blockers and diuretics for a minimum of 12 months were associated with colon cancer and carcinoma in situ. Among the drug class calcium channel blockers, use of individual drugs such as amlodipine, diltiazem and nifedipine with a minimum use of 12 months was associated with colon cancer and carcinoma in situ. Among the drug class diuretics, use of furosemide for a minimum of 12 months was associated with colon cancer and carcinoma in situ. Use of drugs from the drug class statins for a minimum of 12 months was negatively associated with colon cancer and carcinoma in situ. Patients using individual drugs such as combination of amlodipine-atorvastatin, cerivastatin, pravastatin and rosuvastatin with a

minimum use of 12 months were negatively associated with colon cancer and carcinoma in situ.

Table 3.5c Conditional Logistic Regression to test the association between the drug classes and individual drugs (with a minimum use of 12 months) with colon cancer and carcinoma in situ

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
<i>Angiotensin II Receptor Antagonist</i>	1.07	1.01	1.13	1.01	0.95	1.07	1.01	0.95	1.07
Candesartan	0.98	0.79	1.23	0.91	0.73	1.14	0.91	0.73	1.14
Eprosartan	5.01	1.45	17.29	4.45	1.27	15.55	4.43	1.27	15.49
Irbesartan	0.93	0.80	1.08	0.89	0.76	1.04	0.89	0.76	1.04
Losartan	1.10	0.98	1.24	1.04	0.93	1.17	1.05	0.93	1.18
Olmesartan	0.97	0.81	1.17	0.91	0.76	1.10	0.91	0.76	1.10
Telmisartan	1.03	0.76	1.39	0.97	0.71	1.31	0.97	0.72	1.32
Valsartan	1.12	1.03	1.22	1.06	0.97	1.15	1.06	0.97	1.16
<i>ACE Inhibitors</i>	1.04	0.99	1.09	1.02	0.96	1.07	1.02	0.96	1.07
Benazepril	0.97	0.85	1.12	0.98	0.85	1.12	0.97	0.85	1.12
Captopril	0.84	0.63	1.12	0.84	0.63	1.13	0.84	0.63	1.13
Enalapril	1.26	1.12	1.41	1.25	1.11	1.40	1.25	1.12	1.40
Fosinopril	0.77	0.61	0.97	0.76	0.60	0.96	0.76	0.60	0.96
Moexipril	1.08	0.69	1.70	1.07	0.68	1.68	1.07	0.68	1.68
Perindopril	0.77	0.45	1.33	0.75	0.43	1.31	0.74	0.43	1.29
Quinapril	0.97	0.85	1.11	0.93	0.81	1.07	0.93	0.81	1.07
Ramipril	1.03	0.93	1.14	0.99	0.89	1.10	0.99	0.89	1.10
Trandolapril	0.87	0.57	1.33	0.84	0.54	1.30	0.85	0.55	1.31
Trandolapril_Verapamil	1.00	0.90	1.11	0.97	0.87	1.08	0.97	0.87	1.08
<i>Beta Blockers</i>	1.11	1.06	1.15	1.07	1.03	1.11	1.07	1.03	1.11
Acebutolol	1.55	0.88	2.72	1.52	0.86	2.70	1.53	0.86	2.70
Atenolol	0.97	0.91	1.04	0.94	0.88	1.00	0.94	0.88	1.01
Bisoprolol	0.73	0.50	1.06	0.70	0.48	1.02	0.70	0.48	1.02
Carvedilol	1.13	1.02	1.26	1.12	1.00	1.25	1.12	1.00	1.25
Labetalol	1.45	1.12	1.88	1.42	1.09	1.85	1.42	1.09	1.85
Metoprolol	1.15	1.10	1.22	1.12	1.06	1.18	1.12	1.06	1.18
Nadolol	0.81	0.62	1.07	0.75	0.57	0.99	0.76	0.57	1.00
Nebivolol	0.64	0.43	0.95	0.62	0.42	0.93	0.63	0.42	0.93
Pindolol	1.61	0.67	3.88	1.52	0.62	3.73	1.55	0.64	3.79
Propranolol	1.09	0.93	1.29	1.06	0.89	1.25	1.06	0.90	1.25
Sotalol	1.11	0.87	1.42	1.07	0.83	1.37	1.07	0.83	1.37

Table 3.5c Continued

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
<i>Bile Acid Sequestrants</i>	1.86	1.45	2.39	1.66	1.29	2.14	1.68	1.30	2.16
Cholestyramine	4.65	2.83	7.63	4.01	2.43	6.63	4.08	2.47	6.74
Colesevelam	1.15	0.82	1.62	1.04	0.73	1.47	1.04	0.73	1.47
Colestipol	1.34	0.68	2.61	1.25	0.63	2.47	1.27	0.65	2.52
<i>Calcium channel blockers</i>	1.16	1.11	1.22	1.12	1.07	1.18	1.12	1.07	1.18
Amlodipine_Atorvastatin	0.99	0.77	1.27	0.97	0.75	1.25	0.96	0.75	1.24
Amlodipine	1.14	1.08	1.22	1.10	1.03	1.17	1.10	1.03	1.17
Diltiazem	1.23	1.12	1.34	1.18	1.08	1.30	1.19	1.08	1.30
Felodipine	0.98	0.77	1.23	0.94	0.74	1.19	0.94	0.75	1.19
Isradipine	1.03	0.65	1.62	1.00	0.63	1.58	0.99	0.62	1.56
Nifedipine	1.21	1.06	1.38	1.18	1.03	1.35	1.18	1.03	1.35
Nisoldipine	0.66	0.44	0.98	0.61	0.40	0.91	0.61	0.40	0.91
Verapamil	1.13	1.00	1.27	1.09	0.96	1.24	1.09	0.96	1.23
<i>Diuretics</i>	1.12	1.07	1.17	1.09	1.04	1.14	1.09	1.04	1.14
Acetazolamide	0.60	0.26	1.38	0.66	0.28	1.51	0.66	0.29	1.53
Amiloride	1.23	0.51	2.96	1.15	0.47	2.82	1.14	0.46	2.79
Bumetanide	1.12	0.82	1.53	1.17	0.85	1.60	1.16	0.85	1.59
Chlorthalidone	0.94	0.63	1.41	0.89	0.59	1.34	0.89	0.59	1.34
Furosemide	1.24	1.15	1.33	1.22	1.14	1.32	1.22	1.14	1.31
Hydrochlorothiazide	1.03	0.96	1.09	0.99	0.93	1.05	0.99	0.93	1.05
Indapamide	0.81	0.61	1.07	0.77	0.58	1.03	0.78	0.58	1.03
Methazolamide	1.50	0.25	8.97	1.25	0.20	7.74	1.28	0.21	7.88
Metolazone	1.37	1.01	1.87	1.31	0.96	1.79	1.30	0.95	1.78
Spirolactone	1.19	1.03	1.38	1.14	0.98	1.32	1.14	0.98	1.32
Torseamide	1.21	0.93	1.57	1.14	0.87	1.48	1.15	0.88	1.49
<i>Fibrates</i>	0.99	0.90	1.09	0.93	0.84	1.02	0.93	0.85	1.02
Choline	1.08	0.70	1.65	0.94	0.60	1.45	0.93	0.60	1.44
Fenofibrate	1.02	0.92	1.14	0.95	0.85	1.06	0.95	0.85	1.06
Gemfibrozil	0.94	0.80	1.10	0.89	0.76	1.05	0.89	0.76	1.05
<i>Statins</i>	0.93	0.90	0.97	0.86	0.83	0.89	0.86	0.83	0.89
Atorvastatin	0.99	0.77	1.27	0.97	0.75	1.25	0.96	0.75	1.24
Amlodipine_Atorvastatin	0.91	0.88	0.96	0.85	0.81	0.89	0.85	0.81	0.89
Ezetimibe_Simvastatin	0.94	0.83	1.05	0.86	0.76	0.97	0.86	0.77	0.97
Fluvastatin	0.87	0.70	1.08	0.84	0.67	1.05	0.84	0.67	1.05
Lovastatin	1.00	0.90	1.11	0.95	0.86	1.06	0.96	0.86	1.06
Niacin_Lovastatin	0.95	0.67	1.33	0.88	0.62	1.25	0.87	0.61	1.24

Table 3.5c Continued

Drug	Unadjusted Model		Adjusted Model [†]		Fully-adjusted Model with Interactions [‡]	
	Odds ratio	95% Confidence Interval	Odds ratio	95% Confidence Interval	Odds ratio	95% Confidence Interval
Pravastatin	0.88	0.80 0.97	0.83	0.75 0.91	0.83	0.75 0.92
Rosuvastatin	0.91	0.81 1.03	0.83	0.74 0.94	0.83	0.74 0.94
Simvastatin	0.92	0.87 0.98	0.87	0.82 0.92	0.87	0.82 0.92

[†] This model was adjusted using the covariates such as colonoscopy, crohn's disease and ulcerative colitis

[‡] This model was adjusted using covariates such as colonoscopy, crohn's disease and ulcerative colitis; and interactions between colonoscopy and age group, colonoscopy and crohn's disease, colonoscopy and ulcerative colitis

Conditional logistic regression results for patients with colon cancer and carcinoma in situ with evidence of a diagnosis by an oncologist (alternate definition)

The relationship between patients using drugs from a drug class and using individual drugs was studied among the patients with a diagnosis of colon cancer and carcinoma in situ with evidence of a diagnosis by an oncologist. The relationship was studied by using the crude model, adjusted model and adjusted model with interactions.

Table 3.6a depicts the regression results between the drug class, individual results with patients with a diagnosis of colon cancer and carcinoma in situ with evidence of a diagnosis by an oncologist.

Use of drugs from the drug class, bile acid sequestrants was associated with colon cancer and carcinoma in situ (alternate definition). Use of individual drug, cholestyramine was associated with colon cancer and carcinoma insity (alternate definition).

Use of drugs from the drug class, calcium channel blockers was associated with colon cancer and carcinoma in situ (alternate definition). There was no association between use of any individual drugs among calcium channel blockers; and colon cancer and carcinoma in situ.

It was found that patients using diuretics were associated with colon cancer and carcinoma in situ (alternate definition). Use of the diuretic drug, furosemide was associated with colon cancer and carcinoma in situ.

Patients using drugs from the class statins and using individual drugs such as atorvastatin, pravastatin and simvastatin were negatively associated with colon cancer and carcinoma in situ (alternate definition).

Table 3.6a Conditional Logistic Regression to test the association of the drug classes and individual drugs with colon cancer or carcinoma in situ with an evidence of a diagnosis by an oncologist

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
<i>Angiotensin II Receptor Antagonist</i>	0.99	0.88	1.12	0.97	0.85	1.10	0.97	0.86	1.10
Candesartan	0.94	0.58	1.54	0.87	0.53	1.43	0.88	0.53	1.44
Irbesartan	0.95	0.67	1.35	0.96	0.68	1.36	0.97	0.68	1.37
Losartan	1.08	0.91	1.29	1.06	0.89	1.25	1.06	0.89	1.26
Olmesartan	0.93	0.63	1.36	0.89	0.60	1.30	0.89	0.61	1.31
Telmisartan	0.77	0.41	1.46	0.73	0.38	1.37	0.73	0.39	1.38
Valsartan	0.83	0.68	1.02	0.81	0.66	0.99	0.81	0.66	0.99
<i>ACE Inhibitors</i>	1.02	0.90	1.15	1.00	0.89	1.13	1.00	0.89	1.13
Benazepril	0.86	0.64	1.16	0.85	0.63	1.14	0.85	0.63	1.14
Captopril	1.00	0.56	1.78	1.01	0.57	1.81	1.00	0.56	1.79
Enalapril	1.09	0.83	1.43	1.10	0.84	1.44	1.10	0.84	1.44
Fosinopril	0.69	0.40	1.19	0.72	0.42	1.24	0.73	0.42	1.25
Moexipril	1.27	0.65	2.50	1.26	0.64	2.50	1.28	0.65	2.52
Quinapril	0.96	0.70	1.30	0.92	0.67	1.25	0.91	0.67	1.24
Ramipril	1.00	0.79	1.26	0.97	0.77	1.22	0.97	0.77	1.23
Trandolapril_Verapamil	1.24	0.96	1.59	1.23	0.95	1.58	1.22	0.95	1.57
<i>Beta Blockers</i>	1.01	0.89	1.15	0.98	0.86	1.11	0.98	0.87	1.11
Atenolol	1.00	0.85	1.16	0.97	0.83	1.13	0.97	0.83	1.13
Carvedilol	1.10	0.82	1.47	1.08	0.80	1.44	1.08	0.80	1.44
Labetalol	1.50	0.76	2.96	1.43	0.72	2.83	1.43	0.72	2.82
Nadolol	0.99	0.53	1.85	0.91	0.49	1.70	0.92	0.49	1.72
Propranolol	0.82	0.58	1.16	0.78	0.55	1.11	0.78	0.56	1.11
Sotalol	0.63	0.30	1.30	0.60	0.29	1.24	0.60	0.29	1.24

Table 3.6a Continued

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
<i>Bile Acid Sequestrants</i>	1.67	1.17	2.39	1.49	1.04	2.14	1.50	1.05	2.15
Cholestyramine	2.06	1.29	3.30	1.88	1.17	3.02	1.89	1.17	3.04
Colesevelam	1.30	0.73	2.34	1.17	0.65	2.11	1.18	0.65	2.12
<i>Calcium channel blockers</i>	1.19	1.02	1.38	1.16	1.00	1.35	1.16	1.00	1.35
Amlodipine_Atorvastatin	0.87	0.47	1.60	0.86	0.46	1.59	0.85	0.46	1.58
Diltiazem	1.30	1.04	1.63	1.29	1.03	1.62	1.29	1.03	1.62
Felodipine	1.00	0.58	1.70	0.94	0.55	1.61	0.95	0.55	1.62
Nifedipine	1.17	0.85	1.60	1.13	0.82	1.54	1.13	0.82	1.54
Verapamil	1.05	0.78	1.40	1.03	0.77	1.39	1.03	0.77	1.38
<i>Diuretics</i>	1.15	1.04	1.26	1.12	1.02	1.24	1.13	1.02	1.24
Acetazolamide	1.17	0.61	2.23	1.17	0.61	2.25	1.17	0.61	2.24
Bumetanide	0.70	0.35	1.39	0.68	0.34	1.35	0.68	0.34	1.36
Furosemide	1.32	1.13	1.54	1.29	1.10	1.51	1.29	1.10	1.51
Hydrochlorothiazide	1.14	1.00	1.31	1.13	0.98	1.29	1.13	0.98	1.29
Indapamide	1.61	0.85	3.08	1.53	0.80	2.94	1.55	0.81	2.96
Metolazone	1.04	0.58	1.87	0.98	0.54	1.76	1.00	0.55	1.79
Spirolactone	0.96	0.81	1.14	0.94	0.80	1.12	0.94	0.80	1.12
Torsemide	0.97	0.58	1.61	0.96	0.57	1.61	0.97	0.58	1.62
<i>Fibrates</i>	0.91	0.75	1.10	0.87	0.72	1.06	0.87	0.72	1.06
Fenofibrate	1.00	0.80	1.25	0.95	0.75	1.19	0.95	0.75	1.19
Gemfibrozil	0.66	0.47	0.94	0.64	0.45	0.91	0.64	0.45	0.91
<i>Statins</i>	0.85	0.78	0.93	0.82	0.76	0.90	0.82	0.76	0.90
Atorvastatin	0.85	0.76	0.94	0.81	0.73	0.90	0.81	0.74	0.90
Amlodipine_Atorvastatin	0.87	0.47	1.60	0.86	0.46	1.59	0.85	0.46	1.58
Ezetimibe_Simvastatin	1.01	0.76	1.35	0.96	0.72	1.28	0.96	0.72	1.28
Fluvastatin	1.00	0.64	1.57	0.99	0.63	1.55	0.98	0.62	1.54
Lovastatin	0.93	0.73	1.18	0.90	0.70	1.14	0.90	0.71	1.15
Niacin_Lovastatin	1.34	0.68	2.61	1.35	0.69	2.65	1.35	0.69	2.65
Pravastatin	0.76	0.62	0.94	0.76	0.62	0.93	0.76	0.62	0.93

Table 3.6a Continued

Drug	Unadjusted Model		Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval	Odds ratio	95% Confidence Interval	Odds ratio	95% Confidence Interval		
Rosuvastatin	0.92	0.71 1.20	0.88	0.68 1.15	0.89	0.68 1.15		
Simvastatin	0.88	0.76 1.01	0.86	0.74 0.99	0.86	0.75 0.99		

[†] This model was adjusted using the covariates such as colonoscopy, crohn's disease and ulcerative colitis

[‡] This model was adjusted using covariates such as colonoscopy, crohn's disease and ulcerative colitis; and interactions between colonoscopy and age group, colonoscopy and crohn's disease, colonoscopy and ulcerative colitis

Table 3.6b depicts conditional logistic regression results to test the association between the drug class; and the individual drugs with colon cancer and carcinoma in situ with evidence of a diagnosis by an oncologist and with a lag time of 6 months between last date of prescription drug use and index date.

Patients using drugs from the drug class angiotensin II receptor antagonist, ACE inhibitors, beta blockers, fibrates and statins showed a negative association with colon cancer or carcinoma instu with evidence of a diagnosis by an oncologist and with a lag time of 6 months between last date of prescription drug use and index date. Use of individual drugs such as valsartan, propranolol, gemfibrozil, atorvastatin, pravastatin, and simvastatin showed a negative association with colon cancer or carcinoma instu with evidence of a diagnosis by an oncologist and with a lag time of 6 months between last date of prescription drug use and index date.

Table 3.6b Conditional Logistic Regression to test the association of the drug classes and individual drugs with colon cancer or carcinoma in situ with evidence of a diagnosis by an oncologist and with a lag time of 6 months between the last date of prescription drug use and index date.

