NOTE TO USERS

The effects of antidepressant drugs on the risk of colorectal cancer: A population-based case-control study

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ABSTRACT

Background: Experimental studies suggested that tricyclic antidepressants (TCAs) would increase the risk of cancer, whereas selective serotonin reuptake inhibitors (SSRIs) would protect against colorectal cancer. Moreover, studies in fluit flies indicated that TCAs could be classified as two subclasses, genotoxic and non-genotoxic, and genotoxic TCAs would be responsible for increasing the risk of cancer rather than non-genotoxic TCAs.

Objectives: This study was carried out to examine the following hypotheses: 1) The use of TCAs increases the risk of colorectal cancer. 2) In particular, the use of genotoxic TCAs increases the risk of colorectal cancer as compared to non-genotoxic TCAs. 3) The use of (SSRIs) decreases the risk of colorectal cancer.

Methods: A population-based nested case-control study was carried out using as source population who individually participate in the Saskatchewan Prescription Drug Plan (SPDP) aged 5-82.5 years from 1981-2000 with no previous history of cancer since 1967. 6544 histologically proven invasive colorectal cancer cases were identified from the Saskatchewan Cancer Registry (SCR). For each case, 4 eligible non-cancer controls matched on age, gender and calendar time were randomly selected. The effects of antidepressant use on the risk of colorectal cancer were examined by conditional logistic regression, considering dosage, duration and timing of antidepressant use.

Results: 1) A significant increased risk of colorectal cancer was observed for medium dosage and medium duration of any TCA use during 16-20 year period preceding diagnosis without significant dose-response effect ($RR_{medium\ dose}$=1.51, 95%CI=1.09-2.09, p-trend for dose=0.93; $RR_{medium\ duration}$=1.60, 95%CI=1.13-2.27, p-trend for duration=0.60). 2) No significant increased risk was observed among users of genotoxic TCAs, while a significantly increased colorectal cancer risk was observed among persons exposed to medium duration of non-genotoxic TCAs during 16-20 years preceding diagnosis with no significant dose-response effect (RR=1.89, 95%CI=1.14-3.14, p-trend=0.18). 3) Significant decreased risk of colorectal cancer was observed among subjects heavily exposed to SSRIs during 5-year periods preceding diagnosis (RR for

dosage=0.62, 95%CI=0.43-0.90, p-trend=0.01; RR for duration=0.71, 95%CI=0.50-1.00, p-trend=0.008).

Conclusion: 1) No sufficient evidence supporting that the use of TCA class increases the risk of colorectal cancer. 2) No evidence supporting that the use of genotoxic TCAs increases the risk of colorectal cancer as compared to the use of non-genotoxic TCAs. 3) Our results support the priori hypothesis that the use of SSRIs decreases the risk of colorectal cancer. This hypothesis need to be further studied in double blind randomized clinical trials

RÉSUMÉ

Contexte : L'étude des anti-dépresseurs (AD) chez l'animal a révélé que les AD tricycliques (ADT) pouvaient induire le cancer et que les inhibiteurs du recaptage sélectif de la sérotonine (IRSS) pouvaient protéger contre le risque de cancer colorectal (CCR). Par ailleurs, il semble, à partir d'études chez la drosophile, que l'on puisse individualiser parmi les ADT deux sous-classes : génotoxique et non génotoxique.

Objectifs : Cette étude a été réalisée pour vérifier les hypothèses suivantes : 1) L'exposition aux ADT augmente le risque de cancer colorectal; 2) L'exposition aux ADT génotoxiques augmente le risque de cancer colorectal (CCR) par rapport aux ADT non génotoxiques; 3) L'utilisation de IRSS diminue le risque de cancer colorectal.

Méthode : Nous avons réalisé une étude cas-témoins à base populationnelle, nichée dans la population de Saskatchewan qui est couverte par le programme d'assurance médicament (Saskatchewan Prescription Drug Plan on SPDP). Toute personne âgée de 5 à 82.5 ans dans la période 1981 à 2000 et sans antécédent de cancer depuis 1967, était éligible. Au total 6544 cas de cancer colorectal invasif ont été identifiés à partir du registre du cancer de Saskatchewan. Pour chaque cas, 4 contrôles appariés sur l'âge, le sexe et la date du calendrier au moment du diagnostic ont été sélectionnés aléatoirement. La relation entre l'utilisation d'AD et la survenue de cancer a été étudiée à l'aide de modèles logistiques en étudiant les effets respectifs de la dose, de la durée d'exposition et de la période d'exposition.

Résultats : Les trois résultats principaux sont les suivants : 1) Une augmentation significative du risque de CCR a été observée pour les cas exposés à une dose moyenne d'ADT pour une durée moyenne dans la période 16 à 20 ans avant le diagnostic de tumeur, sans qu'il ne soit observé de relation dose-effet significative (RR dose moyenne = 1.51; p 95% CI= 1.09 – 2.09; p-tendance = 0.93; RR durée moyenne = 1.60; 95% CI= 1.13 – 3.27; p-tendance = 0.60); 2) Aucun excès de risque de cancer n'a été trouvé chez les utilisateurs de ADT génotoxiques par rapport aux utilisateurs d'ADT non génotoxiques. En revanche, le risque de CCR a été trouvé significativement élevé chez les

sujets exposés aux ADT non génotoxiques pour une durée d'exposition moyenne pendant la période 16-10 ans avant la date de diagnostic de la tumeur (RR = 1.89; 95% CI = 1.14 – 3.14; p-tendance = 0.18); 3) Une réduction significative du risque de CCR a été constatée chez les utilisateur de fortes doses d'IRSS au cours des 5 années précédant le diagnostic de tumeur (RR fortes doses = 0.62; 95% CI = 0.43 – 0.90; p-tendance = 0.01) ou pour une durée prolongée (RR longue durée = 0.71; 95% CI = 0.5 – 1.00; p-tendance = 0.008).

Conclusion : L'étude ne confirme ni le risque de CCR associé à la prise d'ADT ni celui associé aux produits génotoxiques. L'étude supporte en revanche l'effet positif protecteur de l'exposition aux IRSS qui semblent diminuer le risque de CCR. Ce dernier résultat mériterait d'être confirmé dans un essai randomisé.

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LIST OF ABBREVIATIONS

BMI: Body mass index

CI: Confidence interval

HRT: Hormone replacement therapy

MAOIs: Mono-amine oxidase inhibitors

NSAIDs: Non-steroidal anti-inflammatory drugs

OCs: Oral contraceptives

OR: Odds ratio

P-trend: P value of test for linear trend

RR: (Incidence) rate ratio

TCAs: Tricyclic antidepressants

SCR: Saskatchewan cancer registry

SD: Standard deviation

SPDP: Saskatchewan prescription drug plan

SSRIs: Selective serotonin reuptake inhibitors

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Chapter 1: Introduction

Colorectal cancer is an important public health problem worldwide. It is the third most common cancer and the second leading cause of cancer-related deaths among Canadians. Although the age-standard incidence and mortality rates have declined steadily over the past two decades, the number of new cases has continued to rise due to the growth and aging of the population [McLaughlin 2002].

Implementation of screening programs and changes in exposure to modifiable risk factors for colorectal cancers are believed to contribute to the decrease in both incidence and mortality rates. Physical activity, weight control, a low fat diet, diet with plentiful vegetables and fruits, folate supplementation, calcium intake, as well as the control of smoking and alcohol assumption are suggested as being conductive to reducing the risk of colorectal cancer [Giovannucci 2002, Boyle 2002].

As for medication factors, remarkably consistent evidence indicates that non-steroidal anti-inflammatory drugs (NSAIDs) have anticarcinogenic effects in the colon and rectum. Some epidemiological studies show that women taking postmenopausal hormones have an approximately 30% to 40% decrease in the risk of colorectal cancer, although the definitive results may have to wait for randomized clinical trials [Giovannucci 2002].

Evidence in the early 1990's suggested that antidepressants, at clinically relevant doses, promoted fibrosarcomas, melanomas, and mammary carcinogenesis in rodent models [Brandes 1992]. This interesting finding immediately attracted much attention because antidepressants are so widely used for psychological disorders in general population, as well as for cancer-induced depression and pain in cancer patients.

However, the results of subsequent experimental and epidemiological studies have been inconsistent and inconclusive. Breast cancer and ovarian cancer are the two sites most frequently studied. It seems somewhat surprising that with heavy burden of colorectal

cancer and increased antidepressant use around the world, there has been no epidemiological study focusing on the colorectal cancer until now.

Tricyclic antidepressant (TCAs) has been the most frequently used antidepressant class since 1950's. One of TCAs, desipramine, was shown to accelerate cell proliferation of colon epithelia cells in chemical-induced carcinogenesis in the rat colon, suggesting it might promote colon tumors [Tutton & Barkla 1989, Iishi 1993]. Three epidemiological studies had included the sub-group analysis of the association between TCAs and colorectal cancer, but none of them suggested a significant association [Friedman 1980,1983, Selby 1989, Dalton 2000, Weiss 1998]. However, it is very difficult to make any conclusion based on the small sample size in those sub-analyses.

Among several possible carcinogenic mechanisms of TCAs, the genotoxicity of TCAs was considered to be significant for cancer development. Animal studies [Van Schaik & Graf 1991, 1993] indicated that the TCAs could be classified into two subclasses, genotoxic and non-genotoxic, based on the somatic mutation and recombination test (SMART) in wing cells of fluit flies. The differential chemical structures were considered to be the explanation for their genotoxic effects. A subsequent *post hoc* analysis in a population-based case-control study supported that the genotoxic TCAs were associated with an increased risk of breast cancer, as compared to the non-genotoxic TCAs [Sharp 2002]. Since there is no evidence that this effect is site-specific it is appropriate to ask whether the same effect also applies to colorectal cancer.

In contrast, it appears that another antidepressant class, selective serotonin reuptake inhibitors (SSRIs), has an antineoplastic effect on colorectal cancer. It was demonstrated that SSRIs could slow the growth of some human colonic tumors propagated as xenografts in immune-deprived mice, and suppress the cell division of chemical-induced colonic tumor cells in mice. It was postulated that serotonin may be a mediator of cell proliferation in colonic tumor cells and that the inhibition of serotonin uptake by SSRIs resulted in the suppression of cell proliferation of colon tumor cells [Tutton & Barkla, 1976,1982]. It is important to examine this hypothesis because SSRIs have already

become a "first line" antidepressant and the use has been increasing rapidly since their introduction in 1989; but no epidemiological study has tested it until now.

Examination of the effect of TCAs and SSRIs on the risk of colorectal cancer has obvious implications for physicians prescribing antidepressants. On average, all antidepressants have equivalent clinical efficacy [Beaumont 1989], and thus the side-effects profile becomes the most influential consideration when selecting an appropriate agent. Therefore, if proven, the unfavorable impact of TCAs and favorable impact of SSRIs on development of colorectal cancer may lead to changes in the clinical choice of certain antidepressant agents.

To investigate the potential carcinogenic effect of TCA class and the anti-tumor effect of SSRI class on colorectal cancer, a population-based nested case-control study was carried out using the Saskatchewan databases to test the following hypotheses:

1. The use of TCAs increases the risk of colorectal cancer, as compared to non-use of TCAs.
2. The effects of subclasses of TCAs were further examined to test the hypothesis that the use of genotoxic TCAs increases the risk of colorectal cancer, as compared to the non-genotoxic TCAs.
3. The use of SSRIs decreases the risk of colorectal cancer, as compared to the non-use of SSRIs.

Chapter 2: Literature Review

2.1 Colorectal cancer

2.1.1 Clinical aspects of colorectal cancer

2.1.1.1 Anatomic definition

Colon cancer and rectal cancer develop in the large bowel, which is the lower part of the gastrointestinal (GI) system. Cancer can develop in any of the four sections of the colon (ascending, transverse, descending, and sigmoid colonic regions), or in the rectum which is the final section of large bowel [Harms 2002]. Since colon and rectal cancer have many features in common, they are usually referred to together as colorectal cancer [American cancer society 2002].

2.1.1.2 Natural history

Over 95% of colorectal cancers are adenocarcinomas. These are cancers of the glandular cells that line the inside of the colon and rectum. The development of adenocarcinoma includes multi-step events, from hyperplasia, adenoma, adenoma with high-grade dysplasia, to invasive cancer [Harms 2002].

Most colorectal cancers begin as a polyp (especially adenomatous polyp), which is a growth of tissue into the center of the colon or rectum. Some types of polyps (e.g. inflammatory polyps) are not precancerous. But having adenomatous polyps increases the risk of developing cancer, especially with much numbers and large sizes [American cancer society 2002]. The polyps often start in the innermost layer and can grow into the wall of the colon or rectum. In the wall, the cancer cells can grow into blood vessels or lymph vessels. From there, the cancer cells can then spread to other parts of the body. This process is called metastasis.

2.1.1.3 Latent period

Colorectal cancers is characterized by a long period between the initial etiologic application and the clinical detection of the cancer [Thomas, 1988]. This period can be divided into induction period and latent period. The induction period is defined as the

time between the first exposure of an etiologic factor to cancer initiation. The latent period is from cancer initiation to cancer detection. The transformation from adenomatous polyp to adenocarcinoma is thought to take as long as 10 to 20 years, implying a long latency period in development of colorectal cancer [Tomeo 1999, Hamilton 1996].

2.1.1.4 Staging

Staging is a process that decides how widespread the cancer is. The treatment and survival rates of colorectal cancers depend, to a large extent, on the stage of cancer.