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
<i>Angiotensin II Receptor Antagonist</i>	0.86	0.74	0.99	0.83	0.72	0.96	0.83	0.72	0.96
Candesartan	0.79	0.49	1.28	0.73	0.45	1.18	0.73	0.45	1.18
Irbesartan	0.81	0.57	1.16	0.81	0.56	1.16	0.81	0.57	1.16
Losartan	0.81	0.60	1.09	0.79	0.59	1.06	0.79	0.59	1.07
Olmесartan	0.93	0.62	1.37	0.88	0.59	1.31	0.89	0.60	1.32
Telmisartan	0.85	0.44	1.62	0.79	0.41	1.52	0.80	0.41	1.53
Valsartan	0.77	0.62	0.94	0.74	0.60	0.91	0.74	0.60	0.91
<i>ACE Inhibitors</i>	0.89	0.79	1.01	0.88	0.77	0.99	0.88	0.77	0.99
Benazepril	0.82	0.61	1.11	0.80	0.59	1.08	0.79	0.59	1.08
Captopril	0.74	0.41	1.32	0.75	0.42	1.35	0.74	0.41	1.33
Enalapril	0.99	0.75	1.31	0.99	0.75	1.32	0.99	0.75	1.32
Fosinopril	0.59	0.34	1.02	0.61	0.35	1.07	0.62	0.36	1.08
Moexipril	1.19	0.61	2.32	1.19	0.61	2.32	1.20	0.62	2.35
Quinapril	0.84	0.62	1.14	0.81	0.60	1.10	0.81	0.60	1.09
Ramipril	0.80	0.63	1.02	0.77	0.61	0.99	0.78	0.61	0.99
Trandolapril_Verapamil	1.09	0.85	1.40	1.07	0.83	1.38	1.07	0.83	1.38
<i>Beta Blockers</i>	0.88	0.80	0.97	0.85	0.77	0.94	0.85	0.77	0.94
Atenolol	0.87	0.74	1.01	0.84	0.71	0.98	0.84	0.72	0.98
Carvedilol	1.08	0.78	1.50	1.06	0.77	1.48	1.06	0.77	1.48
Labetalol	1.55	0.72	3.31	1.47	0.68	3.16	1.45	0.68	3.12
Nadolol	0.76	0.40	1.46	0.68	0.35	1.31	0.69	0.36	1.32
Propranolol	0.65	0.46	0.94	0.61	0.43	0.88	0.62	0.43	0.89
Sotalol	0.63	0.30	1.30	0.60	0.29	1.24	0.60	0.29	1.25
<i>Bile Acid Sequestrants</i>	1.09	0.74	1.60	0.95	0.64	1.41	0.95	0.64	1.42
Cholestyramine	1.15	0.68	1.95	1.01	0.59	1.73	1.03	0.60	1.76
Colesevelam	1.10	0.60	2.03	0.99	0.54	1.83	1.00	0.54	1.83
<i>Calcium channel blockers</i>	1.05	0.93	1.18	1.03	0.91	1.16	1.03	0.91	1.16
Amlodipine_Atorvastatin	0.85	0.45	1.63	0.85	0.45	1.64	0.85	0.44	1.62
Diltiazem	1.22	0.97	1.54	1.20	0.95	1.52	1.21	0.96	1.52
Felodipine	0.86	0.49	1.48	0.81	0.47	1.41	0.82	0.47	1.42
Nifedipine	1.04	0.76	1.44	1.01	0.73	1.39	1.01	0.73	1.39
Verapamil	0.92	0.68	1.24	0.91	0.67	1.22	0.90	0.67	1.22

Table 3.6b Continued

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
<i>Diuretics</i>	1.00	0.90	1.12	0.98	0.87	1.09	0.98	0.88	1.09
Acetazolamide	0.84	0.44	1.61	0.83	0.43	1.59	0.81	0.42	1.57
Bumetanide	0.64	0.30	1.37	0.64	0.30	1.38	0.64	0.30	1.38
Furosemide	1.06	0.90	1.26	1.03	0.87	1.22	1.03	0.87	1.22
Hydrochlorothiazide	1.01	0.87	1.16	0.99	0.85	1.14	0.99	0.85	1.14
Indapamide	1.29	0.69	2.39	1.22	0.65	2.27	1.23	0.66	2.29
Metolazone	1.05	0.55	2.01	0.98	0.51	1.88	1.00	0.52	1.91
Spirolactone	0.86	0.61	1.21	0.85	0.60	1.20	0.85	0.60	1.20
Torseamide	1.04	0.60	1.80	1.04	0.60	1.81	1.05	0.60	1.82
<i>Fibrates</i>	0.79	0.64	0.97	0.75	0.61	0.92	0.75	0.61	0.92
Fenofibrate	0.91	0.72	1.15	0.85	0.67	1.08	0.85	0.67	1.08
Gemfibrozil	0.58	0.40	0.84	0.55	0.38	0.80	0.55	0.38	0.80
<i>Statins</i>	0.78	0.71	0.85	0.75	0.69	0.82	0.75	0.69	0.82
Atorvastatin	0.72	0.65	0.80	0.69	0.62	0.77	0.69	0.62	0.77
Amlodipine_Atorvastatin	0.85	0.45	1.63	0.85	0.45	1.64	0.85	0.44	1.62
Ezetimibe_Simvastatin	0.89	0.66	1.20	0.84	0.62	1.14	0.84	0.62	1.13
Fluvastatin	0.92	0.59	1.46	0.91	0.57	1.43	0.90	0.57	1.42
Lovastatin	0.85	0.66	1.09	0.82	0.63	1.05	0.82	0.64	1.06
Niacin_Lovastatin	1.42	0.68	2.99	1.46	0.70	3.08	1.47	0.70	3.08
Pravastatin	0.65	0.53	0.80	0.64	0.52	0.79	0.64	0.52	0.79
Rosuvastatin	0.83	0.64	1.09	0.80	0.61	1.05	0.80	0.61	1.05
Simvastatin	0.78	0.67	0.91	0.76	0.65	0.88	0.76	0.65	0.88

[†] This model was adjusted using the covariates such as colonoscopy, crohn's disease and ulcerative colitis

[‡] This model was adjusted using covariates such as colonoscopy, crohn's disease and ulcerative colitis; and interactions between colonoscopy and age group, colonoscopy and crohn's disease, colonoscopy and ulcerative colitis

Table 3.6c depicts results from the conditional logistic regression to test the association between the drug class; and the individual drugs having minimum use of 12 months with colon cancer and carcinoma in situ with evidence of a diagnosis by an oncologist.

It was found that patients using drugs from the drug class, bile acid sequestrants and calcium channel blockers having a minimum use of 12 months were associated with colon cancer or carcinoma in situ with evidence of a diagnosis by an oncologist. Among

the individual, use of drugs such as cholestyramine, furosemide and spironolactone with a minimum use of 12 months or more was associated with colon cancer or carcinoma in situ with evidence of a diagnosis by an oncologist.

Use of drugs in the drug class, angiotensin II receptor antagonists and statins having a minimum use of 12 months were negatively associated with colon cancer and carcinoma in situ with evidence of a diagnosis by an oncologist. Use of individual drugs such as atorvastatin, pravastatin and simvastatin having a minimum use of 12 months showed a negative association with colon cancer and carcinoma in situ with evidence of a diagnosis by an oncologist.

Table 3.6c Conditional Logistic Regression to test the association between the drug class; and the individual drugs having minimum use of 12 months with colon cancer and carcinoma in situ with evidence of a diagnosis by an oncologist.

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
<i>Angiotensin II Receptor Antagonist</i>	0.84	0.72	0.98	0.82	0.70	0.96	0.82	0.70	0.96
Candesartan	0.97	0.56	1.68	0.91	0.53	1.59	0.91	0.52	1.58
Irbesartan	0.82	0.53	1.28	0.84	0.54	1.30	0.84	0.54	1.30
Losartan	0.95	0.70	1.30	0.95	0.69	1.29	0.95	0.70	1.30
Olmesartan	0.81	0.51	1.28	0.77	0.49	1.21	0.77	0.48	1.21
Telmisartan	0.60	0.29	1.22	0.54	0.26	1.11	0.54	0.26	1.12
Valsartan	0.83	0.67	1.03	0.81	0.65	1.01	0.81	0.65	1.01
<i>ACE Inhibitors</i>	1.00	0.88	1.14	0.99	0.87	1.13	0.99	0.87	1.13
Benazepril	1.00	0.72	1.40	0.98	0.70	1.37	0.98	0.70	1.37
Captopril	0.56	0.28	1.10	0.58	0.30	1.16	0.58	0.29	1.15
Enalapril	1.06	0.79	1.43	1.08	0.80	1.46	1.08	0.80	1.45
Fosinopril	0.64	0.36	1.17	0.67	0.37	1.22	0.67	0.37	1.22
Moexipril	0.80	0.32	2.03	0.79	0.31	2.01	0.80	0.31	2.03
Quinapril	1.02	0.72	1.44	0.99	0.70	1.41	0.99	0.70	1.40
Ramipril	1.03	0.80	1.32	1.00	0.77	1.29	1.00	0.77	1.29
Trandolapril_Verapamil	1.25	0.96	1.63	1.23	0.95	1.61	1.23	0.95	1.61

Table 3.6c Continued

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
<i>Beta Blockers</i>	1.07	0.97	1.19	1.05	0.95	1.16	1.05	0.95	1.16
Atenolol	1.02	0.87	1.21	1.00	0.84	1.18	1.00	0.84	1.18
Carvedilol	1.15	0.87	1.53	1.15	0.87	1.53	1.14	0.86	1.52
Labetalol	1.55	0.73	3.31	1.41	0.66	3.04	1.41	0.66	3.03
Nadolol	1.21	0.60	2.46	1.19	0.58	2.42	1.20	0.59	2.44
Propranolol	0.78	0.51	1.21	0.75	0.48	1.17	0.75	0.48	1.16
Sotalol	0.83	0.42	1.65	0.81	0.41	1.61	0.81	0.41	1.61
<i>Bile Acid Sequestrants</i>	2.14	1.18	3.87	1.93	1.06	3.52	1.94	1.06	3.54
Cholestyramine	8.46	1.96	36.57	7.32	1.68	31.78	7.44	1.71	32.28
Colesevelam	1.17	0.54	2.53	1.09	0.50	2.37	1.08	0.50	2.36
<i>Calcium channel blockers</i>	1.17	1.04	1.32	1.16	1.03	1.31	1.16	1.03	1.31
Amlodipine_Atorvastatin	1.06	0.55	2.02	1.04	0.54	1.99	1.01	0.53	1.94
Diltiazem	1.46	1.14	1.88	1.46	1.13	1.87	1.46	1.14	1.88
Felodipine	0.74	0.41	1.32	0.69	0.38	1.23	0.69	0.39	1.24
Nifedipine	1.44	1.01	2.04	1.41	0.99	2.01	1.41	0.99	2.00
Verapamil	0.97	0.70	1.35	0.98	0.70	1.36	0.97	0.70	1.35
<i>Diuretics</i>	1.08	0.95	1.22	1.07	0.95	1.21	1.07	0.95	1.21
Bumetanide	0.57	0.24	1.36	0.56	0.23	1.34	0.57	0.24	1.35
Furosemide	1.30	1.07	1.57	1.30	1.07	1.57	1.29	1.07	1.57
Hydrochlorothiazide	0.91	0.77	1.08	0.90	0.76	1.07	0.90	0.76	1.07
Indapamide	1.25	0.65	2.41	1.20	0.62	2.33	1.22	0.63	2.36
Metolazone	0.82	0.34	1.98	0.74	0.30	1.78	0.75	0.31	1.83
Spirolactone	1.58	1.06	2.34	1.56	1.05	2.31	1.55	1.05	2.31
Torseamide	1.43	0.75	2.71	1.43	0.75	2.73	1.43	0.75	2.72
<i>Fibrates</i>	0.81	0.65	1.01	0.77	0.62	0.97	0.78	0.62	0.97
Fenofibrate	0.85	0.66	1.09	0.81	0.63	1.05	0.81	0.63	1.05
Gemfibrozil	0.66	0.42	1.04	0.63	0.40	0.99	0.63	0.40	1.00
<i>Statins</i>	0.81	0.74	0.89	0.78	0.72	0.86	0.78	0.72	0.85
Atorvastatin	0.80	0.72	0.89	0.77	0.69	0.86	0.77	0.69	0.86
Amlodipine_Atorvastatin	1.06	0.55	2.02	1.04	0.54	1.99	1.01	0.53	1.94
Ezetimibe_Simvastatin	0.77	0.56	1.08	0.72	0.52	1.01	0.72	0.51	1.00
Fluvastatin	0.96	0.52	1.74	0.94	0.51	1.71	0.93	0.51	1.70
Lovastatin	0.84	0.64	1.11	0.81	0.62	1.07	0.82	0.62	1.08

Table 3.6c Continued

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
Niacin_Lovastatin	1.36	0.62	2.97	1.37	0.63	3.00	1.36	0.62	2.98
Pravastatin	0.71	0.55	0.92	0.71	0.55	0.91	0.71	0.55	0.91
Rosuvastatin	0.89	0.64	1.23	0.85	0.61	1.19	0.85	0.61	1.19
Simvastatin	0.81	0.69	0.93	0.79	0.68	0.92	0.79	0.68	0.91

[†] This model was adjusted using the covariates such as colonoscopy, crohn's disease and ulcerative colitis

[‡] This model was adjusted using covariates such as colonoscopy, crohn's disease and ulcerative colitis; and interactions between colonoscopy and age group, colonoscopy and crohn's disease, colonoscopy and ulcerative colitis

Conditional logistic regression results for patients with colon cancer on the right side (primary definition)

The relationship between patients using drugs from a drug class and using individual drugs was studied among the patients with a diagnosis of colon cancer on the right side.

The relationship was studied by using the crude model, adjusted model and adjusted model with interactions.

Table 3.7a depicts the regression results between the drug classes, individual results with patients with a diagnosis of colon cancer on the right side. Use of drugs from the drug class bile acid sequestrants, calcium channel blockers and diuretics was associated with colon cancer on the right side. Use of individual drugs such as cholestyramine, diltiazem, bumetanide and furosemide is associated with colon cancer on the right side.

Use of drugs from the drug class, fibrates and statins showed a negative association with colon cancer on the right side. Use of individual drugs such as atenolol, gemfibrozil and atorvastatin showed a negative association with colon cancer on the right side.

Table 3.7a Conditional Logistic Regression to test the association between the drug class; and the individual drugs with colon cancer on the right side (primary definition)

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
<i>Angiotensin II Receptor Antagonist</i>	1.08	0.96	1.21	1.05	0.93	1.18	1.04	0.93	1.17
Candesartan	1.09	0.68	1.74	1.02	0.64	1.63	1.03	0.64	1.64
Irbesartan	1.14	0.84	1.54	1.13	0.83	1.53	1.13	0.83	1.53
Losartan	1.09	0.93	1.27	1.06	0.90	1.24	1.06	0.90	1.24
Olmesartan	1.10	0.78	1.53	1.07	0.77	1.50	1.07	0.76	1.49
Telmisartan	1.51	0.83	2.74	1.47	0.80	2.67	1.46	0.80	2.67
Valsartan	0.91	0.75	1.10	0.88	0.73	1.07	0.88	0.73	1.07
<i>ACE Inhibitors</i>	0.97	0.87	1.09	0.96	0.85	1.07	0.96	0.86	1.07
Benazepril	1.01	0.76	1.35	0.98	0.73	1.32	0.99	0.74	1.32
Captopril	1.11	0.67	1.84	1.09	0.65	1.80	1.08	0.65	1.79
Enalapril	1.19	0.94	1.50	1.18	0.93	1.48	1.18	0.93	1.49
Fosinopril	0.86	0.53	1.40	0.89	0.55	1.45	0.89	0.55	1.45
Quinapril	0.85	0.65	1.12	0.82	0.62	1.08	0.82	0.62	1.08
Ramipril	0.87	0.71	1.07	0.86	0.70	1.05	0.86	0.70	1.06
Trandolapril_Verapamil	1.10	0.86	1.39	1.09	0.85	1.38	1.08	0.85	1.38
<i>Beta Blockers</i>	0.96	0.85	1.07	0.94	0.84	1.05	0.94	0.84	1.05
Atenolol	0.88	0.76	1.01	0.86	0.75	0.99	0.86	0.75	0.99
Carvedilol	1.11	0.87	1.41	1.09	0.86	1.39	1.10	0.86	1.39
Labetalol	0.78	0.45	1.32	0.73	0.42	1.25	0.74	0.44	1.28
Metoprolol									
Nadolol	0.76	0.44	1.33	0.74	0.43	1.30	0.75	0.43	1.31
Propranolol	1.01	0.73	1.40	1.02	0.74	1.41	1.02	0.73	1.41
Sotalol	1.13	0.69	1.85	1.11	0.67	1.82	1.10	0.67	1.81
<i>Bile Acid Sequestrants</i>	1.78	1.28	2.47	1.62	1.16	2.25	1.61	1.15	2.25
Cholestyramine	2.73	1.69	4.42	2.49	1.53	4.03	2.50	1.54	4.05
Colesevelam	1.19	0.71	1.99	1.12	0.67	1.88	1.10	0.66	1.85
<i>Calcium channel blockers</i>	1.23	1.08	1.40	1.20	1.05	1.36	1.20	1.05	1.37
Amlodipine_Atorvastatin	0.97	0.56	1.67	0.95	0.54	1.65	0.95	0.55	1.66
Amlodipine	0.50	0.21	1.17	0.45	0.19	1.06	0.46	0.20	1.09