Dukes' classification for colorectal cancers is based on two prognostic features: the depth of direct invasion and metastasis to regional lymph nodes. The four stages are: Dukes' A lesions, where the cancer has grown to the bowel wall; Dukes' B lesions, where the tumor has progressed through the full thickness of the bowel wall; Dukes' C lesions, where the regional lymph nodes are involved; and Dukes' D lesions, where the distant metastases has occurred. Another widely used classification is TNM system (tumor, mode, and metastasis), which is roughly comparable to Dukes' classification.

2.1.2 Epidemiology of colorectal cancer

2.1.2.1 Burden of colorectal cancer

2.1.2.1.1 In Canada

In 2002, an estimated 17,600 new cases of colorectal cancer occurred and 6,600 died from this disease in Canada. When both genders are considered together, it is the third most common cancer and the second most frequent cause of cancer deaths among Canadians [McLaughlin 2002].

Colorectal cancer is more common in men and in the elderly. The estimated 2002 age-standardized incidence rate in Canadians is 59 (for male) and 39 (for female) per 100,000. About 90% of cases occur after age 50, and it is the most frequent type of cancer among persons aged 75 years and older [McLaughlin 2002].

Incidence rates of cancer are different at specific subsite in colon and rectum. In Canada, colorectal cancer occurs most frequently in the proximal colon (the part closer to the origin), followed by the rectum, and least in the distal colon for both men and women [McLaughlin 2002].

The incidence and mortality rates for colorectal cancer continued to decline in past two decades in Canada, especially for women. Age-standardized incidences rates have decreased 8% for men and 19% for women until 2001. However, because of the aging of the population, the number of new cases has continued to increase [McLaughlin 2001].

Three aspects may contribute to the declining trends. Part of the reduction in incidence rates and mortality rates may due to changes in exposure to risk factors. For instance, recent research [Reddy 2000] has suggested that non-steroidal anti-inflammatory drugs (NSAIDS) are protective factors for colorectal cancer. The increased use of these medications in the past two decades may have contributed to incidence declines. Colorectal cancer screening is also responsible for decreasing trend of incidence and mortality. It not only can find the cancer at an early curable stage, but also can prevent it by finding and removing polyps that might have become cancer later. Improvements in treatment could reduce mortality rates, but had no effect on incidence rates.

2.1.2.1.2 International comparisons

There are nearly one million new cases worldwide each year and half a million deaths. The incidence rates vary approximately 20-fold around the world. Canada had intermediate positions for both males and females [Potter 1999, Parkin1993]. Colorectal cancer is not restricted to western lifestyle countries; about 36% (329,529 cases) of new cases occur outside industrialized countries [Ferlay2001, Potter 1993].

Worldwide, age-standardized incidence is higher in men than in women (19.1 and 14.4 per 100,000, respectively in 2000) [Ferlay 2001], and it increased with increased age. The aging in worldwide population will have an obvious impact on the burden of colorectal cancer.

Incidence and mortality rates of colorectal cancer vary substantially by race and ethnicity. However, some studies suggested that environmental factors play a critical role in the etiology of this disease. For instance, the offspring of Japanese who was born in US have three or four times higher risk than those live in Japan [Haenzeal, 1968].

In conclusion, colorectal cancer is an important public health problem worldwide. The decreased trend in Canada makes it desirable to extend the screening program and to identify modifiable risk factors, including the use of medications that may initiate or promote the colorectal cancer.

2.1.2.2 Determinants of colorectal cancer

Approximately 90% of all colorectal cancer cases and deaths are thought to be preventable [Colditz 1996]. Therefore, considerable research efforts are given to investigate the modifiable determinants of colorectal cancer. The potential determinants for development of colorectal cancer are summarized in **Table 1.**

2.1.2.2.1 Lifestyle

2.1.2.2.1.1 Physical activity

It has been a fairly consistent finding that physical activities have a protective effect on development of colorectal cancer, in spite of the variation in outcome definition (eg. recreational or occupational activity) [Thune 1996, Martinez 1997] and exposure assessment (eg. by measuring resting heart rate or by questionnaire) [Giovannucci 1996, Thune 1996]. In 20 observational studies before 1999, only two reported no association, one reported a risk increase, and the remaining 17 studies reported a risk reduction associated with higher physical activity [Potter 1999]. This reverse association remains even after control for effects of potential confounders such as diet and lifestyle.

Physical inactivity is a strongly modifiable lifestyle risk factor for colorectal cancer. National Population Health Survey in Canada (1996-1997) showed that only 21% of Canadian were found to be active, 23% were moderately active and 57% were inactive

[Health Canada 1999]. Increasing physical activity should be considered as an efficient practice to reduce the risk of colon cancer.

2.1.2.2.1.2 Body weight

Most studies indicated that the obesity associated with the increased risk of colorectal cancer. However, we should take into account several factors to explain this association. Firstly, the selection of indicators of body weight or adiposity distribution might affect the association. Body mass index (BMI), waist-to-hip ratio (WHR), and weight gain or loss are all important factors, but have different implications. Secondly, accurate assessment of this factor is difficult in retrospective studies where the subjects may have difficulty recalling the previous body weight accurately. Thirdly, the association between body weight and colorectal cancer are vulnerable to confounding effects of covariates that are difficult to measure, such as physical activity and energy intake.

It was hypothesized that abdominal obesity (or central fat distribution pattern) is more relevant to colorectal cancer risk than an increase in generalized body fat. Martinez et al [Martinez1997] reported an increasing trend with increasing waist-to-hip ratio (WHR) (RR=1.48, 95%CI=0.88–2.49) for comparison of the highest ratio (> 0.833) to the lowest (< 0.728). However, this association appeared to be weaker than that between BMI and colorectal cancer risk, and to be non-significant.

Although the mechanism of association between the obesity and colorectal cancer is not very clear, keeping a normal body weight should be considered as a preventive practice to reduce the risk of developing colorectal cancer.

2.1.2.2.1.3 Tobacco use

The studies of association between smoking and colorectal cancer risk carried out before the 1970s did not show any association [IARC 1986]. After 1970s, however, more than 25 studies in different countries showed a consistent association between tobacco use and increased risk of colorectal cancer. Giovannucci [Giovannucci 2001] pointed out that this temporal pattern is consistent with an induction period of three to four decades between

tobacco use and clinical detection of colorectal cancer. The recent evidence strongly supports that colorectal cancer is a tobacco-related cancer, and tobacco appears to be an initiator of colorectal carcinogenesis.

2.1.2.2.2 Diet and nutrition

2.1.2.2.2.1 Diet fat and energy

There is fairly consistent evidence that high intake of animal fat and red meat is associated with increased risk of colorectal cancer. A meta-analysis of 13 prospective studies of meat consumption and colorectal cancer risk has reported an increased risk (12–17%) with a daily increase of 100 g of all meat or red meat [Sandhu 2001]. However, many studies failed to demonstrate that the association with fat intake is independent of energy intake.

Willett et al provided evidence that increased animal fat consumption is a risk factor for colon cancer after adjustment for total energy intake when the highest quartile (RR=1.89, 95%CI=1.13-3.15, P trend=0.01) is compared to the lowest. No association was found with vegetable fat [Willett 1990].

In another study, Sinha et al. considered that high intake of carcinogenic compounds contained in well-cooked meat at high temperatures has been associated with an increased risk of colorectal adenomas [Sinha 2001].

2.1.2.2.2.2 Fruit, vegetables and fiber

Recent evidence from large prospective cohort and intervention studies contradicted a prior widely accepted protective effect of diet with high fruit, vegetables or fiber on the colorectal cancer risk, and thus such an association needs further confirmation.

In the Nurses' Health Study (88,764 women) and the Health Professionals' Follow-up Study (47,325 men) [Michels 2000], no association was found between decreased colon cancer incidence and high fruit and vegetable consumption. More important evidence came from two randomized clinical trials in US that could not find protective effect of

dietary interventions on risk of recurrent adnomatous polyps. In the Polyp Prevention Trial [Schatzkin 2000] subjects have received a low-fat, high-fiber, fruit and vegetable diet for approximately 4 years. In the Wheat Bran Fiber Study [Alberts 2000], subjects were provided a supervised dietary supplementation with either high amounts (13.5 g per day) or low amounts (2 g per day) of wheat-bran fiber (median follow-up time was 34 and 36 months, respectively). However, one limitation of both studies is that the follow-up period maybe too short to detect the cancerous polyps' occurrence.

2.1.2.2.2.3 Alcohol intake

A review of epidemiological evidence from 1957-1991 and a recent meta-analysis [Bagnardi 2001] of studies from 1966-2000 indicated that high alcohol intake increase the risk of colorectal cancer [Kune 1992] after adjustment of known risk factors of colorectal cancer, although not all studies support such an association.

A meta-analysis of 27 studies [Longnecker 1990] supported the presence of a weak association between alcohol consumption and increased colorectal cancer risk. Results from follow-up studies (RR=1.32, 95%CI= 1.16-1.51) suggested a stronger relationship than those from case-control studies (RR=1.07, 95%CI=1.02-1.12).

It is still unclear whether such an association is due to alcohol per se, its contribution to energy (calories) or its impact on other component of diet. One possibility is the ability of alcohol, particularly its metabolite acetaldehyde, to antagonize foliate and methionine metabolism [Shaw 1989].

2.1.2.2.2.4 Multivitamins containing foliate

Foliate supplements, particularly multivitamins containing foliate, would be beneficial in reducing the risk of colorectal cancer [Giovannucci 1998]. In the United States, multivitamins are a major source of foliate. Studies in US indicated that users of multivitamins for more than 10 years are at lower risk of colon cancer [Jacobs 2001]. In the Nurses' Health Study, women who had taken supplement foliate with multivitamins for at least 15 years had relative risks of 0.25(95%CI=0.13-0.51) for developing colon

cancer compared with women who had never taken multivitamins. Interestingly, women in this study whose diets were high in foliate but who never took multivitamins did not have significant reduction in risk [Giovannucci 1998]. Therefore, folate from supplements was considered to have more protective effect than folate from diet due to the higher dose and bioavailability from this source [Hall 1998].

2.1.2.2.2.5 Calcium

Findings from the large prospective studies consistently showed that calcium intake had a weak association with reduction of colorectal cancer risk [Martinez 1998]. Several recent intervention trials support this result. An intervention trials in North America [Baron 1999a,b] of calcium supplementation (1200 mg of elemental calcium daily *versus* placebo) among 913 participants found a statistically significant reduction in risk of adenoma recurrence (OR=0.81,95%CI=0.67-0.99). In another trial conducted in Europe, 665 patients with a history of colorectal adenomas were randomly assigned to calcium supplementation group (2g elemental calcium daily), fiber treatment group, and placebo group. Similar inverse association, but not statistically significant, was found [Bonithon 2000]

2.1.2.2.3 Medications

2.1.2.2.3.1 Non-steroidal anti-inflammatory drugs (NSAIDs)

There is a general agreement that use of aspirin and other NSAIDs reduces by 40%-50% the risk of colorectal cancer and adenomatous polyps [Giovannucci 2002], and it appears to be related to dose and duration.

In several cohort studies, use of aspirin more than twice a week was correlated with a lower risk of colorectal cancer [Giovannucci 1994]. In the Nurses' Health Study, two aspirin per week for a period of 20 years reduced colorectal cancer risk by 44% [Giovannucci 1995]. In a population-based case-control study using the administrative databases [Collet 1999], a protective effect was observed 10 years after aspirin and other NSAIDs use. In contrast, a randomized trial showed low-dose aspirin with short duration

in the United States Physicians Health Study had no effect on colorectal cancer risk[Gann 1993].

Two randomized trials of sulindac versus placebo to treat familial adenomatous polyps (FAP), which is a hereditary disorder that will cause colon cancer if left untreated, showed a reduction in polyps after treatment [Labayle 1991, Giardello 1993]. Labayle et al. reported the complete regression of rectal polyps in 6 of 9 patients taking sulindac and partial regression in other 3. In the placebo group, polyps increased in 5, remained unchanged in 2 and decreased in the remaining 2.

Effects are biologically plausible because NSAIDs use appears to prevent or reduce the frequency of carcinogen-induced animal colonic tumors by reducing growth rates in colon cancer cell lines. The potential mechanisms include: Inhibition of cyclo-oxygenase directly by NSAIDs, by aspirin (via acetylation of prostaglandin H synthase irreversibly inactivating cyclo-oxygenase), or by specific cyclo-oxygenase-2 (COX-2) inhibitors [Harms 2002].

2.1.2.2.3.2 Exogenous female hormone

Hormone replacement therapy (HRT)

It appears that the use of hormone replacement therapy reduces the risk of colorectal cancer in women. The risk seems lowest among users with long-term period and high dose.

Herbert [Herbert 1998] conducted a meta-analysis of studies before December 1996 to examine the association between the use of menopausal hormones and colon cancer in women. A summary relative risk of 20 estimates of the association between ever use of menopausal hormones and colon cancer was 0.85 (95%CI=0.73-0.99). The estimated relative risk was 0.69 among current or recent users (95%CI=0.52-0.91), 0.73 among users of more than 5 years (95%CI=0.53-1.02), and 0.88 among short-term users (95%CI=0.64- 1.21), as compared to nonusers. However, there are some common

limitations of these studies including rough assessment of exposure and inadequate control of confounding factors.

Grodstein et al [Grodstein 1998] reported a protective effect of HRT for colorectal cancer from Nurses' Health Study (NHS), which had a long follow-up of 14 years, a large study population of 59,002 postmenopausal nurses (601,503person-years), and prospective measurement of important covariates. Self-reported current HRT use, was associated with an adjusted RR of 0.64(95%CI=0.48-0.85) for colon cancer, particularly in proximal subsite. Long duration of use (≥5 years) among current HRT users was associated with greater protective effect (RR=0.56, 95%CI=0.39-0.83). In contrast, past HRT use(≥5 years since last use) was not associated with a reduced risk of colorectal cancer.

This protective effect was confirmed by results from recent Women's Health Initiative randomized controlled trial [Rossouw 2002]. 16608 postmenopausal women aged 50-79 years were recruited and followed for 8.5 years. Intervention group received conjugated equine estrogens (0.625mg/d) plus medroxyprogesteroone acetate (2.5mg/d). Although all-cause mortality and risk of CHD were not reduced during the trial, the risk of colorectal cancer in intervention group was shown to reduced as compared to the placebo group (hazard ratio=0.63, 95%CI=0.43-0.92).

Oral contraceptives

The evidence for a protective association between oral contraceptives and colorectal cancer is mixed. The Nurses' Cohort Study is one of the few studies where a protective of oral contraceptive use has been observed [Martinez 2001]. It was reported that women using oral contraceptives for at least 8 years were found to have a 40% reduction in colorectal cancer compared with women who had never used oral contraceptives.

2.1.2.2.4 Family history

It has been reported that the risk of colorectal cancer in patients with affected first-degree relatives increased 2-4 fold. This risk is even higher if several family members have colon or rectal cancer [Fuchs 1994]. Several hereditary disorders are known to be

strongly associated with colorectal cancer development, including familial adenomatous polyposis (FAP), Gardner's syndrome, and hereditary non-polyposis colorectal cancer (HNPCC)[Harms 2002].

However, the hereditary or genetic connection may not be the only explanation for family tendency of colorectal cancer. Cancers within the same family may result from common exposure to an environmental carcinogen, such as similar diet or lifestyle risk factors.

2.2 Depression and antidepressants use

2.2.1 Depression

2.2.1.1 Burden of depression

In Canada, major depression is the most common psychiatric problems in the general population. The 1-year prevalence of depression among Canadians is between 4% and 10% [Canadian Psychiatric Association 2002]. Women experience depression about twice as often as men do [Patten 2001].

In particular, there is a much higher prevalence of depression among patients with cancer. Streltzer [1983] reported that depression was the most common psychiatric complication of cancer; approximately one-third of all cancer patients is depressed. Depression during cancer not only impacts on quality of life, but also lead to delay in cancer diagnosis and treatment, thereby may reduce long-term cancer survival.

In addition, major depression has a very important impact on public health since it can cause substantial disability [Murray 1996]. It has a heavy economic burden associated with health care costs as well as lost work ability. Brigitte and Claudine [Brigitte 2002] conservatively estimated that the economic burden of depression in Canada in 2000 was approximately CAN$5.4 billions.

2.2.1.2Depression and cancer

There is little convincing evidence to support that depression increases the risk of cancer. Epidemiological studies have important limitations and none of them focuses specifically on the association between depression and risk of colorectal cancer.

One study examined the effect of depressed personality using a nested case-control study conducted [Kune 1991] with the data from Melbourne population-based colorectal cancer study. Among 22 psychological questions, self-reported childhood or adult life 'unhappiness' was statistically associated with colorectal cancer occurrence, which was independent of the known risk factors such as diet, family history, as well as other potential confounding factors of socioeconomic level, marital status, religion and country of birth. This result suggested that depressed personality may play a role in development of colorectal cancer. However, this result must be interpreted with caution given the limitations of retrospective case-control study. When detecting the effect of depression on cancer risk, the validity of retrospective design has been questioned [McGee 1994]. It is reasonable that cancer symptoms or cancer diagnosis would cause depressive mood. In addition, current depressive mood may influence the recalled experiences, with tendency to recall previous unhappy experiences. These two reasons make it difficult to separate the cause-effect relationship in case-control studies. However, all prospective cohort studies provided inconclusive results [Linkins 1990].

Shekelle et al [1981] measured the depression status of 2020 men at baseline and reported an increased relative risk of any cancer death (adjusted RR= 2.3) after 17 years follow-up. This result was confirmed by a 20-year follow-up of the same study population by Persky et al [Persky 1987]. The main problem of these two studies is that they used a single baseline measurement of depression for a relatively long follow-up period [Croyle 1998]. Depression is a chronic mental disorder and cancer development may be due to the long-term exposure to depressive mood. Any later estimate could vary from baseline. Two other prospective studies also have this problem [Linkins1990,Friedman1994].

Penninx et al. improved their design in a population-based cohort study [Penninx 1998], by taking into account the duration of depressive symptoms instead of a single baseline

measurement. The subjects were classified as depressed if they met diagnostic criteria at baseline and 3 and 6 years before baseline. After an averaged 3.8 years follow-up of 4825 persons aged 71 years and older, they found an 88% increase in any cancer risk (adjusted hazard ratio=1.88, 95%CI=1.13-3.14). In further analysis, they found that depression measured at a single time point was not related to cancer. They indicated that cancer development might be related to chronic depression rather than episodic depression. However, control for the possible confounding effect of antidepressant use was insufficient in this study, since they obtained information about antidepressant use for only the 2 weeks preceding the start of the cohort [Sharpe 2002].

A meta-analysis in 1994 [McGee 1994] of 6 longitudinal prospective studies indicated that the early history of depression or depressive symptoms had a small and marginally statistically significant association with later development of cancer (OR=1.14, 95%CI=0.99-1.30).

Other prospective studies provided little supporting evidence for the association between depression and risk of cancer development. The Walnut Creek Contraceptive Drug study showed [Hahn 1988] no relationship between depression and breast cancer after 39 months follow-up. The Alameda Country study [Kaplan 1988] did not find depressive symptoms predicting any cancer deaths. The National Health and Nutrition Examination Survey Follow-up Study [Zonderman 1989] found no increase in either cancer morbidity or cancer mortality. In a recent cohort study [Gallo 2000], major depression had no association with increased risk of any cancer (RR=1.0, 95%CI= 0.5-2.1) after 13-years follow-up. The borderline positive association between baseline major depression and increased risk of breast cancer (RR=3.8, 95%CI=1.0-14.2) was based on only 25 breast cancer cases.

In summary, epidemiological studies provide little convincing evidence for depression as a risk factor in the development of cancer. Stein also indicated that there was no convincing experimental evidence to support the hypothesis that depression impairs immune function [Stein 1991, Croyle 1998].

2.2.2 Antidepressant use

2.2.2.1 Burden of antidepressant use

The use of antidepressants has increased in recent years in Canada. Hemels et al [Helmels 2002] reported that total prescriptions increased from 3.2 to 14.5 million between 1981 and 2000. In a population of more than 1.4 million Ontario residents aged 65 years or older, Mamdani et al [Mamdani 2000] reported that the proportion of antidepressant users increased 24% from 9.3% of the population in 1993 to 11.5% in 1997. Annual antidepressant cost increased by 150% in this elderly population [Mamdani 2000].

Increased prevalence of antidepressant use may reflect increased prevalence of depression, increased availability of new products, increased proportion of patients with detected depression receiving medications, or increased proportion of subjects taking antidepressants for other indications[Helmels 2002].

2.2.2.2 Prescription patterns of antidepressants

The appropriate pattern of antidepressant use, particularly out of hospital, has been discussed for many years. Important concerns include identifying appropriately the patients who need medications, as well as prescribing the right medication at the right dose [Rosholm 1993] and duration [Paykel 2001, Hirschfeld 2000].

2.2.2.2.1 Effectiveness and adverse effect of antidepressant class

There are four main classes of antidepressant **(Table 2)**: Tricyclic antidepressants (TCAs), Selective serotonin reuptake inhibitors (SSRIs), Mono-Amine Oxidase Inhibitors (MAOIs), and an additional class designated as "atypical antidepressant". TCAs and MAOIs were introduced in the early 1950's. SSRIs have been introduced at the end of 1980's.

Neurotransmitters are chemicals in the brain that carry messages from one cell to another. When there are imbalances (too much or too little) in neurotransmitters, various diseases will happen including depression. Antidepressant drugs mainly alter the effective levels of neurotransmitters, by changing the metabolic rate at which the neurotransmitters are

either created or broken down; they may also block the process in which a neurotransmitter is taken by a presynaptic neuron, or interfere with the binding of a neurotransmitter to neighboring cells.

TCAs affect the uptake of norepinephrine, serotonin and dopamine to different degrees. SSRIs primarily inhibit the reuptake of serotonin and thus prolong its activity. MAOIs increase the levels of norepinephrine, serotonin and dopamine by inhibiting an enzyme that inactivates them, and thus increase the synaptic concentration of these neurotransmitters. Several new antidepressants are classified as atypical because their action is not well understood [Canadian Psychiatric Association 2002]. However, there is no way to determine which neurotransmitters a person is deficient in, so it may take several drugs and /or the use of a combination of drugs before the right treatment is identified [Parkel 2001].

Antidepressants are also used for several conditions other than depression. They are frequently used for chronic pain, including cancer pain. Several SSRIs have been used to reduce hot flashes in menopausal women and some cancer survivors who are on anti-estrogens (for breast cancer) or anti-androgens (for prostate cancer). They are also used in treating obsessive-compulsive disorder, panic disorder, anxiety disorder, and to help patients who undertake a smoking cessation program [Allan 1995]. Dosage and duration are usually less and shorter for these indications, except for obsessive-compulsive disorder.

The various antidepressant classes have different side effect profiles. Newer antidepressants (e.g. SSRIs) have been introduced for an equivalent antidepressant effect associated with better tolerance compared to TCAs. In particular, SSRIs do not have significant anticholinergic, hypotensive and cardiac effects, and thus have fewer limitations especially for elderly people. Other considerations for clinical use of SSRIs include the easier dose titration and greater safety in an overdose [Martin 1997].

2.2.2.2.2 Shift among new and old antidepressant classes

The increased use of antidepressants during the last decade is mainly due to the SSRIs [Rosholm 1997]. Concomitant with the increase of SSRIs use, TCAs use decreased in some population.

In a population-based study of more than 1.4 million Ontario residents aged 65 years or older[Mamdani 2000], the greatest shifts in prescribing patterns occurred with the SSRI and TCAs. Prescription for SSRIs increased from 9.6% of all antidepressant prescriptions in the first 30 days of 1993 to 45.1% of those dispensed in the last 30 days of 1997. Prescriptions for TCAs reduced from 79.0% to 43.1% during the same period. The introduction of SSRIs had a substantial impact on the drug-related cost: prescribing shift from TCAs to SSRIs accounted for at least 61% of the cost increase from 1993 to 1997.

2.2.2.2.3 Selection criteria for different antidepressants

On average, all antidepressants appear to have equivalent effects in the treatment of depression [Keller MB 1997]. The selection of a particular agent should take into account several factors such as 1) Medical history, such as a personal history or a family history of good response to a particular agent; 2) side effects profile; 3) data from the physical and laboratory examination (for instance, an electrocardiogram that showed a conduction abnormality should influence the physician against characteristics, such as the absorbed and metabolized routes and half-lives in human beings; 5) interactions with food or other drug administration; 6) the cost of the agent. Besides the side effect profile, cost can also influence compliance to medication use.

2.2.2.2.4 Long-term utilization pattern

Depression is a "recurrent, often chronic, lifetime illness requiring long-term treatment" [Hirschfeld 2000, Paykel 2001]. Short-term treatment provides adequate symptom relief, but longer-term treatment reduces the probability of relapse and recurrence, as well as the number of major disabilities. Hence, long-duration treatment following initial remission of symptoms should be routine. WHO [WHO 1989] recommended 6 months as a minimal period for continuation of treatment after the acute phase. Maintenance treatment is suggested for depression with already recurrent histories or for those with a

clear risk of further episodes, to prevent a recurrence of depression. Antidepressant withdrawal should always be gradual, over a minimum of 3 months and longer after long maintenance periods, to avoid withdrawal symptoms [Parkel 2001]. There is an important concern about underutilization of antidepressants and non-compliance to treatment guidelines. It is indicated that many depressed persons often receive either no antidepressant drug therapy or a drug therapy that is insufficient in dose, duration, or both [Hirschfeld 1997].

2.3 Antidepressant use and the development of colorectal cancer

The possible carcinogenic effect of antidepressants was first suggested in Brandes et al's study [Brandes 1992], in which the antidepressants with histamine-receptor activity (fluoxetine and amitriptyline) were found to promote fibrosarcomas, melanomas, and mammary carcinogenesis in rodents at clinically relevant dose. However, the subsequent Food and Drug Administration's Division of Research and Testing was not able to replicate the effects of the antidepressants studied by Brandes et al, using the same study design and methodology [Mathews 1995].

Nevertheless, this interesting finding attracted much attention since the antidepressants were widely used both in the general population and in cancer patients. However, the overall results have been inconsistent and inconclusive.

2.3.1 Experimental studies of effects of antidepressants on risk of colorectal cancer

The experimental studies of antidepressant use on the development of colorectal cancer were summarized in **Table 3A.** These studies suggested that two antidepressant classes, TCAs and MAOIs, could increase the risk of colorectal cancer. On the other hand, SSRIs could reduce the promotion of colon tumors.