Table 3.7a Continued

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
Diltiazem	1.35	1.11	1.64	1.33	1.09	1.61	1.33	1.09	1.61
Felodipine	0.73	0.44	1.20	0.72	0.44	1.19	0.72	0.44	1.19
Nifedipine	1.31	1.00	1.73	1.28	0.97	1.68	1.28	0.97	1.69
Nisoldipine	0.76	0.37	1.57	0.75	0.36	1.56	0.75	0.36	1.55
Verapamil	1.22	0.95	1.58	1.18	0.91	1.52	1.18	0.91	1.52
<i>Diuretics</i>	1.15	1.05	1.26	1.13	1.03	1.23	1.13	1.03	1.24
Acetazolamide	0.89	0.50	1.55	0.88	0.50	1.56	0.89	0.51	1.57
Bumetanide	1.92	1.10	3.36	1.86	1.06	3.27	1.87	1.07	3.28
Furosemide	1.30	1.14	1.48	1.28	1.12	1.46	1.28	1.12	1.46
Hydrochlorothiazide	1.07	0.94	1.21	1.05	0.93	1.19	1.05	0.93	1.20
Indapamide	0.82	0.45	1.49	0.82	0.45	1.49	0.82	0.45	1.50
Metolazone	0.95	0.61	1.48	0.95	0.61	1.47	0.94	0.60	1.46
Spironolactone	1.02	0.87	1.19	1.00	0.85	1.17	1.00	0.85	1.18
Torsemide	1.16	0.75	1.80	1.12	0.72	1.74	1.13	0.73	1.75
<i>Fibrates</i>	0.80	0.66	0.98	0.79	0.65	0.97	0.79	0.65	0.96
Fenofibrate	0.89	0.70	1.12	0.86	0.68	1.09	0.86	0.68	1.09
Gemfibrozil	0.65	0.47	0.89	0.66	0.48	0.90	0.65	0.48	0.90
<i>Statins</i>	0.93	0.86	1.00	0.88	0.82	0.96	0.89	0.82	0.96
Atorvastatin	0.86	0.78	0.95	0.82	0.75	0.90	0.82	0.75	0.90
Amlodipine_Atorvastatin	0.97	0.56	1.67	0.95	0.54	1.65	0.95	0.55	1.66
Cerivastatin	1.01	0.48	2.12	1.02	0.48	2.15	0.99	0.47	2.10
Ezetimibe_Simvastatin	1.14	0.89	1.47	1.09	0.85	1.41	1.10	0.85	1.42
Fluvastatin	1.14	0.76	1.69	1.11	0.75	1.66	1.11	0.75	1.66
Lovastatin	0.99	0.79	1.24	0.98	0.78	1.22	0.98	0.78	1.22
Niacin_Lovastatin	1.01	0.53	1.90	0.99	0.52	1.88	0.99	0.52	1.88
Pravastatin	1.14	0.94	1.39	1.10	0.91	1.34	1.11	0.91	1.35
Rosuvastatin	0.98	0.77	1.24	0.93	0.73	1.19	0.94	0.74	1.19
Simvastatin	0.99	0.87	1.13	0.96	0.84	1.09	0.96	0.84	1.09

[†] This model was adjusted using the covariates such as colonoscopy, crohn's disease and ulcerative colitis

[‡] This model was adjusted using covariates such as colonoscopy, crohn's disease and ulcerative colitis; and interactions between colonoscopy and age group, colonoscopy and crohn's disease, colonoscopy and ulcerative colitis

Table 3.7b depicts the conditional logistic regression results testing the association between drug classes, the individual drugs having a lag time of at least 6 months between the last date of prescription drug use and index date with colon cancer on the right side. When the lag time of 6 months was applied to the patients with colon cancer on the right side, none of the drug classes showed a significant association with colon cancer on the right side. Patients using drugs from the drug class fibrates and statins showed a negative association with colon cancer.

Among the individual drugs, patients using the drugs cholestyramine and diltiazem with a lag time of 6 months were associated with colon cancer on the right side; whereas drugs such as ramipril, atenolol, gemfibrozil and atenolol showed a negative association.

Table 3.7b Conditional Logistic Regression to test the association of the drug classes and individual drugs with colon cancer on the right side with a lag time of 6 months between the last date of prescription drug use and index date

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
<i>Angiotensin II Receptor Antagonist</i>									
Candesartan	0.99	0.86	1.13	0.95	0.83	1.09	0.95	0.83	1.08
Irbesartan	0.90	0.56	1.43	0.83	0.52	1.33	0.84	0.53	1.34
Losartan	0.92	0.67	1.25	0.89	0.65	1.22	0.89	0.65	1.22
Olmesartan	1.04	0.80	1.35	0.99	0.76	1.28	0.99	0.77	1.29
Telmisartan	1.01	0.71	1.43	0.98	0.69	1.40	0.98	0.69	1.39
Valsartan	1.48	0.80	2.74	1.43	0.77	2.66	1.43	0.77	2.66
	0.87	0.71	1.06	0.84	0.68	1.02	0.83	0.68	1.02
<i>ACE Inhibitors</i>									
Benazepril	0.88	0.79	0.99	0.86	0.77	0.97	0.87	0.77	0.97
Captopril	0.91	0.68	1.22	0.88	0.66	1.19	0.89	0.66	1.19
Enalapril	0.91	0.56	1.50	0.89	0.54	1.47	0.89	0.54	1.46
Fosinopril	1.13	0.89	1.43	1.11	0.88	1.42	1.12	0.88	1.42
Quinapril	0.69	0.43	1.11	0.71	0.44	1.14	0.71	0.44	1.15
Ramipril	0.79	0.60	1.03	0.75	0.57	0.99	0.76	0.58	1.00
Trandolapril_Verapamil	0.75	0.60	0.92	0.73	0.59	0.91	0.73	0.59	0.91
	0.99	0.78	1.27	0.98	0.77	1.25	0.98	0.77	1.25

Table 3.7b Continued

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
<i>Beta Blockers</i>	0.93	0.85	1.02	0.91	0.83	0.99	0.91	0.83	1.00
Atenolol	0.79	0.68	0.91	0.77	0.67	0.89	0.77	0.67	0.89
Carvedilol	1.06	0.82	1.38	1.05	0.81	1.36	1.05	0.81	1.37
Labetalol	0.71	0.40	1.27	0.67	0.37	1.20	0.68	0.38	1.22
Metoprolol	0.97	0.86	1.09	0.94	0.84	1.06	0.95	0.84	1.07
Nadolol	0.70	0.40	1.23	0.69	0.39	1.20	0.69	0.39	1.21
Propranolol	0.83	0.60	1.16	0.83	0.59	1.15	0.82	0.59	1.15
Sotalol	1.23	0.73	2.07	1.20	0.71	2.03	1.20	0.71	2.02
<i>Bile Acid Sequestrants</i>	1.48	1.04	2.12	1.35	0.94	1.94	1.35	0.94	1.94
Cholestyramine	2.02	1.21	3.37	1.83	1.09	3.06	1.83	1.09	3.08
Colesevelam	1.12	0.66	1.91	1.06	0.62	1.81	1.05	0.61	1.79
<i>Calcium channel blockers</i>	1.12	1.01	1.24	1.09	0.98	1.21	1.09	0.98	1.21
Amlodipine_Atorvastatin	0.84	0.46	1.52	0.81	0.45	1.48	0.81	0.45	1.48
Amlodipine	1.07	0.93	1.23	1.04	0.90	1.19	1.04	0.90	1.20
Diltiazem	1.26	1.03	1.54	1.24	1.02	1.52	1.24	1.02	1.52
Felodipine	0.72	0.43	1.20	0.69	0.41	1.16	0.70	0.42	1.17
Nifedipine	1.13	0.86	1.49	1.10	0.83	1.46	1.11	0.84	1.47
Nisoldipine	0.55	0.26	1.14	0.55	0.26	1.15	0.55	0.26	1.15
Verapamil	1.10	0.85	1.43	1.05	0.81	1.37	1.06	0.82	1.37
<i>Diuretics</i>	0.99	0.90	1.09	0.96	0.87	1.07	0.97	0.88	1.07
Acetazolamide	0.64	0.35	1.16	0.64	0.35	1.16	0.64	0.35	1.16
Bumetanide	1.56	0.89	2.75	1.53	0.87	2.70	1.54	0.87	2.72
Furosemide	1.12	0.97	1.28	1.09	0.95	1.25	1.09	0.95	1.26
Hydrochlorothiazide	0.94	0.83	1.07	0.92	0.81	1.05	0.92	0.81	1.05
Indapamide	0.73	0.40	1.32	0.72	0.40	1.30	0.72	0.40	1.31
Metolazone	0.92	0.57	1.48	0.90	0.55	1.45	0.89	0.55	1.45
Spirolactone	1.04	0.78	1.38	1.02	0.76	1.36	1.01	0.76	1.35
Torsemide	1.22	0.77	1.93	1.17	0.73	1.86	1.17	0.74	1.87
<i>Fibrates</i>	0.78	0.63	0.95	0.76	0.62	0.93	0.75	0.61	0.93
Fenofibrate	0.85	0.66	1.09	0.81	0.63	1.04	0.81	0.63	1.05
Gemfibrozil	0.59	0.42	0.81	0.59	0.43	0.82	0.59	0.43	0.82
<i>Statins</i>	0.85	0.79	0.93	0.81	0.75	0.88	0.81	0.75	0.88
Atorvastatin	0.77	0.69	0.84	0.73	0.66	0.80	0.73	0.66	0.80
Amlodipine_Atorvastatin	0.84	0.46	1.52	0.81	0.45	1.48	0.81	0.45	1.48
Cerivastatin	0.70	0.35	1.39	0.71	0.36	1.42	0.70	0.35	1.39
Ezetimibe_Simvastatin	1.13	0.87	1.47	1.06	0.81	1.39	1.07	0.82	1.40

Table 3.7b Continued

Drug	Unadjusted Model		Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval	Odds ratio	95% Confidence Interval	Odds ratio	95% Confidence Interval		
Fluvastatin	1.09	0.73 1.63	1.06	0.71 1.59	1.06	0.71 1.59		
Lovastatin	0.95	0.75 1.19	0.92	0.74 1.16	0.93	0.74 1.16		
Niacin_Lovastatin	0.90	0.48 1.71	0.90	0.47 1.71	0.90	0.48 1.72		
Pravastatin	1.02	0.84 1.24	0.97	0.79 1.18	0.97	0.80 1.19		
Rosuvastatin	0.86	0.66 1.10	0.82	0.63 1.05	0.82	0.63 1.06		
Simvastatin	0.89	0.77 1.01	0.85	0.75 0.98	0.85	0.75 0.98		

[†] This model was adjusted using the covariates such as colonoscopy, crohn's disease and ulcerative colitis

[‡] This model was adjusted using covariates such as colonoscopy, crohn's disease and ulcerative colitis; and interactions between colonoscopy and age group, colonoscopy and crohn's disease, colonoscopy and ulcerative colitis

Table 3.7c depicts the conditional logistic regression results testing the association between drug classes, the individual drugs with a minimum use of 12 months (365 days) with colon cancer on the right side. Patients using drugs from the drug class bile acid sequestrants and calcium channel blockers for at least 12 months were associated with colon cancer on the right side. Patients using fibrates and statins for at least 12 months had a protective effect on colon cancer on the right side. Patients using the drugs diltiazem (calcium channel blockers), cholestyramine (bile acid sequestrants) for at least 12 months were associated with colon cancer on the right side. Patients with at least 12 months use of drugs such as atenolol (beta blockers), gemfibrozil (fibrates), atorvastatin (statin) and simvastatin (statin) showed negative association on colon cancer on the right side.

Table 3.7c Conditional Logistic Regression to test the association of the drug classes and individual drugs having a use of at least 12 months (365 days) with colon cancer on the right side

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
<i>Angiotensin II Receptor Antagonist</i>	0.96	0.83	1.10	0.93	0.81	1.08	0.93	0.81	1.08
Candesartan	0.85	0.47	1.51	0.80	0.45	1.43	0.79	0.44	1.42
Irbesartan	0.97	0.69	1.37	0.94	0.67	1.33	0.94	0.67	1.33
Losartan	0.90	0.69	1.19	0.88	0.67	1.16	0.88	0.67	1.16
Olmesartan	1.13	0.74	1.73	1.12	0.73	1.71	1.11	0.72	1.69
Telmisartan	1.00	0.48	2.10	0.97	0.46	2.04	0.97	0.46	2.04
Valsartan	0.93	0.76	1.15	0.91	0.74	1.12	0.92	0.74	1.12
<i>ACE Inhibitors</i>	0.88	0.78	0.99	0.86	0.76	0.98	0.87	0.76	0.98
Benazepril	0.82	0.59	1.13	0.79	0.57	1.10	0.79	0.57	1.10
Captopril	0.93	0.52	1.63	0.91	0.51	1.61	0.90	0.51	1.60
Enalapril	1.22	0.94	1.58	1.20	0.93	1.56	1.21	0.93	1.57
Fosinopril	0.62	0.34	1.12	0.64	0.35	1.15	0.64	0.35	1.15
Quinapril	0.74	0.53	1.01	0.70	0.51	0.97	0.71	0.51	0.97
Ramipril	0.80	0.63	1.02	0.79	0.62	1.00	0.79	0.62	1.01
Trandolapril_Verapamil	0.97	0.75	1.27	0.95	0.73	1.25	0.96	0.73	1.25
<i>Beta Blockers</i>	1.01	0.92	1.11	1.00	0.91	1.10	1.00	0.91	1.10
Atenolol	0.81	0.70	0.95	0.80	0.69	0.94	0.80	0.69	0.94
Carvedilol	1.00	0.79	1.28	1.00	0.78	1.27	1.00	0.79	1.28
Labetalol	0.83	0.45	1.52	0.76	0.41	1.41	0.77	0.42	1.42
Metoprolol	1.13	1.00	1.28	1.11	0.99	1.26	1.11	0.99	1.26
Nadolol	0.69	0.39	1.22	0.68	0.38	1.20	0.68	0.38	1.21
Propranolol	1.02	0.70	1.50	1.03	0.70	1.52	1.03	0.70	1.51
Sotalol	1.35	0.78	2.31	1.31	0.76	2.25	1.31	0.76	2.25
<i>Bile Acid Sequestrants</i>	2.46	1.32	4.59	2.37	1.27	4.45	2.39	1.28	4.48
Cholestyramine	8.57	1.98	37.02	8.25	1.90	35.76	8.64	1.99	37.45
Colesevelam	1.47	0.68	3.17	1.45	0.67	3.14	1.42	0.65	3.08
<i>Calcium channel blockers</i>	1.16	1.04	1.29	1.13	1.01	1.26	1.13	1.01	1.26
Amlodipine_Atorvastatin	0.66	0.36	1.21	0.63	0.34	1.17	0.63	0.34	1.17
Amlodipine	1.09	0.94	1.26	1.07	0.93	1.24	1.08	0.93	1.25
Diltiazem	1.37	1.10	1.69	1.34	1.08	1.67	1.35	1.09	1.67
Felodipine	0.70	0.40	1.23	0.67	0.38	1.17	0.68	0.39	1.19
Nifedipine	1.22	0.91	1.65	1.20	0.88	1.62	1.20	0.88	1.62
Nisoldipine	0.67	0.30	1.48	0.64	0.28	1.42	0.64	0.29	1.43
Verapamil	1.13	0.85	1.51	1.10	0.82	1.47	1.09	0.82	1.46

Table 3.7c Continued

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
<i>Diuretics</i>	0.99	0.89	1.11	0.98	0.88	1.09	0.98	0.88	1.10
Acetazolamide	0.33	0.03	3.22	0.34	0.04	3.32	0.35	0.04	3.35
Bumetanide	1.63	0.81	3.25	1.66	0.83	3.34	1.67	0.83	3.34
Furosemide	1.14	0.97	1.34	1.14	0.97	1.34	1.14	0.97	1.34
Hydrochlorothiazide	0.87	0.74	1.01	0.85	0.73	0.99	0.86	0.73	1.00
Indapamide	0.59	0.30	1.17	0.58	0.29	1.16	0.59	0.30	1.18
Metolazone	1.51	0.83	2.74	1.50	0.82	2.74	1.49	0.82	2.72
Spirolactone	1.14	0.82	1.57	1.12	0.81	1.55	1.11	0.81	1.54
Torseamide	1.13	0.65	1.96	1.13	0.65	1.96	1.13	0.65	1.96
<i>Fibrates</i>	0.78	0.63	0.98	0.75	0.60	0.94	0.75	0.60	0.94
Fenofibrate	0.88	0.67	1.14	0.84	0.64	1.09	0.84	0.64	1.09
Gemfibrozil	0.55	0.37	0.83	0.55	0.36	0.82	0.55	0.36	0.82
<i>Statins</i>	0.82	0.76	0.89	0.78	0.71	0.85	0.78	0.72	0.85
Atorvastatin	0.75	0.68	0.84	0.71	0.64	0.79	0.72	0.64	0.80
Amlodipine_Atorvastatin	0.66	0.36	1.21	0.63	0.34	1.17	0.63	0.34	1.17
Cerivastatin									
Ezetimibe_Simvastatin	0.90	0.68	1.19	0.86	0.65	1.14	0.86	0.65	1.15
Fluvastatin	1.31	0.79	2.19	1.29	0.77	2.17	1.29	0.77	2.16
Lovastatin	0.89	0.70	1.14	0.87	0.68	1.12	0.88	0.69	1.12
Niacin_Lovastatin	1.11	0.47	2.61	1.12	0.47	2.65	1.13	0.48	2.67
Pravastatin	1.09	0.86	1.38	1.04	0.82	1.32	1.05	0.83	1.33
Rosuvastatin	0.79	0.59	1.07	0.75	0.56	1.01	0.75	0.56	1.01
Simvastatin	0.79	0.69	0.91	0.76	0.66	0.88	0.76	0.66	0.87

[†] This model was adjusted using the covariates such as colonoscopy, crohn's disease and ulcerative colitis

[‡] This model was adjusted using covariates such as colonoscopy, crohn's disease and ulcerative colitis; and interactions between colonoscopy and age group, colonoscopy and crohn's disease, colonoscopy and ulcerative colitis

Conditional logistic regression results for patients with colon cancer on the right side with evidence of a diagnosis by an oncologist (alternate definition)

The relationship between patients using drugs from a drug class and using individual drugs was studied among the patients with a diagnosis of colon cancer on the right side with evidence of a diagnosis by an oncologist. The relationship was studied by using the crude model, adjusted model and adjusted model with interactions.