2.3.1.1 Carcinogenic effect of TCAs and MAOIs on colorectal cancer

In 1989, Tutton and Barkla [1989] reported that the TCA desipramine accelerated intestinal crypt cell proliferation in intact rats, suggesting that desipramine might enhance colon carcinogenesis. To test this possibility, Iishi et al. [1993] investigated the effects of

the desipramine on the incidence, number and histology of colon tumors induced by azoxymethane (AOM) and on the serum norepinephrine (NE) concentration. Rats were treated with 10mg/kg desipramine until the end of the experiment. Treatment significantly increased the incidence, but did not influence the location and the histological appearance of the colon tumor. Furthermore, TCA desipramine significantly increased the serum norepinephrine level during and after azoxymethane treatment. It is thought that increased norepinephrine concentration might stimulate crypt cell proliferation in colon. These results suggested that desipramine could enhance the development of colon tumors and that its effect may be related to its effect in increasing proliferation of colon epithelial cells through its histamine-receptor activity.

Using a similar method, Iishi et al. [1994] also investigated the effects of prolonged administration of monoamine oxidase inhibitors (MAOIs) on the carcinogenesis in rat colon induced by azoxymethane. MAOIs has been classified into two types, type A and type B, and thus the type A inhibitor clorgyline (5mg/kg body weight) and the type B inhibitor pargyline (50mg/kg body weight) were examined separately. Treatment with pargyline significantly increased the incidence of colon tumors, the NE concentration in the colon wall and labeling index of the colon mucosa during and at the end of experiment. In contrast, clorgyline had no influence on the development or histological appearance of colon tumors. These findings indicated that the MAO-B inhibitor, but not MAO-A inhibitor, enhanced colon carcinogenesis, and that its effect may be related to its effect in increasing the NE concentration in the colon wall and subsequently increasing the proliferation of colon epithelial cells.

2.3.1.2 Antineoplastic effect of SSRIs on colon tumor

Several studies provided supportive evidence for an antineoplastic effect of Selective Serotonin Reuptake Inhibitors (SSRIs) on colon cancer. Serotonin is an important stimulant to cell division in many tissues, including adenocarcinomas induced by dimethylhydrazine (DMH) in the large intestine of rat [Tutton & Barkla 1978]. Treatment with serotonin-receptor antagonists retarded the growth of human colorectal tumors propagated as xenografts in immune-deprived mice [Tutton & Steel 1979].

Based upon these findings, Tutton and Barkla [1982] examined the effects of two SSRIs, fluoxetine and citalopram, on the growth of 3 human colon tumors propagated as xenografts in immune-deprived mice, and on the rate of cell division in both the normal intestinal epithelium and in DMH-induced colonic tumors. The histopathology of tumor lines used in the experiment (HXM2, HXM3, and HXM4) ranged from a moderately well-differentiated adenocarcinoma (HXM4) to a poorly differentiated adenocarcinoma (HXM2).

It has been found that these two SSRIs, fluoxetine (10-20mg/kg) and citalopram (20-40mg/kg), significantly slowed the growth of two out of three lines of human colonic tumors (HXM2 and HXM4), as compared to the control groups of mice bearing xenografts of similar size and matched for weight, sex and age but treated only by saline. These inhibitory responses were more intense than the responses previously seen when these tumors were treated with serotonin-receptor antagonists [Barkla & Tutton 1981]. They suggested that the SSRIs affected the proliferation in human tumor cells rather than inhibit the general metabolism function.

These results confirmed previously submitted concept that human colonic tumour cells have a serotonin-uptake mechanism[Tutton and Bakla 1976], and supported that the selective inhibition of serotonin uptake may have antineoplastic effect on human colonic tumors. The authors suggested that these agents should be studied as antineoplastic agents in humans.

2.3.2Epidemiological studies of antidepressant use and colorectal cancer

Following Brandes' experimental study in 1992, 13 published epidemiological studies have investigated the effects of antidepressants on different cancer sites (2 prospective follow-up, 2 retrospective cohort and 9 case-control). Breast cancer and ovarian cancer were the two main study sites. The overall results have been inconsistent, five of them supported a promotion or initiation effect of antidepressants on cancer risk; the remaining eight were not able to confirm this hypothesis. Most of epidemiological studies were not

able to distinguish the effect of depression from antidepressant use due to the difficulty of measuring depression accurately. These epidemiological studies are summarized in **Table 3B**.

It seems somewhat surprising that with the heavy burden of colorectal cancer and increased antidepressant use around the world, only 3 epidemiological studies had included the detection of the association between antidepressants and development of colorectal cancer; and in all of them the association was examined in sub-group analysis.

Friedman et al [Friedman 1980,1983, Selby 1989] conducted a systematic screening of 215 medical drugs or drug groups for assessing the possible carcinogenic effects on 56 cancer sites (including colon and rectum) with a maximum follow-up of 19 years. The accumulated cancer incidence data of 1957 patients who received at least one prescription for amitriptyline (TCAs) and of 308 who received imipramine (TCAs) was recorded. Observed and expected cases of cancer at each site and all sites combined were compared. Neither one of the two antidepressants assessed was found to be significantly associated with the development of colorectal cancer or all sites combined. Among the amitriptyline users, 195 developed cancer and this was not significantly greater than the 182.7 cases expected (standardized morbidity ratio (SMR)=1.07, 95 % CI=0.92-1.23). Among imipramine users, 12 developed cancer, and this was not significantly different from the 15.6 cases expected (SMR=0.77, 95%CI=0.40-1.34). The follow-up time of this study should have been sufficient to detect the promotion or initiation effect of carcinogenic agents. However, most of known or probable risk factors of cancers were not controlled in the analysis. Furthermore, the statistical power may not been sufficient to detect the risk on each cancer site. Finally, only ever/never use was considered as exposure index instead of the dosage, duration and timing of drug use.

Dalton et al [2000] conducted a population-based cohort study to assess the association between the use of antidepressants (TCAs, MAOIs, SSRIs) and the risk of cancer at any site (including colorectal cancer). The exposure data in 30,807 adult users of antidepressants was identified from the Prescription Database of the Country of North

Jutland, Denmark between January 1, 1989 and December 31, 1995. Information on cancer occurrence was obtained from the Danish Cancer Registry. After average 3.2 years of follow-up period, there was no overall increase in cancer risk associated with antidepressant use (Standardized Incidence Ratio(SIR) =1.0, 95%CI=1.0-1.1). The only single cancer site with an increased risk is non-Hodgkin's lymphoma, among people with more than 5 TCA prescriptions (SIR=2.5, 95%CI=1.4-4.2). However, this study was not able to control for most of potential confounders. The relatively short follow-up period in this study might also have limited the ability to detect some long-term drug-cancer association. Finally, noncompliance is a common problem in patients using antidepressant agents and this might also lead toward a null result.

Weiss et al [1998] conducted two nested case-control studies within a cohort of 1467 patients with breast cancer, colon cancer, or melanoma between 1988 and 1994 to assess whether exposure to antidepressants or antihistamines would accelerate tumor growth. Each case patient was matched by five randomly selected control patients according to primary cancer site, primary cancer stage and follow-up period. During an average 2.2 years of follow-up, the use of antidepressants or antihistamines was not found associated with an increased risk of tumor recurrence (OR=0.97, 95%CI=0.52-1.78) in these three sites. These studies were designed to detect primarily the effect of any antidepressant or antihistamine use, and have approximately 80% power. However, use of either antidepressants or antihistamines was lower among the case patients. This could not rule out the possibility that the power was insufficient to detect the possible effect of antidepressant use on the growth of tumors at these sites.

In summary, no increased risk of colorectal cancer was found to be associated with antidepressant use according to these studies. However, all of them were limited and the association was examined in a sub-group analysis; the statistical power was thus insufficient to study some associations. Moreover, most determinants of colorectal cancer were not controlled for in these studies.

2.3.3 Genotoxicity of TCAs and cancer development

2.3.3.1Experimental studies of genotoxicity of TCAs

Van Schaik and Graf [1991,1993] tested the genotoxicity of all tricyclic antidepressants in two similar studies using the somatic mutation and recombination test (SMART) in wing cells of fluit flies, which was used in short-term tests for identifying carcinogens and in examination of the mechanisms of mutagenesis by chemicals [Vogel 1999]. Three-day-old larvae were fed the test antidepressants in water mixed with a standard food for 48 h. Wings of the emerging adult flies were scored for the presence of spots of mutant. They found that *desipramine, imipramine* [1991], and *clomipramine* [1993] were genotoxic, since the frequencies of total spots per wing in treated fluit flies were significantly increased relative to control ranged from 0.1mM to 100mM (the maximum tolerated dose). In contrast, *amitriptyline, nortriptyline, protriptyline* [1991] and *maprotiline* [1993] were not genotoxic. The former three have a nitrogen at position five in the seven-membered central ring, and the latter four have a carbon atom at position five in the six- (*maprotiline*) or seven-membered central ring. Accordingly, the authors hypothesized that the nitrogen atom at position five in the seven-membered ring of tricyclic molecule was responsible for the genotoxicity. The antidepressant *lofepramine* showed a genotoxic impact only at the highest concentration of 100mM (the maximum tolerated dose), although it also have the similar structure with clomipramine and imipramine. This maybe due to its longer and more complex side chain attached to nitrogen at position 5, and is not soluble in water.

Recently, Graf et al [Sharpe 2002] also evaluated the genotoxicity of *amoxapine, doxepin, and trimipramine* using the same assay. As expected on the basis of the structural hypothesis, *trimipramine* was genotoxic (with a nitrogen in the seven-membered central ring). Although *doxepin* has a carbon at position five, it was also genotoxic since its structure is atypical with an oxygen atom at position eleven in the central ring [Budavari 1989]. Similarly, *amoxapine* was genotoxic, since its structure is also atypical having both a nitrogen and an oxygen atom in the central ring.

2.3.3.2 An epidemiological study of the association between genotoxic/non-genotoxic TCAs and the risk of breast cancer

Based on the genotoxicity assessment from experimental studies, Sharpe et al. [Sharpe 2002] conducted post hoc analyses to check whether the two subclasses of TCAs have differentiated carcinogenic effects. That is, whether genotoxic TCAs (clomipromine, desipramine, imipramine, trimipramineclearly, doxepin, and amoxapine), rather than non-genotoxic TCAs (amitriptyline, maprotiline, nortriptyline, protriptyline) associates with an increased risk of breast cancer.

The study extracted data from 2 administrative database: the Saskatchewan Drug Prescription Plan (SPDP) and the Saskatchewan Cancer Registry (SCR). The effect of two sub-classes of TCAs was examined. Dosage, duration, and timing of drug use were considered. In total, 5887 cases of breast cancer and 23,517 age-matched controls were studied. All analyses were controlled for the effects of TCA exposure at various past time intervals, but not for other potential confounding factors.

It was found that a significant increase in the relative risk of breast cancer was associated with TCA exposure in women with more than 10 years' exposure prior to diagnosis, only at the highest exposure category compared with unexposed group (RR=2.02, 95% CI=1.34-3.04). A similar result was found when exposure was measured as the duration of TCA use during each period.

Based on this positive finding, the authors conducted a *post hoc* analysis to compare the effect of genotoxic with non-genotoxic TCAs. Analyses showed an increased risk of breast cancer associated with exposure to genotoxic TCAs 11-15 years prior to diagnosis at the second-highest (adjusted RR=1.93, 95%CI=1.25-2.99) and highest dosages (adjusted RR=2.47, 95%CI=1.47-4.40), compared with unexposed. No increased risk of breast cancer associated with non-genotoxic TCAs was found (during 11-15 years prior to diagnosis, adjusted RR for second-highest dosage = 0.82, 95%CI=0.47-1.41; adjusted RR for highest dosage=0.99, 95%CI=0.49-1.99).

This was the first study that focused on the possible effect of antidepressant genotocixity on the risk of cancer. The advantages of this study included: large sample size and

increased statistical power for sub-group analyses; no selection bias since SPDP provides prescription drug coverage to almost all Saskatchewan residents, and the SCR includes almost all histologically proven cases of cancer in the province; no recall bias since all exposure data were recorded routinely before the diagnosis of cancer; moreover, timing of TCA exposure was also taken into account [Sharpe 2002].

However, the use of administrative database precluded authors from controlling for many known risk factors of cancer, especially those associated with lifestyle and diet. Furthermore, *post hoc* analysis would be more prone to bias than analyses based upon prior hypothesis. Nevertheless, this result generated a huge interesting hypothesis that needs further studies.

2.3.4 Conclusion, rationale and relevance

In summary, the association between antidepressant use and colorectal cancer development is inconclusive.

Tricyclic antidepressant (TCAs) has been the most frequently used antidepressant class. Experimental studies suggested that tricyclic antidepressants (TCAs) might promote colon tumors [Tutton & Barkla 1989, Iishi 1993], but this effect was not able to be confirmed in epidemiological studies [Friedman 1980,1983, Selby 1989, Dalton 2000, Weiss 1998]. However, these epidemiological studies were limited and the association was examined in a sub-group analysis; the statistical power was thus insufficient to study some associations. Moreover, most determinants of colorectal cancer were not controlled for in these studies.

Among several possible carcinogenic mechanisms of TCAs, the genotoxicity of TCAs was considered to be important for cancer development. Animal studies [Van Schaik & Graf 1991, 1993] indicated that TCAs could be classified as two sub-classes: genotoxic and non-genotoxic; genotoxic TCAs would be responsible for cancer development instead of non-genotoxic TCAs. A subsequent *post hoc* analysis in a population-based case-control study supported this hypothesis at breast cancer site [Sharp 2002]. Since

there is no evidence that this effect is site-specific, it is appropriate to ask whether the same effect also applies to colorectal cancer.