Table 3.8a depicts the conditional logistic regression results between drugs class, individual drugs and colon cancer on the right side with evidence of a diagnosis by an oncologist. Patients using drugs from the class statins showed a negative association. Drugs such as gemfibrozil (fibrates), and atorvastatin (statins) showed a negative association. None of the drug classes or individual drugs showed a positive association with colon cancer on the right side with evidence of a diagnosis by an oncologist.

Table 3.8a Conditional Logistic Regression to test the association of the drug classes and individual drugs with colon cancer on the right side and evidence of a diagnosis by an oncologist (alternate definition)

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
<i>Angiotensin II Receptor Antagonist</i>	1.00	0.79	1.28	1.01	0.80	1.29	1.02	0.80	1.29
Irbesartan	0.89	0.45	1.75	0.90	0.46	1.77	0.90	0.46	1.78
Losartan	1.25	0.90	1.75	1.26	0.90	1.76	1.26	0.91	1.76
Olmesartan	0.68	0.33	1.38	0.69	0.34	1.41	0.69	0.34	1.40
Valsartan	0.72	0.50	1.05	0.72	0.49	1.05	0.72	0.49	1.05
<i>ACE Inhibitors</i>	0.93	0.74	1.17	0.94	0.74	1.18	0.93	0.74	1.17
Benazepril	1.14	0.64	2.00	1.15	0.65	2.03	1.15	0.65	2.03
Enalapril	1.00	0.60	1.66	0.99	0.59	1.64	0.98	0.59	1.63
Quinapril	0.76	0.42	1.37	0.75	0.41	1.35	0.74	0.41	1.34
Ramipril	0.84	0.55	1.29	0.86	0.56	1.32	0.86	0.56	1.33
Trandolapril_Verapamil	1.02	0.62	1.66	1.03	0.63	1.68	1.03	0.63	1.68
<i>Beta Blockers</i>	0.94	0.74	1.19	0.93	0.74	1.18	0.94	0.74	1.19
Atenolol	0.82	0.61	1.10	0.81	0.60	1.09	0.82	0.61	1.10
Carvedilol	0.98	0.60	1.61	0.99	0.61	1.62	1.00	0.61	1.64
Propranolol	1.03	0.54	1.98	1.02	0.53	1.95	1.03	0.54	1.98
<i>Calcium channel blockers</i>	1.15	0.87	1.52	1.16	0.88	1.53	1.16	0.88	1.53
Diltiazem	1.10	0.72	1.70	1.12	0.73	1.72	1.12	0.73	1.72
Nifedipine	1.30	0.72	2.33	1.28	0.71	2.31	1.28	0.71	2.31
Verapamil	1.00	0.59	1.72	1.02	0.59	1.74	1.01	0.59	1.73
<i>Diuretics</i>	1.04	0.86	1.25	1.04	0.86	1.26	1.04	0.86	1.26
Furosemide	1.12	0.83	1.51	1.12	0.83	1.51	1.12	0.83	1.52

Table 3.8a Continued

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
Hydrochlorothiazide	1.02	0.79	1.32	1.02	0.79	1.32	1.02	0.79	1.32
Spirolactone	0.93	0.67	1.30	0.94	0.67	1.30	0.94	0.68	1.31
<i>Fibrates</i>	0.78	0.52	1.17	0.78	0.52	1.17	0.78	0.52	1.17
Fenofibrate	0.93	0.59	1.46	0.92	0.58	1.46	0.93	0.59	1.47
Gemfibrozil	0.31	0.13	0.73	0.31	0.13	0.74	0.31	0.13	0.73
<i>Statins</i>	0.79	0.68	0.93	0.79	0.68	0.93	0.79	0.67	0.93
Atorvastatin	0.65	0.53	0.78	0.65	0.53	0.79	0.65	0.53	0.79
Ezetimibe_Simvastatin	0.90	0.54	1.51	0.92	0.55	1.54	0.92	0.55	1.55
Fluvastatin	1.18	0.56	2.48	1.14	0.54	2.41	1.12	0.53	2.38
Lovastatin	1.12	0.72	1.76	1.12	0.72	1.76	1.13	0.72	1.77
Pravastatin	1.21	0.83	1.78	1.23	0.84	1.80	1.23	0.84	1.80
Rosuvastatin	0.98	0.61	1.58	0.95	0.59	1.54	0.95	0.59	1.54
Simvastatin	0.98	0.75	1.27	0.98	0.75	1.27	0.97	0.75	1.26

[†] This model was adjusted using the covariates such as colonoscopy, crohn's disease and ulcerative colitis

[‡] This model was adjusted using covariates such as colonoscopy, crohn's disease and ulcerative colitis; and interactions between colonoscopy and age group, colonoscopy and crohn's disease, colonoscopy and ulcerative colitis

Table 3.8b shows the conditional logistic regression results between the drug class, individual drug with a lag time of at least 6 months with colon cancer on the right side and colon cancer on the right side with evidence of a diagnosis by an oncologist. None of the drug classes or drugs showed a positive association with colon cancer on the right side with evidence of a diagnosis by an oncologist. Drug classes such as statins were negatively associated with colon cancer on the right side with evidence of a diagnosis by an oncologist. Use of drugs such as gemfibrozil (fibrates), and atorvastatin (statins) showed a negative association.

Table 3.8b Conditional Logistic Regression to test the association of the drug classes, individual drugs having a lag time of 6 months and colon cancer on the right side with evidence of a diagnosis by an oncologist

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
<i>Angiotensin II Receptor Antagonist</i>	0.77	0.58	1.03	0.77	0.58	1.03	0.77	0.58	1.03
Irbesartan	0.55	0.26	1.15	0.55	0.26	1.16	0.55	0.26	1.16
Losartan	0.95	0.50	1.79	0.93	0.49	1.76	0.93	0.49	1.76
Olmesartan	0.72	0.35	1.46	0.73	0.36	1.49	0.73	0.35	1.49
Valsartan	0.67	0.45	1.00	0.67	0.45	1.00	0.67	0.45	1.00
<i>ACE Inhibitors</i>	0.84	0.67	1.06	0.84	0.67	1.06	0.84	0.67	1.06
Benazepril	0.96	0.55	1.68	0.98	0.56	1.71	0.98	0.56	1.70
Enalapril	1.04	0.62	1.74	1.02	0.61	1.72	1.01	0.60	1.71
Quinapril	0.63	0.35	1.12	0.62	0.34	1.11	0.61	0.34	1.10
Ramipril	0.70	0.45	1.09	0.71	0.46	1.11	0.72	0.46	1.12
Trandolapril_Verapamil	0.88	0.54	1.42	0.89	0.55	1.44	0.89	0.55	1.44
<i>Beta Blockers</i>	0.85	0.70	1.03	0.85	0.70	1.03	0.85	0.70	1.03
Atenolol	0.74	0.55	1.00	0.74	0.55	1.00	0.74	0.55	1.00
Carvedilol	1.10	0.63	1.93	1.11	0.64	1.95	1.13	0.64	1.98
Propranolol	0.83	0.42	1.66	0.81	0.41	1.63	0.82	0.41	1.63
<i>Calcium channel blockers</i>	0.98	0.78	1.23	0.99	0.79	1.24	0.99	0.79	1.24
Diltiazem	0.95	0.61	1.48	0.97	0.62	1.50	0.97	0.62	1.51
Nifedipine	1.15	0.63	2.10	1.16	0.64	2.13	1.17	0.64	2.14
Verapamil	0.89	0.52	1.54	0.90	0.52	1.56	0.90	0.52	1.55
<i>Diuretics</i>	0.90	0.73	1.11	0.89	0.72	1.10	0.89	0.72	1.10
Furosemide	0.95	0.69	1.30	0.95	0.69	1.30	0.95	0.69	1.30
Hydrochlorothiazide	0.90	0.69	1.18	0.91	0.69	1.19	0.90	0.69	1.18
Spirolactone	0.85	0.45	1.61	0.86	0.45	1.63	0.86	0.45	1.62
<i>Fibrates</i>	0.69	0.45	1.06	0.69	0.45	1.06	0.69	0.45	1.06
Fenofibrate	0.89	0.54	1.45	0.88	0.54	1.44	0.89	0.54	1.45
Gemfibrozil	0.29	0.12	0.74	0.30	0.12	0.74	0.29	0.12	0.74
<i>Statins</i>	0.72	0.61	0.85	0.72	0.61	0.85	0.72	0.61	0.85
Atorvastatin	0.54	0.44	0.66	0.54	0.44	0.66	0.54	0.44	0.66
Ezetimibe_Simvastatin	0.86	0.51	1.47	0.88	0.51	1.49	0.88	0.52	1.50
Fluvastatin	1.10	0.51	2.34	1.06	0.49	2.27	1.04	0.48	2.23
Lovastatin	1.19	0.74	1.91	1.19	0.74	1.91	1.20	0.74	1.93
Pravastatin	1.03	0.70	1.50	1.04	0.71	1.52	1.03	0.71	1.52
Rosuvastatin	0.94	0.57	1.56	0.91	0.55	1.52	0.91	0.55	1.51
Simvastatin	0.83	0.63	1.10	0.83	0.63	1.10	0.83	0.63	1.09

Table 3.8b Continued

Drug	Unadjusted Model		Adjusted Model [†]		Fully-adjusted Model with Interactions [‡]	
	Odds ratio	95% Confidence Interval	Odds ratio	95% Confidence Interval	Odds ratio	95% Confidence Interval

[†] This model was adjusted using the covariates such as colonoscopy, crohn's disease and ulcerative colitis

[‡] This model was adjusted using covariates such as colonoscopy, crohn's disease and ulcerative colitis; and interactions between colonoscopy and age group, colonoscopy and crohn's disease, colonoscopy and ulcerative colitis

Conditional logistic regression results between drug class; and individual drugs having at least 12 months of use colon cancer on the right side (with evidence of a diagnosis by an oncologist) are presented in Table 3.8c. Patients using drugs from the drug class statins were negatively associated with colon cancer on the right side (with evidence of a diagnosis by an oncologist). Use of drugs such as gemfibrozil (fibrates) and simvastatin (statins) for at least 12 months with a lag time showed a negative association with colon cancer on the right side (with evidence of a diagnosis by an oncologist).

Table 3.8c Conditional Logistic Regression to test the association of the drug classes, individual drugs having drug use for at least 12 months and colon cancer on the right side with evidence of a diagnosis by an oncologist

Drug	Unadjusted Model			Adjusted Model [†]			Fully-adjusted Model with Interactions [‡]		
	Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval		Odds ratio	95% Confidence Interval	
<i>Angiotensin II Receptor Antagonist</i>	0.73	0.54	0.99	0.73	0.54	0.99	0.73	0.54	0.99
Irbesartan	0.57	0.24	1.37	0.58	0.24	1.39	0.58	0.24	1.39
Losartan	0.74	0.39	1.39	0.72	0.38	1.36	0.72	0.38	1.35
Olmesartan	0.90	0.38	2.13	0.92	0.39	2.17	0.90	0.38	2.13
Valsartan	0.78	0.52	1.19	0.79	0.52	1.20	0.79	0.52	1.20
<i>ACE Inhibitors</i>	0.96	0.75	1.24	0.97	0.76	1.25	0.97	0.75	1.25
Benazepril	1.37	0.73	2.58	1.39	0.74	2.61	1.38	0.73	2.59
Enalapril	1.37	0.78	2.39	1.35	0.77	2.37	1.35	0.77	2.36
Quinapril	0.77	0.38	1.56	0.78	0.39	1.58	0.78	0.38	1.57
Ramipril	0.82	0.52	1.30	0.83	0.52	1.33	0.84	0.53	1.34
Trandolapril_Verapamil	0.98	0.57	1.69	1.00	0.58	1.71	1.00	0.58	1.72
<i>Beta Blockers</i>	1.08	0.89	1.32	1.09	0.89	1.32	1.09	0.89	1.32
Atenolol	0.93	0.67	1.30	0.92	0.66	1.29	0.92	0.66	1.29
Carvedilol	0.90	0.53	1.53	0.91	0.54	1.54	0.91	0.54	1.55
Propranolol	1.01	0.44	2.34	1.02	0.44	2.37	1.01	0.44	2.34
<i>Calcium channel blockers</i>	1.20	0.95	1.51	1.21	0.96	1.52	1.21	0.96	1.52
Diltiazem	1.60	0.99	2.60	1.63	1.00	2.64	1.63	1.01	2.64
Nifedipine	1.56	0.83	2.93	1.53	0.81	2.89	1.52	0.80	2.86
Verapamil	0.71	0.38	1.32	0.71	0.38	1.33	0.71	0.38	1.33
<i>Diuretics</i>	0.97	0.77	1.23	0.98	0.78	1.24	0.98	0.78	1.24
Furosemide	1.21	0.85	1.72	1.22	0.85	1.73	1.22	0.86	1.73
Hydrochlorothiazide	0.72	0.53	1.00	0.74	0.53	1.01	0.74	0.54	1.01
Spirolactone	2.13	0.96	4.72	2.14	0.97	4.76	2.13	0.96	4.74
<i>Fibrates</i>	0.66	0.41	1.05	0.65	0.41	1.04	0.65	0.41	1.04
Fenofibrate	0.79	0.47	1.32	0.78	0.47	1.31	0.78	0.47	1.31
Gemfibrozil	0.18	0.04	0.80	0.18	0.04	0.81	0.18	0.04	0.81
<i>Statins</i>	0.76	0.64	0.90	0.76	0.64	0.90	0.76	0.64	0.90
Atorvastatin	0.66	0.53	0.81	0.66	0.54	0.82	0.66	0.54	0.82
Ezetimibe_Simvastatin	0.65	0.35	1.20	0.66	0.36	1.22	0.66	0.36	1.22
Fluvastatin	1.54	0.63	3.79	1.47	0.60	3.64	1.46	0.59	3.60
Lovastatin	0.97	0.58	1.60	0.96	0.58	1.59	0.98	0.59	1.62
Pravastatin	1.40	0.82	2.38	1.41	0.83	2.40	1.40	0.82	2.39
Rosuvastatin	1.00	0.56	1.79	0.96	0.53	1.72	0.95	0.53	1.71
Simvastatin	0.71	0.53	0.94	0.72	0.54	0.95	0.71	0.53	0.95

Table 3.8c Continued

Drug	Unadjusted Model		Adjusted Model [†]		Fully-adjusted Model with Interactions [‡]	
	Odds ratio	95% Confidence Interval	Odds ratio	95% Confidence Interval	Odds ratio	95% Confidence Interval

[†] This model was adjusted using the covariates such as colonoscopy, crohn's disease and ulcerative colitis

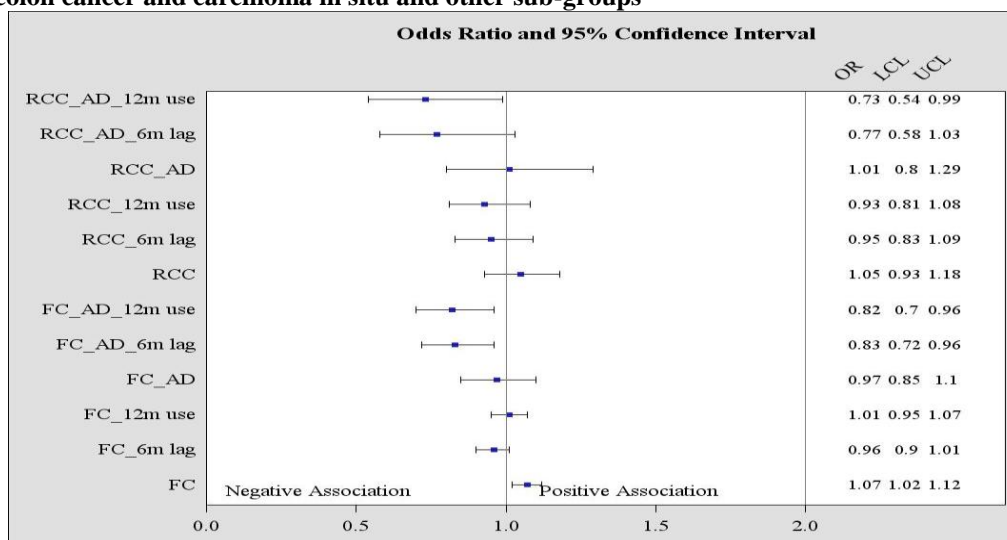
[‡] This model was adjusted using covariates such as colonoscopy, crohn's disease and ulcerative colitis; and interactions between colonoscopy and age group, colonoscopy and crohn's disease, colonoscopy and ulcerative colitis

Association between use of cardiovascular drugs and colon cancer

Conditional logistic regression was used to investigate the relationship between the drug class (and the respective drug included in the drug class) with the outcome. After studying the relationship in the full cohort (patients with colon cancer and carcinoma in situ), it was observed the use of drugs from the following drug classes was associated with colon cancer or carcinoma in situ: angiotensin II receptor antagonist, ACE inhibitors, bile acid sequestrants, calcium channel blockers and diuretics.