In contrast, it appears that another antidepressant class, selective serotonin reuptake inhibitors (SSRIs), has an antineoplastic effect on colon cancer [Tutton & Barkla, 1976,1982]. It is important to examine this hypothesis because SSRIs have already become a "first line" antidepressant and the use has been increasing rapidly since their introduction in 1989; but no epidemiological study has tested it until now.

Examination of the effect of TCAs and SSRIs on the risk of colorectal cancer has obvious implications for physicians prescribing antidepressants. First, given the heavy burden of colorectal cancer, it is helpful to examine and control the modifiable risk factors such as antidepressant use. Secondly, all antidepressants, on average, have equivalent clinical efficacy [Beaumont 1989], and thus the side-effects profile becomes the most influential consideration when selecting an appropriate agent. If proven, the unfavorable impact of TCAs and favorable impact of SSRIs on colorectal cancer development may lead to changes in the clinical choice of certain antidepressant agents.

To verify the potential carcinogenic effect of TCA class and the anti-tumor effect of SSRI class on colorectal cancer, we decided to conduct a population-based nested case-control study using the Saskatchewan databases.

Chapter 3: Objectives and hypotheses

3.1 Objectives

The general objective of this study is to determine whether the use of antidepressant drugs increases the risk of colorectal cancer. More specifically, we decided to conduct a case-control study using Saskatchewan databases to verify whether TCAs increases the risk of colorectal cancer; in particular, whether genotoxic TCAs is responsible for the colorectal cancer development instead of non-genotoxic TCAs; and whether SSRIs protects against the colorectal cancer development. The MAOI class and "atypical" class was not examined in this study because the number of subject exposed was too small to analyze their effect.

3.2 Hypotheses

This study was aimed to test the following hypotheses:

1. The use of TCAs increases the risk of colorectal cancer, as compared to non-use of TCAs.
2. In particular, the use of genotoxic TCAs increases the risk of colorectal cancer, as compared to the non-genotoxic TCAs.
3. The use of SSRIs decreases the risk of colorectal cancer, as compared to the non-use of SSRIs.

Chapter 4: Methods

4.1 Study design

A population-based nested case-control design was used. The dynamic cohort was residents of Saskatchewan who were registered in Saskatchewan Prescription Drug Plan (SPDP) from January 1, 1981 to December 31, 2000. The colorectal cancer patients were identified from Saskatchewan Cancer Registry (SCR). Each case and 4 randomly selected non-cancer controls matched on age, gender and calendar time formed each risk set.

4.2 Source of data

Saskatchewan Prescription Drug Plan (SPDP) and Saskatchewan Cancer Registry (SCR) constituted the primary sources of data.

The information about subjects' medication was obtained from SPDP. SPDP has been functioning since September1975, and covers 91% of Saskatchewan residents (about 1 million) for their expense of outpatient prescription drugs. Non-eligible subjects include people whose health care was covered by federal government (members of the Royal Canadian Mounted Police and Canadian Forces, and registered Indians). Immigrants become eligible to benefit from SPDP three months after arriving, which is recorded as the coverage initiation date. Emigrants lose their eligibility three months after leaving. The data from the July 1, 1987 to December 31, 1988 was not available for this study since SPDP database was incomplete because of administrative changes [Downey 2000].

Information on subjects' cancer status was obtained from the Saskatchewan Cancer Registry (SCR). Complete computerized data was available since 1967. Approximately 95% of cancer ascertainments are from specialist referral or a pathology report, 5% are from death registrations or autopsy, and a small number are through physician claims [Downey 2000]. Two mechanisms ensure that approximately 98% of new diagnosed cancer cases within the province were registered: Provincial law mandates medical professionals and hospitals to report all cancer cases and send copies of malignant

pathology diagnoses to the Registry; to be eligible for payments under this plan, the physicians are required to report all new cases to the Registry [Parkin 1997].

A lifetime unique Health Service Number (HSN) is given to each person who was eligible to benefit. It enables linking records from the SPDP and SCR.

4.3 Study population

The study population included people who were eligible to benefit from SPDP at least five years from January 1, 1981 to December 31, 2000, aged between 5 and 82.5 years, and with no previous cancer history since 1967 (other than non-melanoma skin cancer and carcinoma in situ of the cervix).

To be in this study, subjects must have had at least 5 years exposure information available before the date of diagnosis of cases or the sampling date of the controls. This ensured that sufficiently long records of their drug use would be available for analysis.

The age of study subject ranged from 5 to 82.5 years. Children younger than 5 years of age were excluded since antidepressants have an impact on the development of the central nervous system of small children and thus are rarely prescribed to very young children [Coyle 2000]. Subjects older than 82.5 were excluded because the small number of subjects made the matching difficult.

Eligible subjects had no prior history of cancer since 1967, except for non-melanoma skin cancer or carcinoma in situ of the cervix. These two cancers are often difficult to be registered completely because they are usually treated successfully without requiring hospitalization or the review of a pathologic specimen.

Subjects entered the study population on the latest of the following dates (defined as "entry date"): at the beginning of the study (January 1, 1981) if they were 5-82.5 years of age, on their 5^{th} birthday, or on their coverage initiation date if they were between 5 and 82.5 years of age. Subjects left the study population on the earliest of the following dates

(defined as "exit date"): at the end of the study (December 31, 2000), on the date of diagnosis of colorectal cancer, on the date of death, or on the date of emigration.

The date of diagnosis for cases and the date of sampling for controls were designated as the "index date".

4.4 Cases identification

The cases were subjects who were diagnosed with primary histological proven invasive colorectal cancer that was registered in the SCR since 1967, and had at least 5 years exposure information available from SPDP. Colon cancer (ICD-O-2 code: C18.0-C18.9), cancer at rectosigmoid junction (C19.9), rectal cancer (C20.9), and overlapping lesion of rectum, anus and anal canal (C21.8) were referred to together as colorectal cancer.

4.5 Controls selection

For each case, four controls were randomly selected from the list of potential controls matched on gender, age and sampling date. We selected four controls per case when more available because there would be only a small increase in statistical power with each additional control beyond this point, as compared to the time and cost to obtain more data [Hennekens 1987]. For each case, the controls had to fall into the same age categories (±2.5 years) as the case; the controls had to be alive and free of cancer in the month that the case was diagnosed with colorectal cancer.

Since this study was a part of larger project that studied the effect of antidepressant use on 19 cancer sites, the control selection for each colorectal cancer case was actually a combined procedure that is described as below.

Cases from any of 19 cancer sites were categorized into one of cells defined by gender (male and female), age (2.5 years each), and index date (1-month each). Most cells that contained colorectal cancer cases also contained cases from other cancer sites. The number of controls was determined to ensure at least 4 controls for each case in this cell, i.e. 4 controls per case for the most frequent cancer cases in any special cell. The same

set of controls was then selected for all cases in the same cell. For instance, the cell defined by "female, 60-62.5 years of age, diagnosed with any of 19 cancers in March 1995" may contain 5 colorectal cancer cases, 10 breast cancer cases, 4 ovarian cancer cases, and fewer of other cancer cases. Then 40 female subjects (4 controls per one breast cancer case) who were in the same age category, alive and free of cancer during March 1995 were randomly selected as potential controls for this cell. Thus, there were 8 controls for each colorectal case. For the specific purpose of this study, 4 out of 8 controls were randomly selected finally to ensure 4 controls per colorectal cancer cases.

4.6 Exposure assessment

In this study, we examined the effects of two antidepressant classes, TCAs and SSRIs, instead of individual drugs since the number of subjects using each individual drug was small and may not provide enough power for analyses. TCAs were further separated as genotoxic and non-genotoxic subclasses. The MAOIs and "atypical" antidepressants were not examined because the number of subject exposed was too small.

For each prescription dispensed to the subject, the following information was obtained: the study identification number, the class of antidepressants dispensed (TCAs or SSRIs), the dispensing date, the drug strength (mg/pill), the quantity dispensed (number of pills dispensed), as well as dosage form (pills for all antidepressants).

In this study, two time windows and five exposure definitions were used to estimate the effects of antidepressant on the risk of colorectal cancer:

Time windows	**Exposure definitions**
Overall exposure history	Ever exposed
	Cumulative dosage
	Cumulative duration
Different time periods preceding index date	Average daily dosage during each time period
	Proportion of time (duration) of drug use during each time period

4.6.1 Two Time windows

4.6.1.1 Overall exposure history

Ever and cumulative exposure to antidepressant was estimated based on the overall exposure history. However, this exposure history for different subjects may vary according to the length of time period between the entry date and the index date.

All subjects in this study were required by inclusion criteria to have at least 5 years exposure history available. The longest exposure history used for analyses was 20 years. Although some subjects had exposure history more than 20 years, the number was too small and thus excluded.

For estimating effects of TCAs, the exposure during the year immediately preceding the index date was excluded from the analysis. According to the biological model and the theory of latent period, the exposure in the year immediately preceding diagnosis is unlikely to induce the cancer. Furthermore, the symptoms induced by as-yet-undiagnosed cancer (eg. depression and pain) may increase the prescription of antidepressant agents among cases, and thus results in "reverse causality".

Studies suggest that the latent period of colorectal cancer is at least 10-20 years. Accordingly, the ever exposure and cumulative exposure were estimated only for subjects who had overall exposure history more than 10 years (exposed during 2-15 years and 2-20 years preceding the diagnosis). Since we considered that the effect of cumulative exposure might be attenuated by including the 2-10 years period preceding diagnosis that is irrelevant to cancer initiation, we also examined this effect for 11-20 years exposure period preceding diagnosis.

For SSRIs, we included exposure during the year immediately preceding the index date into analysis. Because we hypothesize that the exposure to SSRIs has an anti-tumor effect, the possible "reverse causality" issue would only attenuate this association. The maximum exposure history for SSRIs was 10 years since they were introduced more recently on the market (since 1989).

4.6.1.2 Successive time periods preceding the index date

To study the effect of the timing of TCA exposure, we divided overall exposure history into four periods: 2-5 years, 6-10 years, 11-15 years, and 16-20 years. For SSRIs, the overall exposure history was divided into two periods: 1-5 years and 6-10 years.

4.6.2 Five exposure definitions

4.6.2.1 Ever exposure

A subject who had at least one prescription for a particular agent during his/her overall exposure history was considered to have ever been exposed to that agent.

4.6.2.2 Cumulative dosage

To combine dosage of different drugs in the same class and ensure the comparability between their effects, we considered the dosage as the number of moles for each drug. It represents the number of molecules reaching the target organ if all prescribed agents were consumed. The total number of moles of each drug dispensed was calculated from the quantity (number of pills), the strength (mg/pill), and the molecular weight given in the Merck Index [Budavari 1989]. The total number of moles dispensed for each class or subclass of antidepressant during the overall exposure history was summed up to represent cumulative dosage for a given class.

4.6.2.3 Cumulative duration

The duration of antidepressant treatment was not recorded in SPDP. To get an estimate of this duration we calculated the number of 3-month periods during which a drug had been prescribed. The overall exposure history of a patient was divided into successive periods of 3-months (91 days). The total number of 3-month periods during which at least one prescription for a particular class of antidepressant was dispensed was then counted. The cumulative duration was estimated by the total number of periods during which a given class of antidepressant was prescribed. This method of characterizing drug duration was considered to be appropriate for antidepressants that are prescribed for continuous daily use over relatively long time period.

4.6.2.4 Average daily dose during each time period

The average daily moles of a given class of antidepressant during each 5-year time period preceding the index date was calculated. The number of moles dispensed for each drug class was calculated according to drug quantity and strength. The sum of moles for a given class of antidepressant during a given period was then divided by the number of days during this period. For instance, during the 6-10 years period preceding the index date, if a subject was prescribed clomipramine (genotoxic TCA) for the first 6 month, followed by amitripline (non-genotoxic TCA) for the next 6 month, followed by desipramine (genotoxic TCA) for the next 12 months, followed by fluoxetine (SSRIs) by the next 30 months, followed by no antidepressant for the last 6 months, we added the total numbers of moles of clomipramine and desipramine dispensed during this 5-year period and divided by 1825 days (365days/year x 5 years) to obtain the average daily moles for genotoxic TCAs dispensed. We then calculated the total moles of amitriptyline and fluoxetine dispensed, respectively, and divided this number by 1825 days to get the average daily moles for non-genotoxic TCAs and SSRIs, respectively, during this 5-year period.

4.6.2.5 Duration of exposure during each time period

Each 4-year (2-5 years) or 5-year period (6-10 years, 11-15 years, and 16-20 years) was divided into 16 or 20 periods of 3-months (91 days). The number of 3-month periods during which a prescription for an antidepressant was dispensed was counted. Duration of drug use during a given time period was estimated as the proportion of time during which the subject was dispensed at least one agent. For instance, a presumed drug use during 11 of 20 three-month periods will be considered to be exposed 55% of time.

4.6.3 Categorization of exposure distribution

The distribution of cumulative dosage and average daily dose for TCAs were used to divide those exposed into three equal intervals (low, medium and high). Similarly, the distribution of cumulative duration and duration during each time period were used to divide those exposed into 3 equal intervals (short, medium and long). However, the

distribution for SSRIs was divided into two intervals (low and high, or short and long) as the number of SSRI users was small.