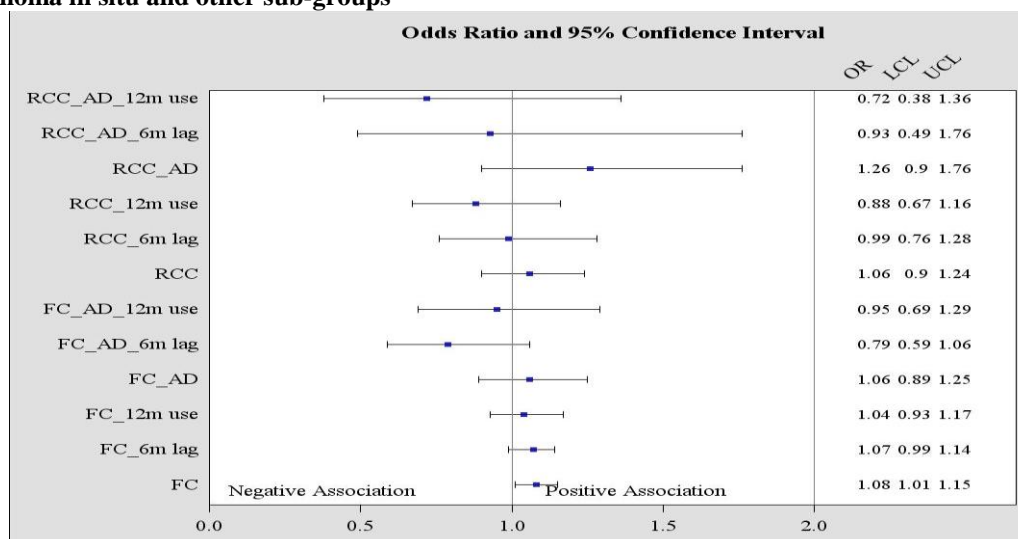
Angiotensin II receptor antagonists were associated with colon cancer and carcinoma in situ but the association was not significant when compared across different subgroups (See Figure 3.2). Among the drugs classified as angiotensin II receptor antagonists, none of the drugs except losartan was positively associated with colon cancer and carcinoma in situ (primary definition) (See Figure 3.3). Use of angiotensin II receptor antagonists and losartan showed a significant association only among the full cohort of cases with colon cancer and carcinoma in situ (primary definition). A significant positive association was not observed among the different subgroups.

Figure 3.2 Conditional logistic regression results for angiotensin II receptor antagonists among cases with colon cancer and carcinoma in situ and other sub-groups



FC: Full cohort (cases with colon cancer and carcinoma in situ); **AD:** Alternate definition;
6mlag: Lag time of 6 months between the last date of prescription drug use and index date;
12m use: Minimum duration of use for 12 months; **RCC:** Cases with colon cancer on the right side;
OR: Adjusted odds ratio; **LCL:** 95% confidence interval, lower limit; **UCL:** 95% confidence interval, upper limit

Figure 3.3 Conditional logistic regression results for losartan among cases with colon cancer and carcinoma in situ and other sub-groups

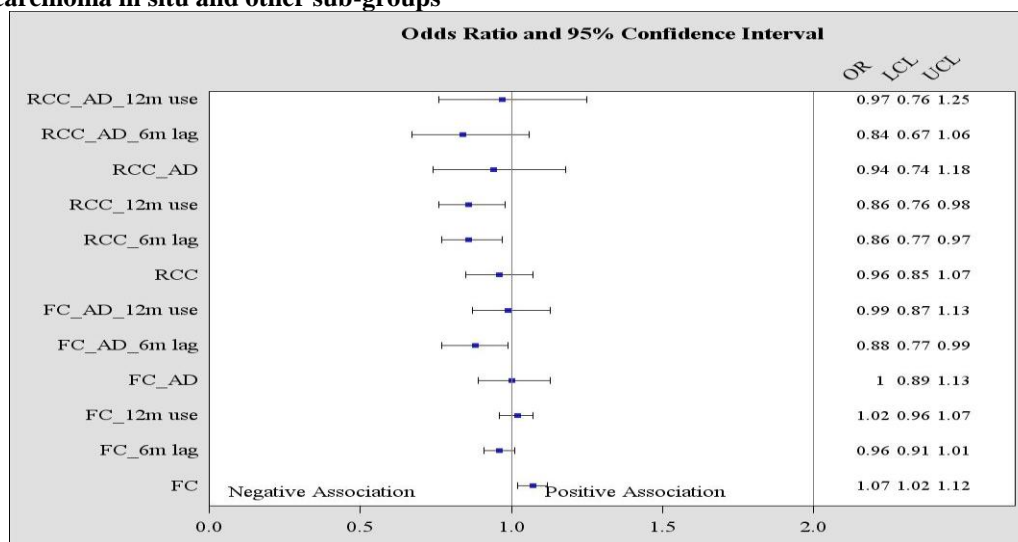


FC: Full cohort (cases with colon cancer and carcinoma in situ); **AD:** Alternate definition;
6mlag: Lag time of 6 months between the last date of prescription drug use and index date;
12m use: Minimum duration of use for 12 months; **RCC:** Cases with colon cancer on the right side;
OR: Adjusted odds ratio; **LCL:** 95% confidence interval, lower limit; **UCL:** 95% confidence interval, upper limit

Use of drugs from the drug class ACE inhibitors was associated with colon cancer and carcinoma in situ (primary definition) but the association was not significant when

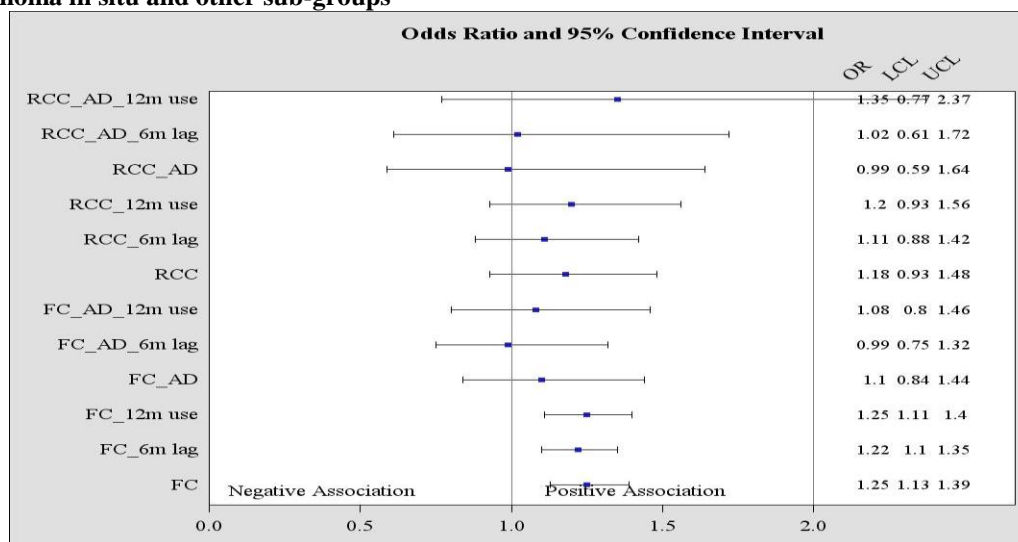
compared across different subgroups (See Figure 3.4). Among the drugs classified as ACE inhibitors, none of the drugs except enalapril was positively associated with colon cancer and carcinoma in situ. Use of enalapril showed a significant positive association among the primary definition for cases with colon cancer and carcinoma in situ, and among the sub-groups with cases having a lag time of 6 months between the last date of prescription drug use and index date; and among cases having a minimum duration of use of 12 months for enalapril (See Figure 3.5).

Figure 3.4 Conditional logistic regression results for ACE inhibitors among cases with colon cancer and carcinoma in situ and other sub-groups



FC: Full cohort (cases with colon cancer and carcinoma in situ); **AD:** Alternate definition;
6mlag: Lag time of 6 months between the last date of prescription drug use and index date;
12m use: Minimum duration of use for 12 months; **RCC:** Cases with colon cancer on the right side;
OR: Adjusted odds ratio; **LCL:** 95% confidence interval, lower limit; **UCL:** 95% confidence interval, upper limit

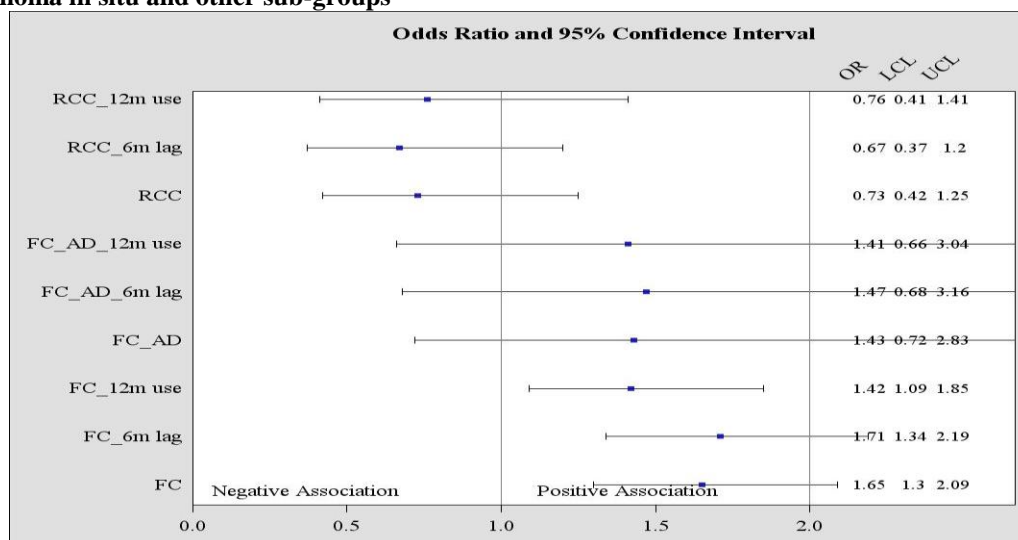
Figure 3.5 Conditional logistic regression results for enalapril among cases with colon cancer and carcinoma in situ and other sub-groups



FC: Full cohort (cases with colon cancer and carcinoma in situ); **AD:** Alternate definition;
6mlag: Lag time of 6 months between the last date of prescription drug use and index date;
12m use: Minimum duration of use for 12 months; **RCC:** Cases with colon cancer on the right side;
OR: Adjusted odds ratio; **LCL:** 95% confidence interval, lower limit; **UCL:** 95% confidence interval, upper limit

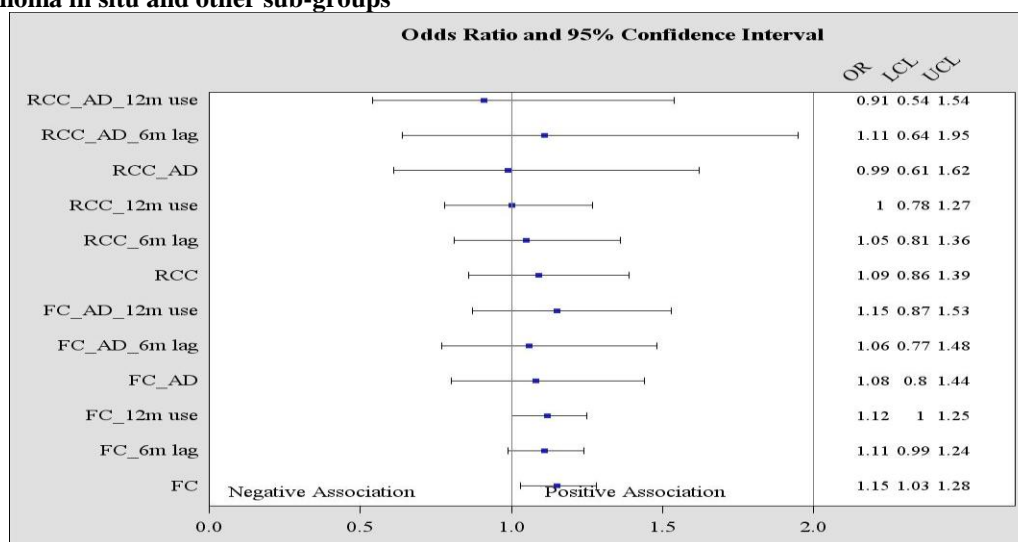
Use of drugs from the drug class beta blockers did not show a positive association with colon cancer and carcinoma in situ. Drugs such as labetalol and carvedilol from the same drug class were associated with colon cancer and carcinoma in situ. Figure 3.6 and 3.7 depicts the conditional logistic regression results for the full cohort and different sub-groups. Use of labetalol and carvedilol showed a significant positive association among the primary definition for cases with colon cancer and carcinoma in situ. Labetalol also showed a positive association for the sub-groups with cases having a lag time of 6 months between the last date of prescription drug use and index date; and among cases having a minimum duration of use of 12 months.

Figure 3.6 Conditional logistic regression results for labeltolol among cases with colon cancer and carcinoma in situ and other sub-groups



FC: Full cohort (cases with colon cancer and carcinoma in situ); **AD:** Alternate definition;
6mlag: Lag time of 6 months between the last date of prescription drug use and index date;
12m use: Minimum duration of use for 12 months; **RCC:** Cases with colon cancer on the right side;
OR: Adjusted odds ratio; **LCL:** 95% confidence interval, lower limit; **UCL:** 95% confidence interval, upper limit

Figure 3.7 Conditional logistic regression results for carvedilol among cases with colon cancer and carcinoma in situ and other sub-groups

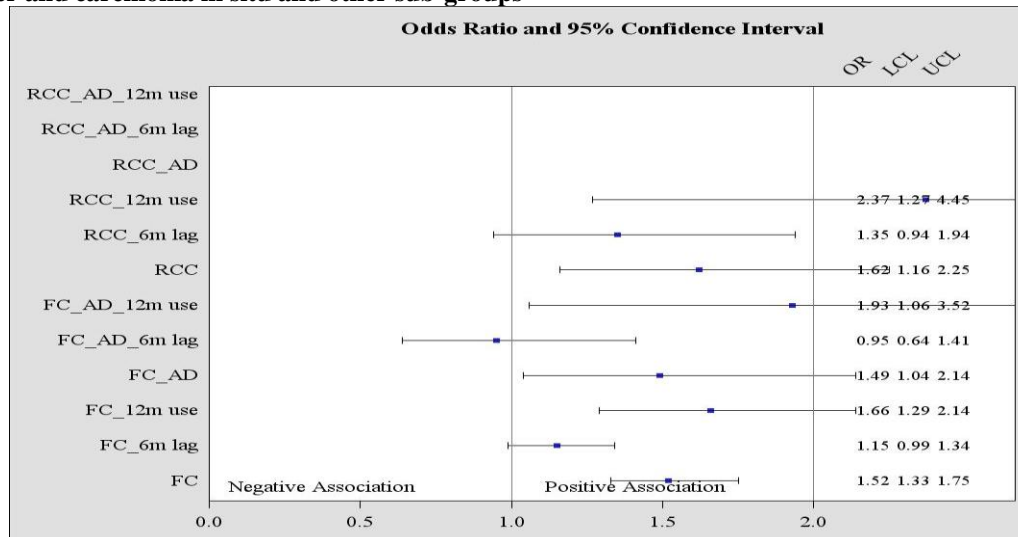


FC: Full cohort (cases with colon cancer and carcinoma in situ); **AD:** Alternate definition;
6mlag: Lag time of 6 months between the last date of prescription drug use and index date;
12m use: Minimum duration of use for 12 months; **RCC:** Cases with colon cancer on the right side;
OR: Adjusted odds ratio; **LCL:** 95% confidence interval, lower limit; **UCL:** 95% confidence interval, upper limit

Use of bile acid sequestrants showed a significant association among the cases with colon cancer and carcinoma in situ (both primary and alternate definition), cases with colon cancer and carcinoma in situ having a minimum duration of use for 12 months (both

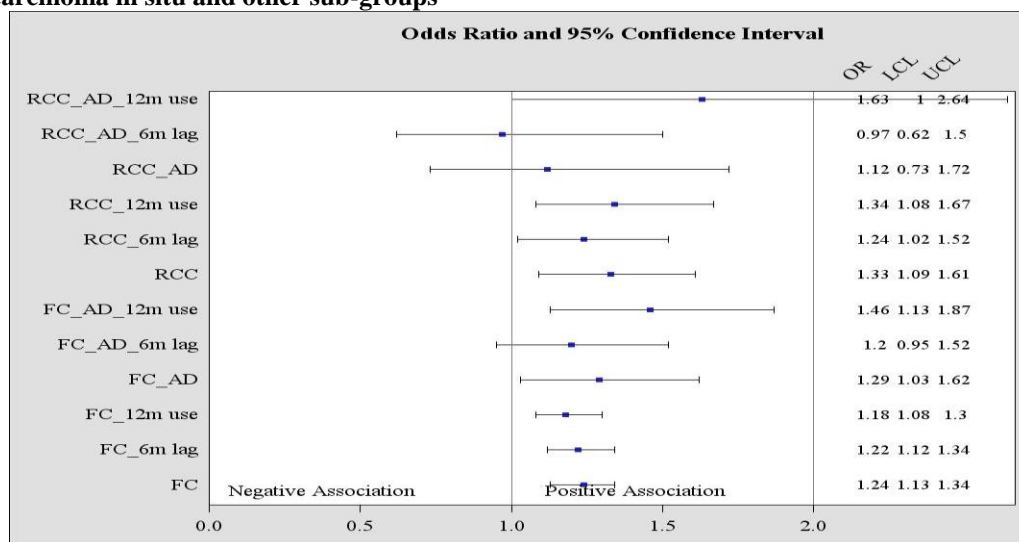
primary and alternate definition), cases with colon cancer on the right side, and cases with colon cancer on the right side with a minimum duration of use for 12 months (See Figure 3.8). The alternate definition for colon cancer on the right did not have a sufficient sample size. Among the drugs classified as bile acid sequestrants, cholestyramine was positively associated with colon cancer and carcinoma in situ (both primary and alternate definition), and all the sub-groups except alternate definition of cases with colon cancer and carcinoma in situ having a lag time of 6 months between the last date of prescription drug use and index date; and the alternate definition for colon cancer cases on the right side (See Figure 3.9). The association between bile acid sequestrants and cholestyramine was confirmed among both primary and alternate definitions of cases with colon cancer and carcinoma in situ.

Figure 3.8 Conditional logistic regression results for bile acid sequestrants among cases with colon cancer and carcinoma in situ and other sub-groups



FC: Full cohort (cases with colon cancer and carcinoma in situ); **AD:** Alternate definition;
6mlag: Lag time of 6 months between the last date of prescription drug use and index date;
12m use: Minimum duration of use for 12 months; **RCC:** Cases with colon cancer on the right side;
OR: Adjusted odds ratio; **LCL:** 95% confidence interval, lower limit; **UCL:** 95% confidence interval, upper limit

Figure 3.9 Conditional logistic regression results for cholestyramine among cases with colon cancer and carcinoma in situ and other sub-groups

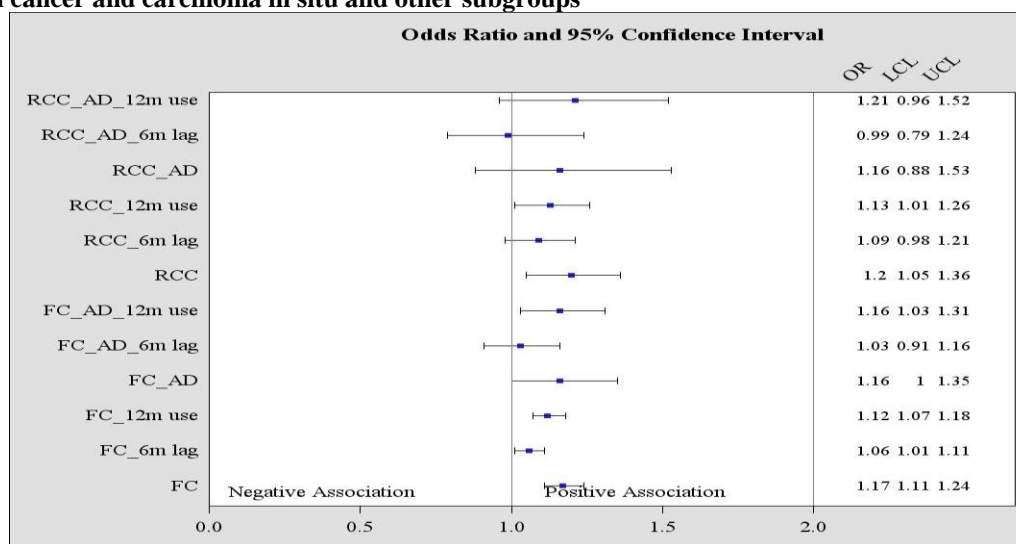


FC: Full cohort (cases with colon cancer and carcinoma in situ); **AD:** Alternate definition;
6mlag: Lag time of 6 months between the last date of prescription drug use and index date;
12m use: Minimum duration of use for 12 months; **RCC:** Cases with colon cancer on the right side;
OR: Adjusted odds ratio; **LCL:** 95% confidence interval, lower limit; **UCL:** 95% confidence interval, upper limit

Use of calcium channel blockers showed a positive association with cases with colon cancer and carcinoma in situ (primary definition); and the sub-groups for colon cancer and carcinoma in situ having a lag time of 6 months between the last date of prescription drug use and index date; and having minimum duration of use for 12 months (See Figure 3.10). Use of calcium channel blockers also showed a positive association with cases of colon cancer on the right side (primary definition); and the sub-group with a minimum duration of use for 12 months. Among the drugs classified as calcium channel blockers, diltiazem, nifedipine and verapamil showed positive associations with colon cancer and carcinoma in situ. Users of the drug diltiazem showed positive associations in all the sub-groups except the alternate definition for cases with colon cancer and carcinoma in situ, cases with colon cancer on the right side both having a lag time of 6 months between the last date of prescription drug use and index date; and the alternate definition for cases with colon cancer on the right side (See Figure 3.11). The association was confirmed

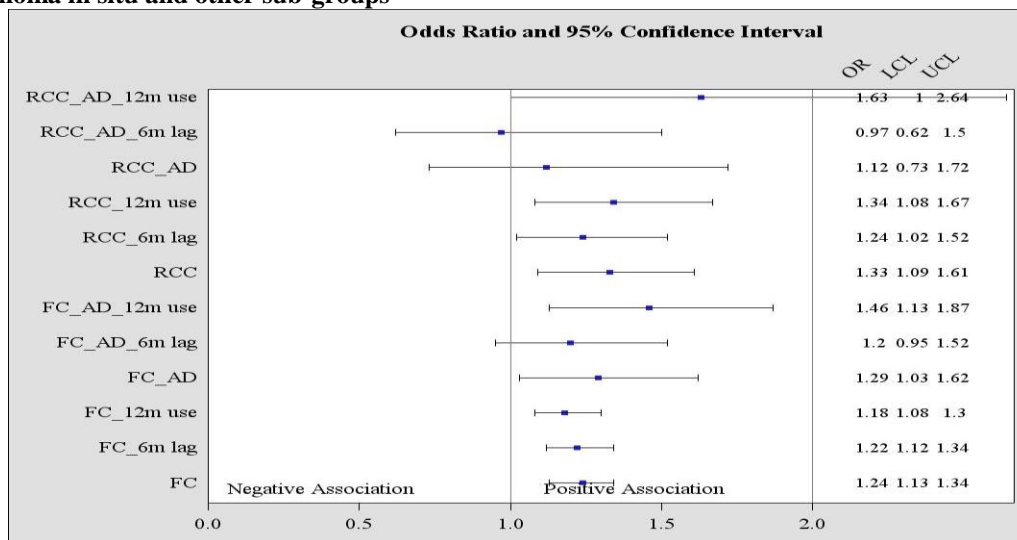
among both the primary and alternate definition of cases with colon cancer and carcinoma in situ; whereas the association was confirmed only for the primary definition of colon cancer on the right side. Patients using nifedipine showed a positive association with the primary definition of cases with colon cancer and carcinoma in situ; and the sub-groups having a lag time of 6 months between the last date of prescription drug use and index date; and minimum duration of use for 12 months (See Figure 3.12). Patients using verapamil showed significant associations only among the primary definition of cases with colon cancer and carcinoma in situ; and the sub-group having a lag time of 6 months between the last date of prescription drug use and index date (See Figure 3.13).

Figure 3.10 Conditional logistic regression results for calcium channel blockers among the cases with colon cancer and carcinoma in situ and other subgroups



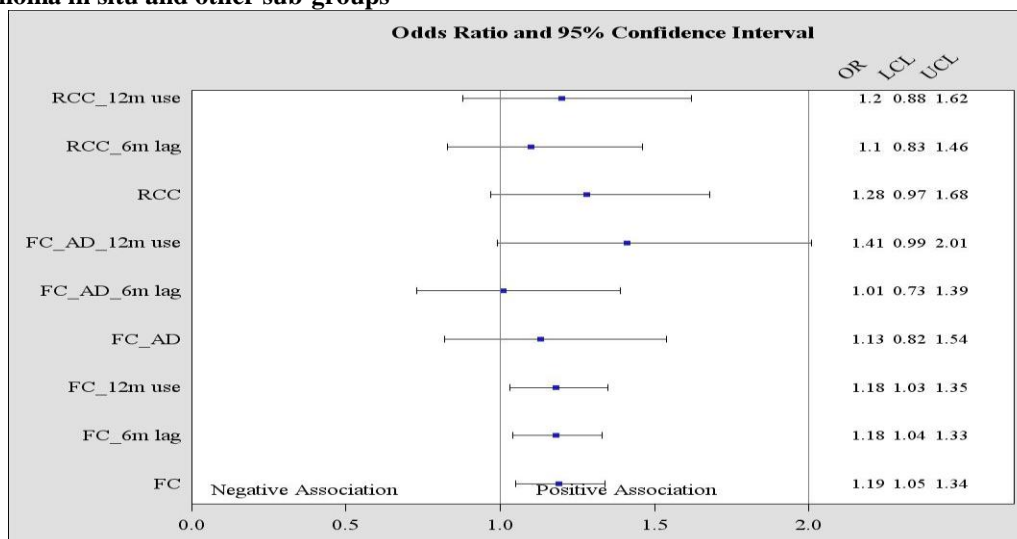
FC: Full cohort (cases with colon cancer and carcinoma in situ); **AD:** Alternate definition;
6mlag: Lag time of 6 months between the last date of prescription drug use and index date;
12m use: Minimum duration of use for 12 months; **RCC:** Cases with colon cancer on the right side;
OR: Adjusted odds ratio; **LCL:** 95% confidence interval, lower limit; **UCL:** 95% confidence interval, upper limit

Figure 3.11 Conditional logistic regression results for diltiazem among cases with colon cancer and carcinoma in situ and other sub-groups



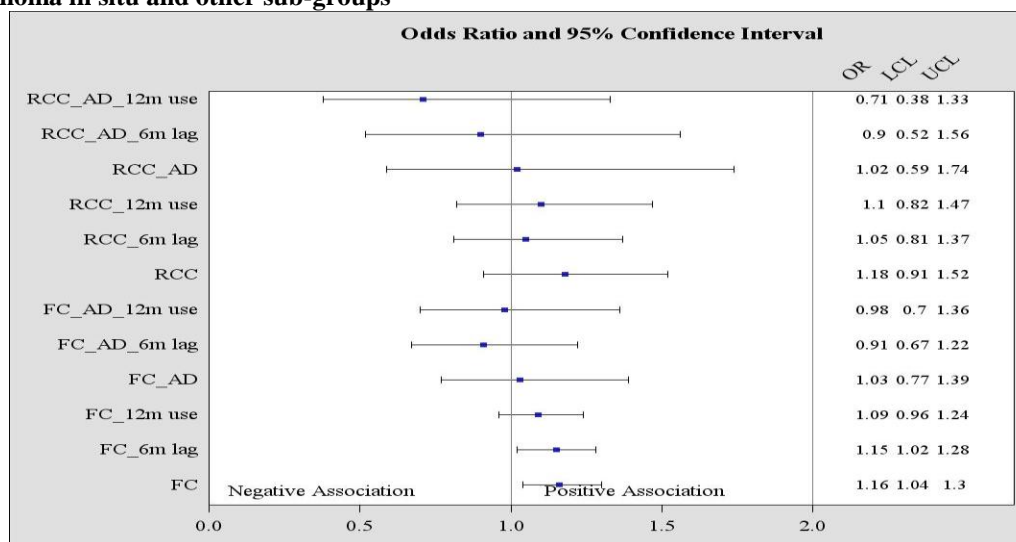
FC: Full cohort (cases with colon cancer and carcinoma in situ); **AD:** Alternate definition;
6mlag: Lag time of 6 months between the last date of prescription drug use and index date;
12m use: Minimum duration of use for 12 months; **RCC:** Cases with colon cancer on the right side;
OR: Adjusted odds ratio; **LCL:** 95% confidence interval, lower limit; **UCL:** 95% confidence interval, upper limit

Figure 3.12 Conditional logistic regression results for nifedipine among cases with colon cancer and carcinoma in situ and other sub-groups



FC: Full cohort (cases with colon cancer and carcinoma in situ); **AD:** Alternate definition;
6mlag: Lag time of 6 months between the last date of prescription drug use and index date;
12m use: Minimum duration of use for 12 months; **RCC:** Cases with colon cancer on the right side;
OR: Adjusted odds ratio; **LCL:** 95% confidence interval, lower limit; **UCL:** 95% confidence interval, upper limit

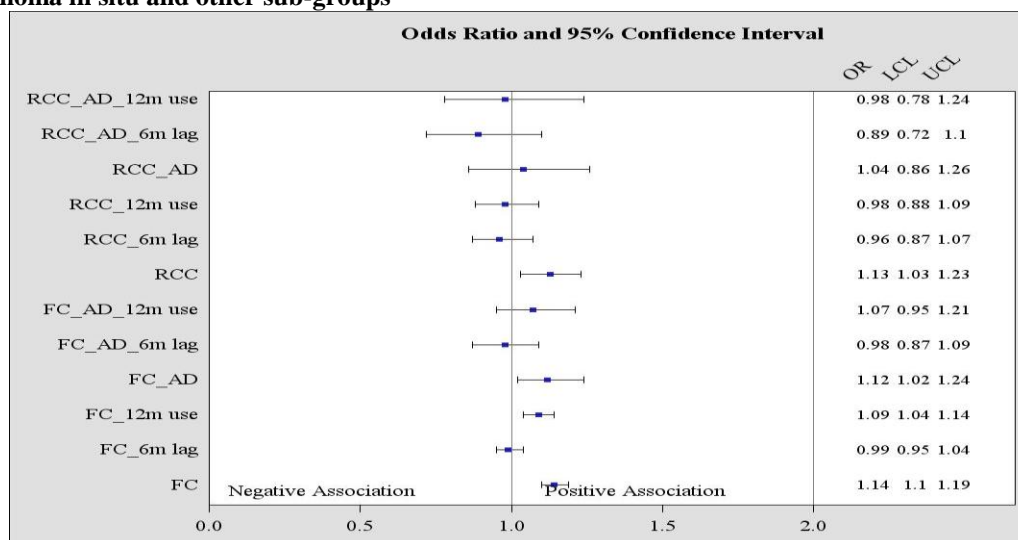
Figure 3.13 Conditional logistic regression results for verapamil among cases with colon cancer and carcinoma in situ and other sub-groups



FC: Full cohort (cases with colon cancer and carcinoma in situ); **AD:** Alternate definition;
6mlag: Lag time of 6 months between the last date of prescription drug use and index date;
12m use: Minimum duration of use for 12 months; **RCC:** Cases with colon cancer on the right side;
OR: Adjusted odds ratio; **LCL:** 95% confidence interval, lower limit; **UCL:** 95% confidence interval, upper limit

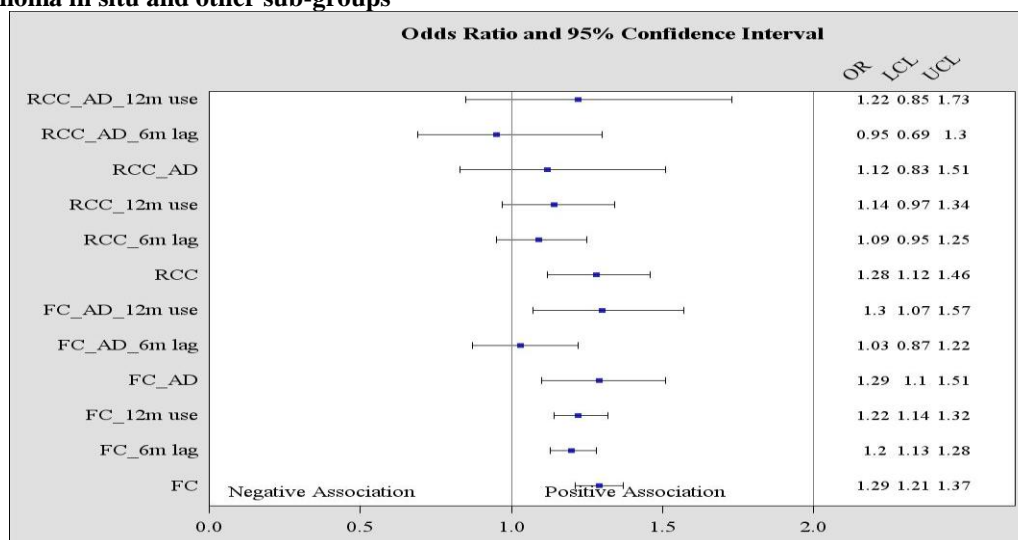
Use of diuretics was associated with colon cancer and carcinoma in situ (primary definition); and the sub-group with a minimum duration of use for 12 months; the alternate definition for cases with colon cancer and carcinoma in situ; and the cases with colon cancer on the right side (primary definition) (See Figure 3.14). The positive association was confirmed among the primary and alternate definition of colon cancer and carcinoma in situ. Among the drugs classified as diuretics, furosemide and hydrochlorothiazide were associated with colon cancer (See Figure 3.15 and 3.16). The positive association between use of furosemide was confirmed among the primary and alternate definition for colon cancer and carcinoma in situ. Use of hydrochlorothiazide showed an association with cases with colon cancer and carcinoma in situ (primary definition).