4.7 Covariates assessment

4.7.1 Demographic factors

Age and gender were taken into account by matching between cases and controls as described in section 3.5.

4.7.2 Other prescribed medications

Besides antidepressants, information on other outpatient prescription medications is available from the SPDP. Among them, the NSAIDs, estrogen, and oral contraceptives were considered as potential confounders and their exposures were estimated.

The only information available for potential drug confounders included the dispensing date and the class of drug dispensed. The total number of prescriptions during overall exposure history was used to estimate the cumulative exposure to a given class of drug confounders. The average number of prescriptions per year for a given class of drug confounders during each time period preceding the index date was also used to estimate the average exposure to each drug class during that period. The distribution of estimated exposure was used to divide those exposed into 2 equal intervals (low and high).

4.8 Incomplete information

Firstly, the exposure information between the July 1, 1987 and December 31, 1988 was not available for this study. Therefore, all subjects whose index date occurred after July 1, 1987 may have some missing exposure information due to this 1.5-year gap. In this situation, we considered subjects to be unexposed to any drug during this time period.

The second source of incomplete exposure data is due to varied entry date of subjects. If, for instance, an immigrant was eligible to benefit from SPDP 8 years before his/her index date, the exposure information was complete during years 2-5, incomplete during years 6-10, and missing during years 11-15 and 16-20. In this situation, we categorized this

subject into a separate exposure category designated as "other" during periods for which we have incomplete or missing information, distinct from unexposed group (referent) and any of exposed groups. This approach permitted each subject to contribute to the periods during which they have complete information, rather than excluding those with incomplete information.

4.9 Statistical analyses

We calculated odds ratios (ORs) to estimate incidence rate ratios (RRs) with conditional logistic regression for matched data [Allison 1999]. 95% confidence interval was computed and $p<0.05$ (two-sided) was used as the criterion of statistical significance. Exposure to antidepressant was represented by categorical variables to estimate the RRs for each category. We also tested the linear trends of the continuous variable itself, by examining the significance of the coefficients with a chi-squared test (p-tend represents the p value of test for linear trend). The power of estimated association would be larger by considering the exposure as continuous scale.

The basic model used to represent the average exposure during successive time periods before the index date is: $\mathbf{Log(p/1-p)= \beta_1 X_{2\text{-}5years} + \beta_2 X_{6\text{-}10years} + \beta_3 X_{11\text{-}15years} + \beta_4 X_{16\text{-}20years}}$
Where p represents the probability of being diagnosed with colorectal cancer, the values of β_i represents regression coefficients, and the values of X_i represents drug exposure during different time periods preceding the index date.

The exposures during different time periods were included in the same model because antidepressants are usually used to treat chronic conditions and thus exposure during one period is likely to be associated with exposure during another.

Because some subjects used both genotoxic and non-genotoxic TCAs, we included exposures to them into a single model to control the potential confounding between them. This confounding was also controlled by restriction: the RRs according to exclusive exposure to each TCA subclass and exposure to both subclasses were estimated, as compared to the common referent group of unexposed to any TCAs.

The effect of NSAIDs exposure was always controlled in analyses because there is a general agreement that use of NSAIDs is associated with reduced risks of colorectal cancer. Estrogen and OCs were included in the multivariate model to check whether they would significantly affect the association between antidepressants and colorectal cancer. If RRs were changed above 10% by including estrogen or OCs, their effects would be adjusted in the multivariate model.

4.10 Power calculation

The following information were used to calculate the statistical power to detect increased incidence rate ratio (RR) in those exposed to TCAs, as compared to those unexposed to TCAs: The number of colorectal cancer cases (6544); the estimated prevalence of exposure to TCAs in non-cancer control population; the minimum incidence rate ratio to be detected; the matching ratio (1:4); as well as the type I error (0.05). Statistical power is shown in the table according to prevalence of exposure and detectable minimum RRs.

		Prevalence of exposure to TCAs in control population				
Minimum RRs to be detected		0.02	0.05	0.1	0.12	0.15
	1.2	51%	85.5%	98%	99%	99.8%
	1.3	82%	99%	100%	100%	100%
	1.4	96%	99.99%	100%	100%	100%
	1.5	99.5%	100%	100%	100%	100%
	2.0	100%	100%	100%	100%	100%

4.11 Ethical Consideration

Research ethics committee of the Sir Mortimer B. Davis-Jewish General Hospital approved the study design and conduct (Appendix). Precautions were taken to maintain the anonymity of the study participants. Employees of the Saskatchewan Cancer Agency and Saskatchewan Health prepared the data from SCR and SPDP, and designated "study identification numbers" for each subject. This number was used to link different databases in this study, but could not be associated in anyway to the "health service identification number" in Saskatchewan databases. It was not deemed necessary to collect an individual consent from each individual.

Chapter 5: Results

5.1 Descriptive analyses

The study population consisted of 6544 cases and 26176 controls. **Figure 1** shows that the annual incidence of colorectal cancer (1981-2000) fluctuated without showing any obvious trend.

The case group and control group comprised 57% males and 43% females, respectively, with a ratio of 1.3:1 **(Figure 2).** The age of cases and controls ranged from 24.6 to 81 years and from 24 to 82.5 years, respectively, with a mean age of 66.8 years. 80% of cases (5037) and controls (20148) were over 60 years of age **(Figure 3).**

Some 8.5% of the cases and 8.9% of the controls had received a prescription for a TCA. Some 2.7% of the cases and 3.2% of the controls had received a prescription for a SSRI.

5.2 Effects of TCAs on colorectal cancer

5.2.1 Ever exposed, cumulative dosage, and cumulative duration

5.2.1.1 Fifteen years overall exposure history

Table 4 shows the rate ratios of colorectal cancer according to ever exposed, cumulative dosage and cumulative duration of TCAs for subjects who had 15 years of overall exposure history. Overall, the use of TCA class tends to protect against colorectal cancer although with no statistical significant.

After taking into account the effects for matching factors, the RRs for colorectal cancer according to ever exposed to any TCAs, to genotoxic TCAs, and to non-genotoxic TCAs were all lower than 1, with borderline statistical significance among subjects ever exposed to any TCAs (RR=0.89, 95%CI=0.80-0.99).

After adjustment for matching factors and cumulative exposure to NSAIDs, neither cumulative dose nor cumulative duration was found to be significantly associated with an increased risk of colorectal cancer during the 2-15 year period preceding the index date

(for cumulative dose of any TCAs: RR_{high}=0.89, 95%CI=0.73-1.07, RR_{medium}=0.94, 95%CI=0.79-1.12, RR_{low}=0.95, 95%CI=0.81-1.12; for cumulative duration of any TCAs: RR_{long}=0.74, 95%CI=0.52-1.06, RR_{medium}=0.92, 95%CI=0.70-1.20, RR_{short}=0.98, 95%CI=0.81-1.17).

5.2.1.2 Twenty years overall exposure history

Table 5 shows the rate ratios for colorectal cancer according to ever exposed, cumulative dosage and cumulative duration of TCAs for those who had completed 20 years of overall exposure history.

After taking into account the effects of matching factors, the RRs according to ever exposed to any TCAs and to TCA subclasses were shown to be lower than or close to 1 without statistical significance (RR for any TCAs=0.96, 95%CI=0.84-1.10; RR for genotoxic TCAs=0.79, 95%CI=0.63-1.10; RR for non-genotoxic TCAs=1.01, 95%CI= 0.83-1.24).

The risk of colorectal cancer tended to increase with higher cumulative dose of any TCAs although there was no statistical significance (RR_{low}=0.89, 95%CI= 0.72-1.10; RR_{medium}=1.06, 95%CI=0.82-1.29, RR_{high}=1.20, 95%CI=0.94-1.53). The exposure to medium cumulative duration of any TCAs was found to be associated with a higher risk of colorectal cancer (RR=1.29, 95%CI=1.02-1.62), compared to the non-use of any TCAs.

No increased risk of colorectal cancer was found for cumulative exposure to genotoxic TCAs. While the cumulative exposure to non-genotoxic TCAs were found to be associated with an increased risk of colorectal cancer among those exposed to high cumulative dosages (RR=2.04, 95%CI=1.30-3.22) and long cumulative duration (RR=1.95, 95%CI=1.17-3.25), after adjustment for age, gender and cumulative exposure to NSAIDs. The risk of colorectal cancer tended to increase with heavier use of non-genotoxic TCAs, but there is no significant p-trend was found (p-trend for cumulative dose=0.32, p-trend for cumulative duration=0.61).

Since we considered that exposure during the 10 years period preceding diagnosis might attenuate the effect of cumulative exposure, we also analyzed the effect of cumulative exposure to TCAs during the 11-20 year period preceding diagnosis **(Table 6).** The increased risk of colorectal cancer was associated with cumulative exposure to any TCAs among medium duration category (RR=1.41, 95%CI=1.07-1.85), as well as cumulative exposure to non-genotoxic TCAs among medium duration group (RR=1.83, 95%CI=1.14-1.96).

5.2.2 Average daily dosage during different time periods preceding the index date

Table 7 shows the RRs for colorectal cancer associated with exposure to any TCAs and to each subclass of TCAs, according to the average daily dosage during different time periods preceding the index date. A subject was categorized into "other" group if exposure information was incomplete or missing during a given time period.

The right panel of table 7 shows the RRs for colorectal cancer associated with exposure to any TCAs, after adjustment for matching factors, exposure to NSAIDs, and exposure to TCAs during other time periods. Only exposure to any TCAs among medium category during 16-20 years period was associated with a significantly increased risk of colorectal cancer (RR=1.51, 95%CI=1.09-2.09). However, no significant p-trend was found for any time period.

The middle two panels of table 7 show the RRs for colorectal cancer associated with exposure to genotoxic and non-genotoxic TCAs, after adjustment for matching factors, exposure to NSAIDs, and exposures to TCAs during other time periods. Because some subjects used both genotoxic and non-genotoxic TCAs, we included variables representing exposure to each subclass in a single logistic model to control possible confounding effect of one subclass by another.

No significantly increased risk of colorectal cancer was found for genotoxic or non-genotoxic TCAs during any of the time periods studied. Several slightly increased RRs

were found during the 16-20 years preceding the index date, with 95% CI covered 1 (For non-genotoxic TCAs: RR_{low}=1.20, 95%CI=0.87-1.67; RR_{medium}=1.33, 95%CI=0.84-2.12; RR_{high}=1.43, 95%CI=0.75-2.73; p-trend=0.78; For genotoxic TCAs: RR_{low}=0.91, 95%CI=0.64-1.29; RR_{medium}=1.34, 95%CI=0.89-2.10, RR_{high}=0.69, 95%CI=0.36-1.34; p-trend=0.65).

5.2.3 Exclusive exposure to genotoxic and non-genotoxic TCAs (average daily dosage) during different time periods preceding the index date

Table 8 shows the RRs for colorectal cancer associated with exclusive exposure to each TCA subclass and exposure to both subclasses, as compared to the common referent group of the unexposed to any TCAs.

The highest RR for exclusive exposure to genotoxic TCAs was found in the medium exposed category during the 16-20 years period (RR=1.38, 95%CI=0.84-2.26). The highest RR for exclusive exposure to non-genotoxic TCAs was found in the high exposed category during the 16-20 years period (RR=1.87, 95%CI=0.85-4.12). However note that in both cases the 95%CIs included the null value of 1.0.

The right panel of table 8 shows the ratios between RRs for exclusive genotoxic TCAs and RRs for exclusive non-genotoxic TCAs. The ratios did not suggest that the use of genotoxic TCAs was associated with an increased risk of colorectal cancer, as compared to the non-genotoxic TCAs.

5.2.4 Duration of exposure during different time periods preceding the index date

Table 9 shows the RRs for colorectal cancer associated with exposure to each subclass of TCAs and to any TCAs, according to the duration (proportion of time) of exposure during different time periods preceding the index date.

The right panel of Table 9 shows the RRs for colorectal cancer associated with exposure to any TCAs after adjustment for matching factors, exposure to NSAIDs, as well as exposure to TCAs during other time periods. Exposure to any TCAs among the

long duration group during the 16-20 year period was associated with a significantly increased risk of colorectal cancer (RR=1.60, 95%CI=1.13-1.27). Whereas exposure to any TCAs among the short duration group during the 6-10 years period was associated with a significant decreased risk of colorectal cancer (RR=0.84, 0.71-0.98). However, no significant P-trend was found during any time period.

The middle two panels of Table 9 show the RRs for colorectal cancer associated with exposure to genotoxic and non-genotoxic TCAs, after adjustment for matching factors, exposure to NSAIDs, and exposure to TCA during other time periods. No significantly increased risk of cancer was found among subjects exposed to genotoxic TCAs. Only exposure to non-genotoxic TCAs among the medium duration category during the 16-20 years period preceding the index date was associated with a significantly increased risk (RR=1.89, 95%CI=1.14-3.14). However, again no significant P-trend was found.

5.2.5 Exclusive exposure to genotoxic and non-genotoxic TCAs (duration) during different time periods preceding the index date

Table 10 shows the RRs for colorectal cancer associated with the duration of exclusive use of TCAs overall and to each subclass, as compared to the common referent group of the unexposed to any TCAs.

The exposure to genotoxic TCAs among the short duration group during the 6-10 years period was associated with a decreased risk of colorectal cancer (RR=0.72, 95%CI=0.57-0.92). However, no significant P-trend was found.

The highest RRs associated with genotoxic and non-genotoxic TCAs were both found among the medium duration group during the 16-20 years period ($RR_{genotoxic}$=1.25, 95%CI=0.71-2.21, $RR_{non\text{-}genotoxic}$=1.74, 95%CI=0.92-3.28), without statistical significance. No significant P-trend was found for either subclass during any time period.

5.3 Effect of SSRIs on colorectal cancer

5.3.1 Ever exposed, cumulative dosage, and cumulative duration

5.3.1.1 Ten years exposure history

Table 11 shows the rate ratios for colorectal cancer according to ever exposed, cumulative dosage and cumulative duration of SSRIs for those who had a complete 10 years of overall exposure history (3787 cases and 15113 controls).

Ever exposed to SSRIs during the 10 year period preceding the index date tended to be associated with a decreased risk of colorectal cancer (RR=0.85, 95%CI=0.70-1.04) although the reduction was not statistically significant at the 0.05 level.

A significant decreased risk of colorectal cancer was found to be associated with the exposure to a high cumulative dosage during the 10 years preceding diagnosis (RR=0.69, 95%CI=0.50-0.97), but not with exposure to low cumulative dosage (RR=1.01, 95%CI=0.78-1.30). Also shown was a significantly decreased trend in the risk of colorectal cancer as the cumulative dosage of SSRIs exposure increased (P-trend=0.04).

The exposure to both short (<6months) and long (>6months) cumulative duration of SSRIs were associated with a decreased risk of colorectal cancer (RR_{short}=0.93, 95%CI=0.71-1.21; RR_{long} =0.80, 95%CI= 0.59-1.09, P-trend=0.08). However, none of these associations were statistically significant.

5.3.1.2 Five years exposure history

Table 12 shows the rate ratios of colorectal cancer according to ever exposed, cumulative dosage and cumulative duration of SSRIs for those who had a complete 5 years exposure history (3859 cases and 15436 controls).

Being ever exposed to SSRIs during 5 years period preceding the index date was associated with a decreased risk of colorectal cancer (RR=0.83, 95%CI=0.67-1.02).

A significantly decreased risk of colorectal cancer was found to be associated with the exposure to a high cumulative dosage during the 5 years preceding the index date (RR_{long}=0.64, 95%CI=0.45-0.92), but not with exposure to a low cumulative dosage

(RR=0.98, 95%CI=0.75-1.29). There was also a significantly decreased trend in the risk of colorectal cancer as the cumulative dosage of SSRIs exposure increased (P-trend=0.02).

The exposure to both short and long cumulative duration of SSRIs were associated with decreased risk of colorectal cancer, with borderline significance among those exposed for a long time (RR_{short}=0.93, 95%CI=0.70-1.23; RR_{long}=0.71, 95%CI= 0.51-1.00). There was also a significant decreased trend for risk of colorectal cancer as the cumulative duration increased (P trend=0.02).

5.3.2 Average daily dosage of SSRI exposure during different time periods preceding the index date

Table 13 shows the RRs for colorectal cancer according to average daily dosage of SSRIs in each 5-year period preceding the index date.

The exposure to SSRIs during the 1-5 year period was associated with a decreased risk of colorectal cancer, with statistical significance among high exposure group (RR_{low}=0.99, 95%CI=0.75-1.30; RR_{high}=0.62, 95%CI=0.43-0.90; P-trend=0.01). No such association was found during the 6-10 years period (RR_{low} =1.18, 95%CI=0.76-1.85; RR_{high}=1.29, 95%CI=0.67-2.50, P-trend=0.24). These associations were adjusted for matching factors, exposure to NSAIDs, as well as exposure to SSRIs during the other 5-years period.

5.3.3 Duration of SSRI exposure during different time periods preceding the index date

Table 14 shows the RRs for colorectal cancer according to duration of SSRI use in each 5-year period preceding the index date.

The exposure to SSRIs during the 1-5 year period preceding diagnosis was associated with a decreased risk of colorectal cancer, with statistical significance among the long duration group (RR_{short}=0.92,95%CI=0.70-1.22; R_{long}=0.71, 95%CI=0.50-1.01, P-trend=0.008). No such association was found in the 6-10 years period preceding

diagnosis (RR_{short} =1.12, 95%CI=0.71-1.76; RR_{long} = 1.38, 95%CI=0.72-2.64, P-trend=0.26). These associations were adjusted for matching factors, exposure to NSAIDs, as well as exposure to SSRIs during the other 5 years period.

5.3.4 Separate estimate of the effect of SSRI exposure during the year immediately preceding the index date

Table 15 shows adjusted RRs for colorectal cancer according to the average daily dosage of SSRI use during 0-1, 2-5 and 6-10 years preceding diagnosis. The decreased risks of colorectal cancer were still observed during the 2-5 years period preceding diagnosis, with a significantlyx decreasing trend (RR_{low}=0.93, 95%CI=0.66-1.30; RR_{high}=0.51, 95%CI=0.32-0.82; P-trend=0.03).

However, the exposure during the 0-1 year period preceding diagnosis was not found to be significantly associated with the decreased risk of colorectal cancer (RR_{low}=0.84, 95%CI=0.44-1.62; RR_{high}=1.22, 95%CI=0.84-1.75, P trend=0.08).

Table 16 shows adjusted RRs for colorectal cancer according to the duration of SSRI use during the 0-1, 2-5 and 6-10 years preceding diagnosis. The decreased risks of colorectal cancer were observed during the 2-5 years period preceding diagnosis, with a borderline significantly decreasing trend of cancer risk (RR_{short}=0.89, 95%CI=0.64-1.24; RR_{high}=0.64, 95%CI=0.40-1.05; P trend=0.056).

During the year immediately preceding diagnosis, a decreased risk of colorectal cancer was observed among those exposed to long duration (RR_{long}=0.71, 95%CI=0.39-1.30, P trend=0.42), but not among those exposed to short duration (RR_{low}=1.26, 95%CI=0.80-1.79, P trend=0.42).

A slightly increased risk of colorectal cancer was found among subjects exposed to SSRIs during the 6-10 year peered preceding diagnosis, but with wide confidence intervals covered 1 (RR_{short}= 1.13, 95%CI=0.72-1.79; RR_{high}=1.53, 95%CI=0.79-2.97, P trend=0.12).

Chapter 6: Discussion

6.1 Strengths and limitations of the study

6.1.1 Advantages of using administrative databases

The population-based case-control design used data from the Saskatchewan administrative databases (SPDP and SCR). There are four main advantages associated with this approach: large sample size, minimization of selection bias, avoidance of recall bias, and availability of long exposure history.

Firstly, the provincial coverage databases allowed us to identify all the cases and to randomly select controls within the whole Province (more than 1 million persons). The large sample size increased the statistical power and precision of estimates for primary analyses and created opportunities for subgroup analyses.

Secondly, selection bias was minimized because the SCR includes almost all colorectal cancer cases in the Province. Selection bias with respect to controls is very unlikely since the SPDP covers prescription drug expenses for almost all Saskatchewan residents, and it is unlikely that the random sampling of controls from the database was in any way related to antidepressant use.

Thirdly, recall bias was avoided since all the medication exposure information was routinely recorded before the diagnosis of cancer, and there were a number of validation checks made of the data [Downey 2000].

Finally, relatively long overall exposure history was available (maximum 20 years in our study) since the SPDP has been functioning since 1976. Psychological conditions requiring antidepressants are usually of a chronic nature, with use of antidepressants extending into the remote past. Moreover, a long lag period is generally thought to be needed between initiation and the diagnosis of colorectal cancer. Thus the availability of long exposure history allowed us to detect the roles of both remote and recent uses of antidepressant on the development of colorectal cancer.

6.1.2 Advantage of using multiple exposure definitions

Different exposure definitions (ever exposed, cumulative exposure, and timing of exposure) were used to represent the different aspects of antidepressant exposure and to complement each other.

Ever use of antidepressants was considered as a preliminary and crude estimate since the development of cancer is related to both dosage and duration of exposure. The cumulative dosage and cumulative duration of exposure were then used to address these aspects. However, cumulative exposure during overall exposure history may mix recent exposure which is not relevant to the initiation of cancer and remote exposure which is more relevant to initiation. The timing of exposure was then used to detect what would be the respective effects of recent and past exposure on the development of colorectal cancer, after controlling the mutually confounding effect due to exposure during other time periods. This could also help to determine whether antidepressant use was more likely to have effect at the initiation or promotion phase of colorectal cancer development.

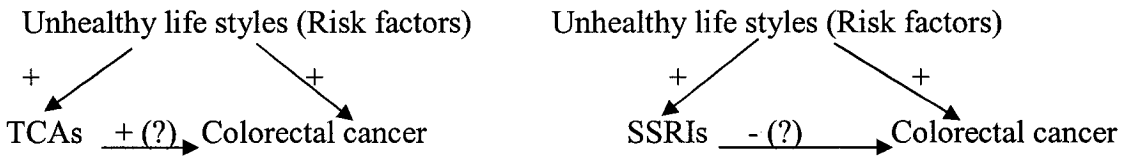
In this study, we did not distinguish the effects between those exposed to high doses during short time periods and those exposed to low doses with prolonged duration since major depression is characterized by long initial treatment and even longer maintenance treatment to prevent early relapse or recurrence (section 2.2.2.2.4). In clinical settings, it is unusual to use extremely high dosage antidepressant during a short period.

6.1.3 Control of confounding

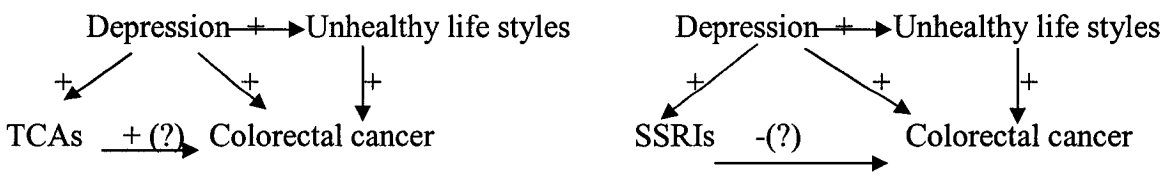
6.1.3.1 Uncontrolled confounding

In our study, it was impossible to adjust for some important determinants of colorectal cancer except for medication use because such information was not recorded in the databases (e.g. smoking, diet, etc). This is the main limitation of using an administrative database containing previously collected data.

Uncontrolled confounding may affect the estimated association between use of TCA class or SSRI class and the risk of colorectal cancer. For instance, people with unhealthy life style are more likely to be exposed to the risk factors of colorectal cancer (Table 1), such as obesity, physical inactivity, smoking, alcohol drinking, diet with high fat and red meat, and diet with low vegetables and fruits. These people may also tend to use more medications including antidepressants than healthy subjects do. Therefore, uncontrolled confounding effects of these risk factors may lead to an overestimation of carcinogenic effect of TCA use and an underestimation of anti-tumor effect of SSRI use on colorectal cancer.



Despite little convincing evidence there is a general concern that depression may be associated with the development of cancer. However, most of epidemiological studies were not able to distinguish the effect of depression from antidepressant use due to the difficulty of measuring depression accurately. Depression is considered as a positive confounder for TCA-cancer association and a negative confounder for SSRI-cancer association because depressive symptoms increase antidepressant use and may associated with colorectal cancer through two pathways. Firstly, depression may increase the risk of colorectal cancer as a result of immunology and endocrine dysfunction. Secondly, depressive people may be associated with unhealthy lifestyle and diet habit (obesity, little physical activities, more smoking and alcohol drinking, and diet with high fat and low fiber), and thus increase the risk of colorectal cancer.



Nevertheless, it is unlikely that the uncontrolled confounding effect would have an impact on our second research question, i.e. whether the use of genotoxic TCA increases

the risk of cancer as compared to the use of non-genotoxic TCA. To estimate this association, two incidence rate ratios were compared. One is the rate ratio of exposure to exclusive genotoxic TCAs compared to those unexposed to any TCAs (RR_G). The other is the rate ratio of exposure to exclusive non-genotoxic TCAs compared to those unexposed to any TCAs (RR_N). Although the RR_G and RR_N themselves might be affected by uncontrolled confounders, the ratio of these two rate ratios (RR_G/RR_N) should provides an unbiased estimate of the relative risk of colorectal cancer among subjects exposed to genotoxic TCAs compared to those exposed to non-genotoxic TCAs as there is no evidence that the choice of genotoxic or non-genotoxic TCAs is related to any recognized determinants of colorectal cancer.

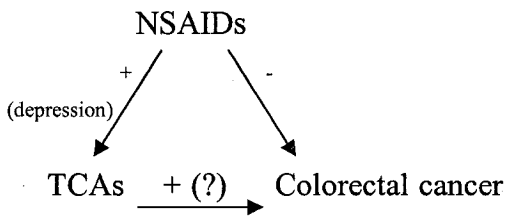
6.1.3.2 Residual confounding of other medication use

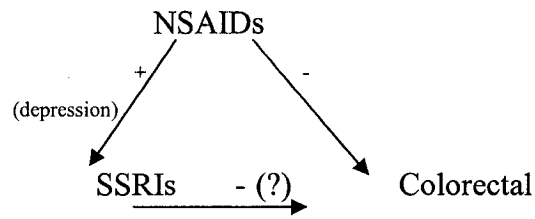
Some patients may be "mixed users", i.e. switched from one class of antidepressant to another because of either ineffectiveness or unfavorable adverse effects. However, we did not control for the effects of other antidepressant classes when we estimated the effect of a given class. For instance, when we examined the effect of TCAs, we did not controlled for other antidepressant classes such as SSRIs. When we estimated the effect of genotoxic TCAs, the only controlled antidepressant class is non-genotoxic TCAs. By doing so, residual confounding may exist since both reference group (e.g., non-use of TCAs) and exposure group (e.g., use of TCAs) may be "non-exclusive" TCAs users.