Figure 3.14 Conditional logistic regression results for diuretics among cases with colon cancer and carcinoma in situ and other sub-groups



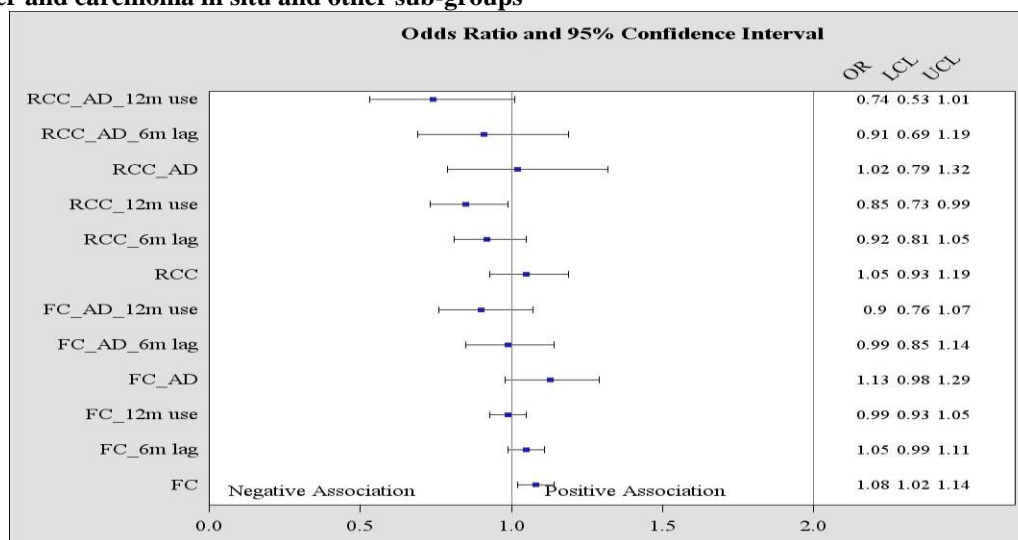
FC: Full cohort (cases with colon cancer and carcinoma in situ); **AD:** Alternate definition;
6mlag: Lag time of 6 months between the last date of prescription drug use and index date;
12m use: Minimum duration of use for 12 months; **RCC:** Cases with colon cancer on the right side;
OR: Adjusted odds ratio; **LCL:** 95% confidence interval, lower limit; **UCL:** 95% confidence interval, upper limit

Figure 3.15 Conditional logistic regression results for furosemide among cases with colon cancer and carcinoma in situ and other sub-groups



FC: Full cohort (cases with colon cancer and carcinoma in situ); **AD:** Alternate definition;
6mlag: Lag time of 6 months between the last date of prescription drug use and index date;
12m use: Minimum duration of use for 12 months; **RCC:** Cases with colon cancer on the right side;
OR: Adjusted odds ratio; **LCL:** 95% confidence interval, lower limit; **UCL:** 95% confidence interval, upper limit

Figure 3.16 Conditional logistic regression results for hydrochlorothiazide among cases with colon cancer and carcinoma in situ and other sub-groups

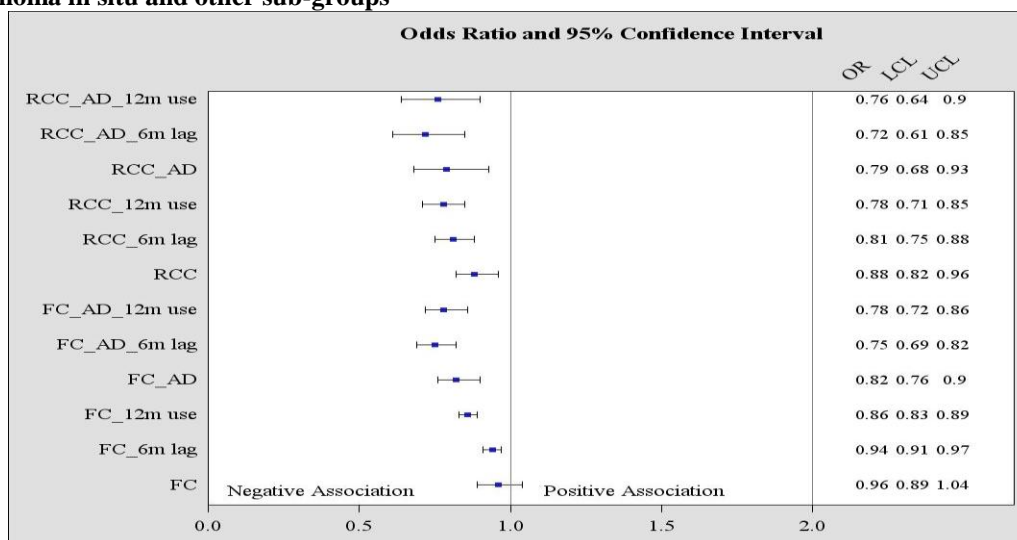


FC: Full cohort (cases with colon cancer and carcinoma in situ); **AD:** Alternate definition;
6mlag: Lag time of 6 months between the last date of prescription drug use and index date;
12m use: Minimum duration of use for 12 months; **RCC:** Cases with colon cancer on the right side;
OR: Adjusted odds ratio; **LCL:** 95% confidence interval, lower limit; **UCL:** 95% confidence interval, upper limit

The drug class statins showed a negative association with all the sub-groups except the primary definition for cases with colon cancer and carcinoma in situ (See Figure 3.17).

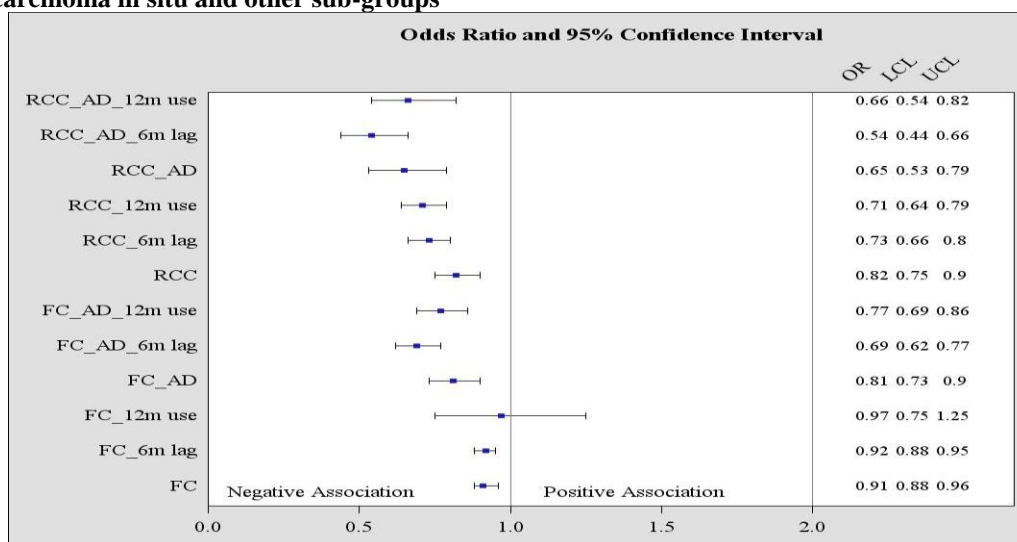
Among the drugs classified as statins, atorvastatin (See Figure 3.18), pravastatin (See Figure 3.19) and simvastatin (See Figure 3.20) showed a negative association with colon cancer and carcinoma in situ. The negative association between use of statins and colon cancer was confirmed among both the primary and alternate definition of cases with colon cancer on the right side. The negative association between use of atorvastatin and colon cancer was confirmed among the primary and alternate definition for both: cases with colon cancer and carcinoma in situ; and cases with colon cancer on the right side.

Figure 3.17 Conditional logistic regression results for statins among cases with colon cancer and carcinoma in situ and other sub-groups



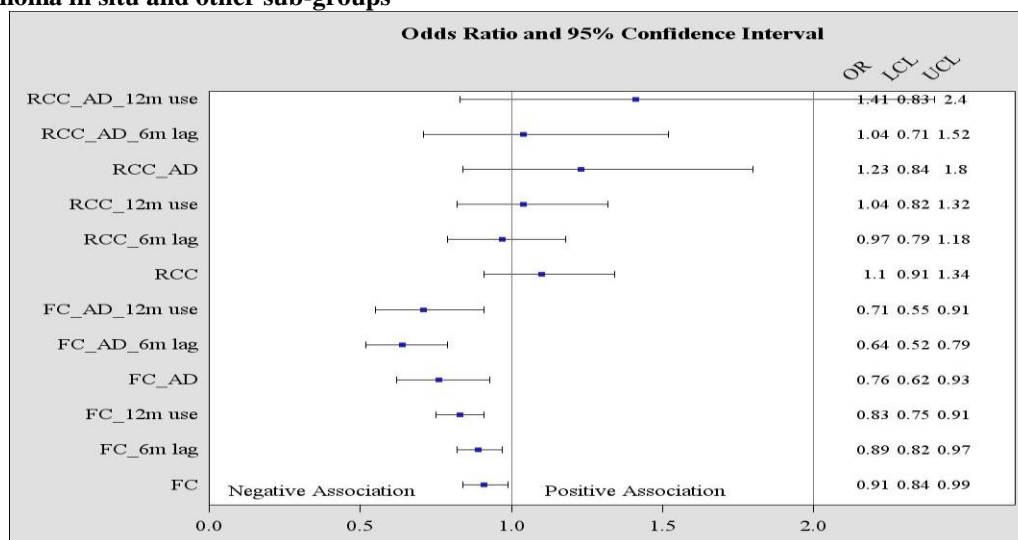
FC: Full cohort (cases with colon cancer and carcinoma in situ); **AD:** Alternate definition;
6mlag: Lag time of 6 months between the last date of prescription drug use and index date;
12m use: Minimum duration of use for 12 months; **RCC:** Cases with colon cancer on the right side;
OR: Odds ratio; **LCL:** 95% confidence interval, lower limit; **UCL:** 95% confidence interval, upper limit

Figure 3.18 Conditional logistic regression results for atorvastatin among cases with colon cancer and carcinoma in situ and other sub-groups



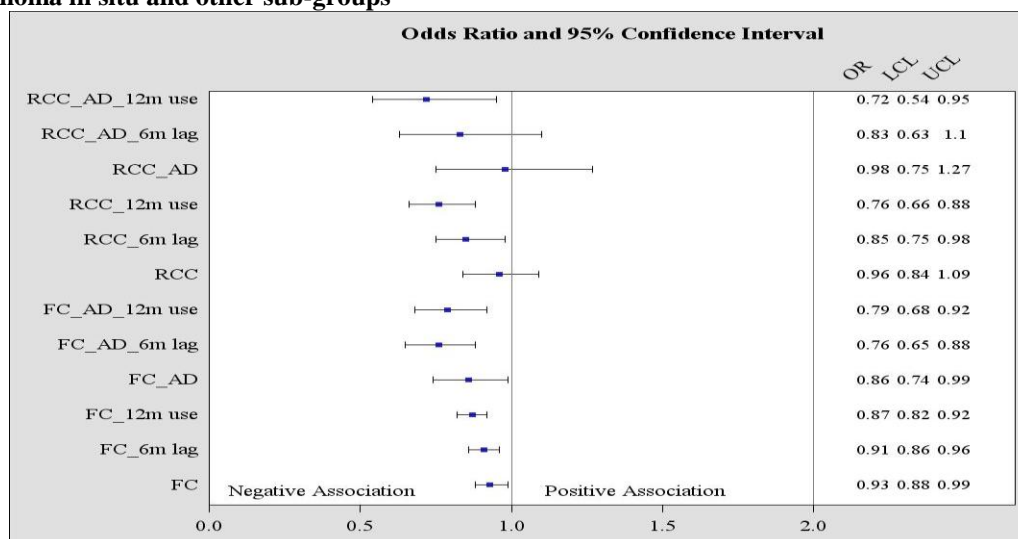
FC: Full cohort (cases with colon cancer and carcinoma in situ); **AD:** Alternate definition;
6mlag: Lag time of 6 months between the last date of prescription drug use and index date;
12m use: Minimum duration of use for 12 months; **RCC:** Cases with colon cancer on the right side;
OR: Adjusted odds ratio; **LCL:** 95% confidence interval, lower limit; **UCL:** 95% confidence interval, upper limit

Figure 3.19 Conditional logistic regression results for pravastatin among cases with colon cancer and carcinoma in situ and other sub-groups



FC: Full cohort (cases with colon cancer and carcinoma in situ); **AD:** Alternate definition;
6mlag: Lag time of 6 months between the last date of prescription drug use and index date;
12m use: Minimum duration of use for 12 months; **RCC:** Cases with colon cancer on the right side;
OR: Adjusted odds ratio; **LCL:** 95% confidence interval, lower limit; **UCL:** 95% confidence interval, upper limit

Figure 3.20 Conditional logistic regression results for simvastatin among cases with colon cancer and carcinoma in situ and other sub-groups



FC: Full cohort (cases with colon cancer and carcinoma in situ); **AD:** Alternate definition;
6mlag: Lag time of 6 months between the last date of prescription drug use and index date;
12m use: Minimum duration of use for 12 months; **RCC:** Cases with colon cancer on the right side;
OR: Adjusted odds ratio; **LCL:** 95% confidence interval, lower limit; **UCL:** 95% confidence interval, upper limit

It is observed from the results that the association of the individual drugs is not consistent with that of a therapeutic class as a whole. Not all the drugs in the given class have shown a similar association as the therapeutic class where only one or a couple of drugs

from the given therapeutic class have shown a significant association. These results demonstrate that the risk differs by individual agent within a therapeutic class. This can also be explained by the fact that the patients from the study population are prominent users of only one (or a couple of drugs) in a given therapeutic class. For example, diltiazem, verapamil and nifedipine (classified under the therapeutic class diuretics) are the most commonly used drugs among patients with colon cancer and carcinoma in situ. It is observed that the association if present for a given drug class is driven by the drugs that are used most frequently in that given class. Most of the studies conducted in the past have reported risk of cancer and/or colon cancer as a class effect. The results presented as a class effect could be misleading where the risk associated with cancer was primarily driven by the predominant agents used in that study population. The findings from this study answer the research question that the association of colon cancer differs by the individual cardiovascular drug for a given class.

Association between the individual cardiovascular drugs among the patients with a diagnosis of colon cancer on the right side

Based on the study rationale, certain drugs have properties that inhibit the bile acid reuptake in the intestine. Hence it is expected that patients who are frequent users of drugs with the inhibition properties of bile acid reuptake will demonstrate a strong association for colon cancer on the right side. For the drugs that showed a significant association, the results were compared to see that if the association was stronger among the patients with a diagnosis for colon cancer on the right side.

For the drug class angiotensin II receptor antagonists, losartan showed a positive association with cases with colon cancer and carcinoma in situ (primary definition) (See

Figure 3.3). The association was not significant among other sub-groups, but the point estimate increased when comparing the odds ratio among the alternate definition of colon cancer and carcinoma in situ and the cases with colon cancer on the right side.

For the drug class bile acid sequestrants, cholestyramine showed a positive association with cases with colon cancer on the right side (See Figure 3.9). When comparing the association for the cases with colon cancer and carcinoma in situ with the cases with colon cancer on right side, it was observed that the point estimate increased when comparing the primary definition for cases with colon cancer and carcinoma in situ with the cases with colon cancer on the right side. The increase in association although small was slightly higher when comparing across the sub-group with a minimum duration of 12 months use for cases with colon cancer and carcinoma in situ and the cases with colon cancer on the right side.

For the drug class calcium channel blockers, diltiazem, nifedipine and verapamil showed a significant association (See Figure 3.11, 3.12 and 3.13). It was observed that the odds ratio increased when comparing across cases with colon cancer and carcinoma in situ; and cases with colon cancer on the right side (primary definition); and for the sub-group with a minimum duration of use for 12 months (primary definition).

Association between drugs identified as bile acid reuptake inhibitors and colon cancer

As per the rationale, the bile acid inhibition in the intestine can eventually lead to a higher risk of cancer. This is measured by the K_i value where lower the K_i value higher is the inhibition. A listing of the K_i values for certain classes of cardiovascular drugs is

given in Appendix C. Drugs with a K_i value less than 100 are expected to have high bile acid reuptake inhibition properties.

Among the drug class calcium channel blockers, drugs listed as follows have a K_i value less than 100: nifedipine, nisoldipine, nimodipine, isradipine, niguldipine, nemadipine, nicardipine, nitrendipine, amlodipine, cilnidipine, felodipine, azelnidipine and manidipine. Not all the drugs listed above were used in the sample population. Among the drugs that were used in the sample population, only nifedipine demonstrated significant association with colon cancer (See figure 3.12). Use of nifedipine demonstrated a positive association among cases with colon cancer and carcinoma in situ (primary definition), and the sub-group having a lag time of 6 months between the last date of prescription drug use and index date; and the sub-group with minimum duration of use for 12 months. A positive association was observed between nifedipine and cases with colon cancer on the right side but the association was not significant. A possible explanation could be because nifedipine was used among less than 2 percent of the total sample (Table 3.4). Drugs such as amlodipine, isradipine, nisoldipine and nimodipine were used by less than 1 percent of the total sample. Use of prescription drugs such as diltiazem and verapamil demonstrated a positive association among the primary definition of cases with colon cancer and carcinoma in situ and some other sub-groups (See figure 3.11 and 3.13); but the K_i value for those drugs was greater than 200. This could be due to some other mechanisms at work which can lead to a higher risk of cancer. Studies conducted by Boudreau et al²⁴ and Bangalore et al²⁵ did not find a significant association with colon cancer. The ALLHAT trial⁵⁰ showed that there was no increased risk of cancer, which was a prespecified secondary endpoint with calcium channel

blockers. But the results from this study demonstrate that risk associated with individual drugs is different than class effect observed on the risk of colon cancer. Furthermore, a significant risk was observed in spite of low exposure to drugs such as nifedipine (1.5%), diltiazem (3.2%) and verapamil (1.8%) in the sample population (See Table 3.4) and. This should be noted in future research for exploring the risk associated with the individual agents.

Among the drug class diuretics, bendroflumethiazide has a K_i value less than 100 but this drug was not used in the sample population. Drugs such as furosemide and hydrochlorothiazide showed a positive association, especially furosemide which showed a positive association in both primary and alternate definitions of the cases with colon cancer and carcinoma in situ; and the primary definition for colon cancer on the right side.

Statins were the most commonly used drugs in the sample population where atorvastatin (15.9%), simvastatin (7.9%) and pravastatin (3.4%) were the commonly used drugs in the drug class. Use of drugs from the drug class statins, along with use of individuals drugs such as atorvastatin, simvastatin and pravastatin have shown negative association with colon cancer and carcinoma in situ and other sub-groups (See Figure 3.17, 3.18, 3.19, 3.20). These results are consistent with the results observed in other studies.^{13;15;32-34}

IV. DISCUSSION

This dissertation research was conducted using the HealthCore Integrated Research Database (HIRDSM) to determine the association between commonly used cardiovascular drugs and colon cancer and determine if a drug's ability to inhibit bile acid reuptake (as measured by K_i value) impacts the risk. The study had three specific aims: 1) to determine if there is an association between the use of cardiovascular drugs (by each class) and colon cancer; and does the association of colon cancer differ by individual cardiovascular drug for the given class? 2) Is the association between the individual cardiovascular drugs strongest among the patients with a diagnosis of colon cancer in the proximal location (right side)? 3) Are the cardiovascular drugs identified as inhibitors of bile acid reuptake (as measured by K_i value) associated with colon cancer?

This study was unique where the association between the use of individual drugs and colon cancer was studied. The association observed for a therapeutic class was compared with the association observed among use of individual drugs in the given therapeutic class. Based on the findings, it is established that the association with use of individual drug may not be similar to the therapeutic class. This was prominent from the results seen among the drug class ACE inhibitors. Most of the studies in the past have not reported the risks associated with individual drugs in the class. Hence it is very essential for regulatory agencies to consider the risk associated with individual drugs instead of the class effect on the risk of colon cancer especially in case of ACE inhibitors. Making inferences based on the class effect may hide the association observed among individual drugs. The risk observed among the drug classes beta blockers and statins was consistent with the study findings where the risk observed in the drug class was not very different

than the risk observed among individual agents. Hence any inferences related to the class effect of statins and beta blockers are similar to the risks associated with individual drugs for those given classes.

Furthermore, an alternate definition was used that was nested within a primary definition for cases. The alternate definition was more stringent in identifying cases and use of alternate definition provided a range of plausible values for the association. Significant associations observed for use of drug class, bile acid sequestrants, diuretics, and statins along with use of individual drugs such as cholestyramine, furosemide, atorvastatin, and pravastatin were confirmed in both primary and alternate definitions for cases with colon cancer and carcinoma in situ. It is possible that the positive association observed with cholestyramine could be attributed to production of excess bile acid for years. Patients using the bile acid sequestrants are already at an increased risk of colon cancer because of many years of malabsorption of bile acids. Furosemide is a commonly used diuretic and even a slight positive association can have important public health implications. It is essential to explore this association further to understand if use of furosemide poses a risk for colon cancer.

Significant associations were observed for the use of drugs from the drug class, bile acid sequestrants, diuretics; and use of individual agents such as cholestyramine, furosemide and pravastatin with a diagnosis of colon cancer on the right side (primary definition).

These associations observed among the use of drugs listed above could not be confirmed with the alternate definition for colon cancer on the right side. A possible explanation could be the lack of sample size in the sub-group with alternate definition of diagnosis of colon cancer on the right side. Significant association was also observed in different

subgroups requiring a lag time of 6 months between the last date of prescription drug use and index date; and minimum duration of use for 12 months.

This study is also unique by studying the association with the drug use among cases with a diagnosis of colon cancer on the right side. Based on the current literature, many studies have shown an increase in the percentage of right sided colon cancer in the United States^{51;52} which has led to a focus on the potential etiologies for variation by anatomic sites of colon cancer. Differences have been noted in characteristics of right-sided colon cancers when compared with the left-sided colon cancers.^{53;54} Analysis of tumor specimens has also shown difference in gene expressions between tumors in the right and left colon.^{55;56;57;58} This study takes a step closer towards understanding if a difference in association is observed among cases with a diagnosis of colon cancer on the right side. As per the rationale, this study helps answer the question if the differences in the risk of colon cancer on the right side are due to the bile acid reuptake inhibition properties of the respective drug. A small increase in association was observed for cholestyramine, diltiazem and nifedipine when comparing the association among cases with colon cancer and carcinoma in situ (primary definition); and the cases with colon cancer on the right side (primary definition). This small excess risk warrants a further exploration to determine if the use of these drugs has increased risk of colon cancer on the right side. Several unmeasured confounding factors may influence the study results. Information on lifestyle factors such as smoking, alcohol use, inactivity and obesity was not available. These factors can influence the risk of colon cancer. However this research looked at surrogate markers for the lifestyle factors where presence of diabetes can serve as a

marker for obesity, and chronic obstructive pulmonary disease as a marker for smoking. Higher frequencies of diabetes and COPD were observed among cases than the controls. A majority of adults in the United States (about 56%) use at least one or more prescription medications.⁵⁹ This study did not account for multiple prescription drug use. In this study the exposure for some prescription medications was rare and introducing categories based on multiple prescription drug use would further stratify leading to insufficient sample sizes thus producing non-significant estimates. Use of multiple prescription drugs or switching should be accounted for in future research. Also this study did not account for drug overlap. Overlap of drugs in this category is commonly observed. There may be residual confounding due to unobserved factors. This is limitation for observational studies, especially those using automated databases. The results generated from this study are generalizable to the commercially insured population in the United States. Overall, individuals in the HIRDSM approximate the US population well, with the HIRDSM population being slightly younger as all the members are commercially insured.

Conclusion

This observational study demonstrated that the association between use of cardiovascular drugs by each class differs by individual cardiovascular drug for the given class. The findings add to the knowledge that the risk for individual drugs may not be similar to the entire class; especially ACE inhibitors. Hence the regulatory agencies should consider the risk associated with the individual drug as opposed to the risk associated with the therapeutic class. Cardiovascular medications such as anti-hypertensive and lipid lowering medications are among the most commonly used prescription medications.⁵⁹ It

was also observed that the risk for colon cancer between the individual cardiovascular drugs (such as nifedipine, diltiazem and verapamil) was strongest among the patients with a diagnosis of colon cancer in the proximal location. The higher risk among patients with a diagnosis of colon cancer in the proximal location can be explained by the bile acid reuptake inhibition properties for the drug. Based on the findings from this study, further clinical research is warranted to better understand if use of these drugs (nifedipine, diltiazem and verapamil) is associated with an increased risk of colon cancer on the right side.

V. APPENDICES

Appendix A ICD-9-CM diagnosis codes and descriptions for definition of comorbidities

Comorbidity	At least one medical claim with an ICD-9-CM diagnosis code	
	Code	Description
Myocardial infarction	410	Acute myocardial infarction
	412	Old myocardial infarction
Congestive heart failure	428	Heart failure
Peripheral vascular disease	441	Aortic aneurysm and dissection
	443.9	Peripheral vascular disease, unspecified
	785.4	Symptoms involving cardiovascular system, Gangrene
	V43.4	Organ or tissue replaced by other means, Blood vessel
Cerebrovascular disease	430	Subarachnoid hemorrhage
	431	Intracerebral hemorrhage
	432	Other and unspecified intracranial hemorrhage
	433	Occlusion and stenosis of precerebral arteries
	434	Occlusion of cerebral arteries
	435	Transient cerebral ischemia
	436	Acute, but ill-defined, cerebrovascular disease
	437	Other and ill-defined cerebrovascular disease
438	Late effects of cerebrovascular disease	
Dementia	290	Dementias
Chronic obstructive pulmonary disease	506.4	Chronic respiratory conditions due to fumes and vapors
	490	Bronchitis, not specified as acute or chronic
	491	Chronic bronchitis
	492	Emphysema
	493	Asthma
	494	Bronchiectasis
	495	Extrinsic allergic alveolitis
	496	Chronic airway obstruction, not elsewhere classified
	500	Coal workers' pneumoconiosis
	501	Asbestosis
	502	Pneumoconiosis due to other silica or silicates
	503	Pneumoconiosis due to other inorganic dust
	504	Pneumonopathy due to inhalation of other dust
505	Pneumoconiosis, unspecified	
Rheumatological disease	725	Polymyalgia rheumatica
	714.81	Other specified inflammatory polyarthropathies, Rheumatoid lung
	710.0	Diffuse diseases of connective tissue, Systemic lupus erythematosus
	710.1	Diffuse diseases of connective tissue, Systemic sclerosis
	710.4	Diffuse diseases of connective tissue, Polymyositis
	714.0	Rheumatoid arthritis

Comorbidity	At least one medical claim with an ICD-9-CM diagnosis code	
	Code	Description
	714.1	Felty's syndrome
	714.2	Other rheumatoid arthritis with visceral or systemic involvement, Rheumatoid carditis
Peptic ulcer disease	531.4	Gastric ulcer, Chronic or unspecified with hemorrhage
	531.5	Gastric ulcer, Chronic or unspecified with perforation
	531.6	Gastric ulcer, Chronic or unspecified with hemorrhage and perforation
	531.7	Gastric ulcer, Chronic without mention of hemorrhage or perforation
	532.4	Duodenal ulcer, Chronic or unspecified with hemorrhage
	532.5	Duodenal ulcer, Chronic or unspecified with perforation
	532.6	Duodenal ulcer, Chronic or unspecified with hemorrhage and perforation
	532.7	Duodenal ulcer, Chronic without mention of hemorrhage or perforation
	533.4	Peptic ulcer, site unspecified, Chronic or unspecified with hemorrhage
	533.5	Peptic ulcer, site unspecified, Chronic or unspecified with perforation
	533.6	Peptic ulcer, site unspecified, Chronic or unspecified with hemorrhage and perforation
	533.7	Peptic ulcer, site unspecified, Chronic without mention of hemorrhage or perforation
	534.4	Gastrojejunal ulcer, Chronic or unspecified with hemorrhage
	534.5	Gastrojejunal ulcer, Chronic or unspecified with perforation
	534.6	Gastrojejunal ulcer, Chronic or unspecified with hemorrhage and perforation
	534.7	Gastrojejunal ulcer, Chronic without mention of hemorrhage or perforation
	531.0	Gastric ulcer, Acute with hemorrhage
	531.1	Gastric ulcer, Acute with perforation
	531.2	Gastric ulcer, Acute with hemorrhage and perforation
	531.3	Gastric ulcer, Acute without mention of hemorrhage or perforation
	532.0	Duodenal ulcer, Acute with hemorrhage
	532.1	Duodenal ulcer, Acute with perforation
	532.2	Duodenal ulcer, Acute with hemorrhage and perforation
	532.3	Duodenal ulcer, Acute without mention of hemorrhage or perforation
	533.0	Peptic ulcer, site unspecified, Acute with hemorrhage
	533.1	Peptic ulcer, site unspecified, Acute with perforation
	533.2	Peptic ulcer, site unspecified, Acute with hemorrhage and perforation

Comorbidity	At least one medical claim with an ICD-9-CM diagnosis code	
	Code	Description
	533.3	Peptic ulcer, site unspecified, Acute without mention of hemorrhage and perforation
	534.0	Gastrojejunal ulcer, Acute with hemorrhage
	534.1	Gastrojejunal ulcer, Acute with perforation
	534.2	Gastrojejunal ulcer, Acute with hemorrhage and perforation
	534.3	Gastrojejunal ulcer, Acute without mention of hemorrhage or perforation
	531.9	Gastric ulcer, Unspecified as acute or chronic, without mention of hemorrhage or perforation
	532.9	Duodenal ulcer, Unspecified as acute or chronic, without mention of hemorrhage or perforation
	533.9	Peptic ulcer, site unspecified, Unspecified as acute or chronic, without mention of hemorrhage or perforation
	534.9	Gastrojejunal ulcer, Unspecified as acute or chronic, without mention of hemorrhage or perforation
	Mild liver disease	571.2
571.4		Chronic hepatitis
571.5		Cirrhosis of liver without mention of alcohol
571.6		Biliary cirrhosis
Diabetes (mild to moderate)	250.0	Diabetes mellitus without mention of complication
	250.1	Diabetes mellitus without mention of complication, type I [juvenile type], not stated as uncontrolled
	250.2	Diabetes mellitus without mention of complication, type II or unspecified type, uncontrolled
	250.3	Diabetes mellitus without mention of complication, type I [juvenile type], uncontrolled
	250.7	Diabetes with peripheral circulatory disorders
Hemiplegia or Paraplegia	342	Hemiplegia and hemiparesis
	344.1	Other paralytic syndromes, Paraplegia
Moderate to severe renal disease	585	Chronic kidney disease (CKD)
	586	Renal failure, unspecified
	582	Chronic glomerulonephritis
	588	Disorders resulting from impaired renal function
	583.0	Nephritis and nephropathy, not specified as acute or chronic, With lesion of proliferative glomerulonephritis
	583.1	Nephritis and nephropathy, not specified as acute or chronic, ,With lesion of membranous glomerulonephritis
	583.2	Nephritis and nephropathy, not specified as acute or chronic, With lesion of membranoproliferative glomerulonephritis
	583.3	Nephritis and nephropathy, not specified as acute or chronic,
	583.4	Nephritis and nephropathy, not specified as acute or chronic, With lesion of rapidly progressive glomerulonephritis

Comorbidity	At least one medical claim with an ICD-9-CM diagnosis code	
	Code	Description
	583.5	Nephritis and nephropathy, not specified as acute or chronic,
	583.6	Nephritis and nephropathy, not specified as acute or chronic, With lesion of renal cortical necrosis
	583.7	Nephritis and nephropathy, not specified as acute or chronic,
Diabetes + complications	250.4	Diabetes mellitus , Diabetes with renal manifestations
	250.5	Diabetes mellitus, Diabetes with ophthalmic manifestations
	250.6	Diabetes mellitus , Diabetes with neurological manifestations
Moderate to severe liver disease	572.2	Liver abscess and sequelae of chronic liver disease, Hepatic encephalopathy
	572.3	Liver abscess and sequelae of chronic liver disease, Portal hypertension
	572.4	Liver abscess and sequelae of chronic liver disease, Hepatorenal syndrome
	572.5	Liver abscess and sequelae of chronic liver disease,
	572.6	Liver abscess and sequelae of chronic liver disease,
	572.7	Liver abscess and sequelae of chronic liver disease,
	572.8	Liver abscess and sequelae of chronic liver disease, Other sequelae of chronic liver disease
	456.0	Esophageal varices with bleeding
	456.1	Esophageal varices without mention of bleeding
456.2	Esophageal varices in diseases classified elsewhere	
Autoimmune disease (AIDS)	042	Human immunodeficiency virus [HIV] disease
Crohn's disease	555	Crohn's disease
Ulcerative colitis	556	Ulcerative colitis

Appendix B Description of codes used to define Screening (colonoscopy)

Code	Description
ICD-9-CM diagnosis code	
45.22	Endoscopy of large intestine through artificial stoma
45.23	Colonoscopy
45.25	Closed [endoscopic] biopsy of large intestine, Colonoscopy with biopsy
45.41	Excision of lesion or tissue of large intestine
45.42	Endoscopic polypectomy of large intestine
45.43	Endoscopic destruction of other lesion or tissue of large intestine
CPT codes	
44388	Colonoscopy through stoma; diagnostic, with or without collection of specimen(s) by brushing or washing (separate procedure)
44389	Colonoscopy through stoma; diagnostic,with biopsy, single or multiple
44390	Colonoscopy through stoma; diagnostic,with removal of foreign body
44391	Colonoscopy through stoma; diagnostic, with control of bleeding (eg, injection, bipolar cautery, unipolar cautery, laser, heater probe, stapler, plasma coagulator)
44392	Colonoscopy through stoma; diagnostic, with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps or bipolar cautery
44393	Colonoscopy through stoma; diagnostic, with ablation of tumor(s), polyp(s), or other lesion(s) not amenable to removal by hot biopsy forceps, bipolar cautery or snare technique
44394	Colonoscopy through stoma; diagnostic,,with removal of tumor(s), polyp(s), or other lesion(s) by snare technique
45355	Colonoscopy, rigid or flexible, transabdominal via colotomy, single or multiple
45378	Colonoscopy, flexible, proximal to splenic flexure; diagnostic, with or without collection of specimen(s) by brushing or washing, with or without colon decompression (separate procedure)
45379	Colonoscopy, with removal of foreign body
45380	Colonoscopy, with biopsy, single or multiple
45381	Colonoscopy, with directed submucosal injection(s), any substance
45382	Colonoscopy, with control of bleeding (eg, injection, bipolar cautery, unipolar cautery, laser, heater probe, stapler, plasma coagulator)
45383	Colonoscopy with Lesion Ablation or Removal, with ablation of tumor(s), polyp(s), or other lesion(s) not amenable to removal by hot biopsy forceps, bipolar cautery or snare technique
45384	Colonoscopy, with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps or bipolar cautery.
45385	Colonoscopy with Lesion Ablation or Removal, with removal of tumor(s), polyp(s), or other lesion(s) by snare technique
HCPCS codes	
G0105	Colorectal cancer screening; colonoscopy on individual at high risk
G0121	Colorectal cancer screening; colonoscopy on individual not meeting criteria for high risk

Appendix C Cardiovascular drugs and their K_i values⁴⁷

Calcium channel blockers	K_i value (μM)	HMG-CoA reductase inhibitors	K_i value (μM)	Diuretics	K_i value (μM)
Nifedipine	3.87±0.64	Simvastatin ^a	10.4± 2.1	Bendroflumethiazide ^a	92.7 ±12.7
Nisoldipine	4.77±1.05	Fluvastatin ^a	11.5±0.8	Spironolactone	110±17
Nimodipine ^a	5.75±0.72	Lovastatin ^a	21.6±2.3	Bumetanide ^a	225±17
Isradipine	19.4±3.0	Mevastatin	64.7±9.2	Trichlormethiazide ^a	377 ±79
Niguldipine	15.6±2.6	Pravastatin ^a	1360±360	Althiazide ^a	391±56
NemadipineA	23.1±4.1			Torasemide ^a	292±28
Nicardipine	32.4±3.1			Metolazone	456±69
Nitrendipine	34.1± 5.1			Indapamide	502±78
Amlodipine ^a	42.1±7.7			Chlorthalidone	707±58
Cilnidipine	45.2±8.3			Cyclothiazide	1000*
Felodipine	49.7±7.0			Chlorothiazide ^a	1220±140
Azelnidipine	85.6±13.5			Benzthiazide	1570±440
Manidipine	92.4±21.1			Hydrochlorothiazide ^a	2020±330
Diltiazem	211±21			Furosemide	5000*
Verapamil	266±22				

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