The impact of this residual confouding may lead to impredictable consequences in terms of the magnitude of the "adjusted" estimates. For instance, it is possible that few of subjects exposed to TCAs have used SSRIs whereas many subjects in unexposed group have used SSRIs due to their insensitivity to or side-effects of TCAs. If most of SSRIs users in the unexposed group were cases of colorectal cancer and the SSRIs use protected against the cancer, it might lead to an increase of association. On the other hand, if most of SSRIs users in the unexposed group were non-cases, the increased risk of the cancer due to TCAs use might be underestimated. The similar impact may exist for estimating the effect of SSRIs.

The other source of residual confounding is the limited information available for controlled medication covariates. For instance, the exposure to NSAIDs and estrogen were roughly estimated by the number of prescriptions per year without taking dosage and duration into account since the only information available with respect to these medications is the prescription date.

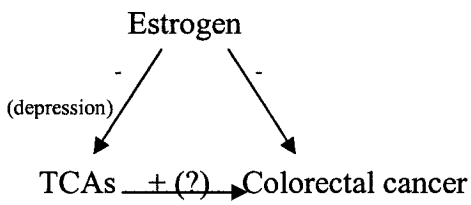
We considered NSAIDs as a negative confounder in the association between TCA use and colorectal cancer risk, whereas a positive confounder in the association between SSRI use and risk of colorectal cancer. Because there is a general agreement that NSAIDs is a protective factor of colorectal cancer; some anti-inflammatory and analgesic drugs might precipitate depression (indomethacin, phenylbutazone, etc) [Scott 1996, Well 1997] and thus tend to increase the use of antidepressants. Moreover, depressive patients might tend to use more medications including NSAIDs than healthy subjects.

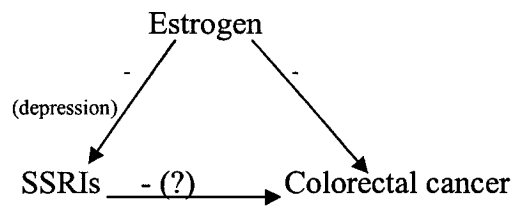




cancer

We considered estrogen as a possible positive confounder for associations between antidepressant use (both TCAs and SSRIs) and the risk of colorectal cancer. It is suggested that exogenous estrogen is a protective factor for colorectal cancer development, although the evidence is not as strong as that for NSAIDs. On the other hand, there is growing evidence suggesting that "estrogen may be efficacious as a sole antidepressant for depressed perimenopausal women" [Halbreich 2001]. That is, women who use exogenous estrogen are less likely to develop depression and use antidepressants as compared to women who do not use it.





6.1.4 Representation of exposure

6.1.4.1 Incomplete or missing information

We considered subjects whose exposure history covered the period July 1, 1987 to December 31, 1988 to be unexposed to any drug during this 1.5-year period. This would result in the underestimation of exposure if subjects had some prescriptions during this time period. However, since it was unlikely that this misclassification of exposure was related to the status of case and control, this nondifferential misclassification would attenuate the estimates of association towards the null. We consider that the extent of this attenuation would not be large because the 1.5-year is a short time period relative to overall exposure history (5-20years).

Due to the different coverage initiation date of subjects who benefit from SPDP, the length of the subjects' exposure records varied, which ranged from 5-20 years in length. The number of subjects reduced as the required length of exposure history increased. For instance, the number of subjects who had complete 20 years exposure record was much smaller than the number of subjects who had complete 5 years exposure record. Hence, the study would have less statistical power to detect significant associations between exposure in the remote past and the diagnosis of cancer than between recent exposure and the diagnosis of cancer. For instance, we can see from table 7 that the number of exposed cases during 15-20 years is smaller than that during 1-5 years, 6-10 years and 11-15 years because most of subjects had no complete records during 16-20 years preceding diagnosis and was categorized to the "other" group.

6.1.4.2 Prescription instead of consumption

Although a study using the Medicaid database demonstrated that the assessment of antidepressant use through claims for filled prescriptions to be an accurate assessment of drug exposure [Lessler 1984], there is no such an evidence based on the Saskatchewan Prescription Drug Plan. The total amounts of molecules that actually reach the target organ might be overestimated if subjects filled prescriptions for antidepressants but did not consume all the medication. It is unlikely that this overestimation of exposure is

associated with the disease status, so this non-differential misclassification would bias the association between antidepressant use and colorectal cancer risk.

6.1.4.3 Drug class instead of individual drugs

The analysis was stratified by pharmacological class of drug because the numbers of subjects using each individual agent within each class was small, and switching drugs between classes was less frequent than switching within class. We assumed that each class of antidepressant had the same effect on the development of colorectal cancer, although the classification was based on their chemical mechanisms to treat psychological illness.

6.1.5 Representation of disease

The identification of cancer cases unlikely depends on exposure status of study subjects and has little effect on observed association of antidepressant use and the risk of colorectal cancer.

It is possible that diagnostic criteria could have changed over 20 years or varied among pathologists. This might lead to misclassification with respect to the diagnosis of the tumors: some tumors classified as "invasive" could have actually been "non-invasive" (e.g. adenoma) or vice versa. However, there is no evidence that the diagnosis of invasiveness would depend on antidepressant exposure. Also, pathologists do not consider antidepressant exposure when examining colorectal tissues. There is no evidence that antidepressant use alters the appearance of colon or rectum tissues so as to affect pathological diagnosis. This non-differential misclassification might slightly bias the results towards the null.

The cancer registry is likely to have been nearly complete (approximately 98%) because of strategies described in section 4.2. The number of controls who had actually been diagnosed with invasive colorectal cancer but which was not reported before the sampling date would be very small and have no effect on the results.

6.1.6 Statistical analysis

As the number of statistical tests rises, the probability of wrongly rejecting the null hypothesis increases. For instance, an experiment with 20 independent statistical tests, with each test assigned a standard level of 0.05, the probability of finding at least one spurious significant association is 64%. This increases to 79% with 30 tests [Fisher 1993]. While adjusting for multiple tests would not have affected the point estimates, it would have widened the confidence intervals and erased the "significant" associations reported. Therefore, each result should be interpreted according to the strength of the priori hypothesis we had regarding drug effects.

To study the effect of timing of exposure, we considered exposure during different time periods to represent separate determinants. So we included exposures during different time periods in the same multivariate model to control their mutual confounding. Although most of point estimates were changed very little by adjustment of exposure during other time period, there are a few big changes (above 10% of crude rate ratios). For instance, the rate ratio for long duration of any TCA use during 16-20 years is 0.98 (95%CI=0.62-1.54) before adjustment and 1.22 (95%CI= 0.74-2.01) after adjustment (Table 9, crude RRs not shown). The rate ratio for medium duration of exclusive genotoxic TCA use during 11-15 years is 1.38 (95%CI= 0.89-2.12) before adjustment and 0.80 (95%CI= 0.51-1.26) after (Table 10, crude RRs not shown). Moreover, because of the large number of estimates in tables, we decided to report only adjusted RRs in final tables to keep them simple and clear.

There was no highly correlation between exposures during different time period (correlation coefficient<0.55). The multicollinearity was not a problem in analyses (the "tolerance" for any variable was above 0.40).

6.2 Interpretation of results

Of 10 published epidemiological studies that investigated the association between antidepressants and the risk of cancer, only three studies included a sub-group analysis of this association on colorectal cancer (section 2.3.2).

Friedman et al [1980,1983,1989,1992] conducted a systematic screening of 215 medical drugs or drug groups for possible carcinogenic effects on 56 cancer sites (including colon and rectum) with a maximum follow-up of 19 years. Neither of the two tricyclic antidepressants assessed (amitriptyline: non-genotoxic; imipramine: genotoxic) was found to be significantly associated with the development of all cancers combined or with any specific cancer. However, insufficient statistical power, rough assessment of exposure (ever/never), and failing to control most of the known cancer-related risk factors were the main limitations in this study.

Dalton et al [2000] conducted a population-based cohort study to assess the association between the use of antidepressants (TCAs, MAOIs, SSRIs) and the risk of cancer in any site (including colon and rectum). No overall increased cancer risk or increased risk of colorectal cancer was found. However, the problems of insufficient statistical power and uncontrolled known risk factors for cancer also existed. The short follow-up period (average 3.2 years) in this study also limited the ability to detect long term drug-cancer associations.

Weiss et al [1998] indicated that the use of any antidepressants or antihistamines would not accelerate tumor growth. During an average 2.2 years follow-up, the use of these two medications showed no association with the increased risk of colon cancer recurrence. However, this study could not rule out the possibility that antidepressant use could affect the growth of colorectal cancer because the power was insufficient.

In summary, no conclusions about the association between antidepressant use and the risk of colorectal cancer can be made based on these studies because of their obvious limitations.

6.2.1 The effect of TCA class on colorectal cancer risk

6.2.1.1 The potential carcinogenic effect of TCA class on colorectal cancer: no sufficient supporting evidence

Overall, there is no sufficient supporting evidence in this study for the primary hypothesis that the use of TCAs increases the risk of colorectal cancer, as compared to non-use of TCAs.

6.2.1.1.1 Ever exposed and cumulative exposure to TCA class

According to the ever exposed and cumulative exposure measures during 20 years preceding the index date (Table 5), we found that the high cumulative dose of any TCA use, and medium and long cumulative duration of any TCA use are associated with increased risk of colorectal cancer, but only the association between medium cumulative duration and colorectal cancer risk had a statistical significance ($RR_{low\ dose}$=0.89, 95%CI=0.72-1.10, $RR_{medium\ dose}$=1.03, 95%CI= 0.82-1.29, $RR_{high\ dose}$=1.20, 95%CI=0.94-1.53, p-trend for dose=0.55; $RR_{short\ duration}$=0.83, 95%CI=0.68-1.01, $RR_{medium\ duration}$= 1.29, 95%CI=1.02-1.62; $RR_{long\ duration}$=1.14, 95%CI= 0.87-1.50, p-trend for duration=0.61). This is not a strong supporting evidence for the primary hypothesis because of the general weakness of the association and the consistent absence of a dose response effect. Moreover, it is unlikely that the association between cumulative TCA exposure and colorectal cancer risk would be underestimated by failing to take the latent period into account, uncontrolled confounding effects and multiple comparisons.

Firstly, failing to take the induction and latent period of colorectal cancer into consideration might result in an underestimation of these associations. That is, including the exposure during irrelevant recent periods may result in nondifferential misclassification of exposure and attenuate the association [Rothman 1981]. It is suggested that the latency period for colorectal cancer development is at least 10 years [Tomeo 1999, Hamilton 1996]. If TCA class act to initiate tumors, an increased risk for exposure in the remote past would be expected. Therefore, we examined the effect of cumulative exposure to TCAs during the 11-20 year period preceding diagnosis, i.e. excluding any exposure during the 10-year period immediately preceding diagnosis considered as irrelevant exposure for cancer initiation (Table 6). However, there is no big change in point estimate, confidence interval and p-trend as compared to analyses during overall 20 years ($RR_{high\ dose}$=1.13, 95%CI=0.83-1.52, p-trend for dose=0.58; $RR_{medium\ duration}$= 1.41, 95%CI=1.07-1.85; $RR_{long\ duration}$=0.95, 95%CI= 0.65-1.39, p-trend for

duration=0.67). These results suggest that TCA class may be not an initiator of colorectal cancer even after taking the latent period into account. Since we have no exposure information longer than 20 years, it is impossible to examine whether TCA exposure before 20 years would initiate the colorectal cancer.

Secondly, we considered uncontrolled confounding effects by depression and other main risk factors of colorectal cancer (e.g., obesity, physical inactivity, smoking, alcohol drinking, and diet with high fat and low fiber) as positive confounding for TCA-colorectal cancer association (section 6.3.1.1). That is, these confounders would only bias the association between cumulative exposure to TCA class and colorectal cancer risk away from the null. The potential residual confounding effect due to rough classification of estrogen use is also considered as a positive confounding for TCA-colorectal cancer association (section 6.3.1.2). Only the residual confounding by NSAIDs might be associated with an underestimation of TCA-colorectal cancer association (section 6.3.1.2), but this residual confounding effect would be much weaker than other positive confounding effects. It is difficult to estimate the uncontrolled confounding effect by other antidepressant classes (SSRIs, MAOIs and atypical antidepressants) because it is difficult to estimate their association with the use of TCA class. One possibility is that subjects who use more TCAs would tend to use more other antidepressants due to depressive symptoms. The other possibility, however, is that patients tend to switch between different antidepressant class because of the unfavorable side effect. In this situation, more use of one antidepressant class (eg, SSRIs) would be associated with the less use of the other antidepressant class (eg, TCAs).

Finally, the multiple comparisons would only increase the probability of wrongly rejecting the null hypothesis, but not induce an underestimation of the TCA-colorectal cancer association.

In summary, according to the estimation of associations between cumulative TCA use and colorectal cancer risk, there is no supporting evidence for the primary hypothesis that the use of TCAs increases the risk of colorectal cancer, as compared to non-use of TCAs.

6.2.1.1.2 Exposure to TCA class during different time periods preceding the index date

The association between TCA use and colorectal cancer risk was further examined during different time periods preceding the index date. The main objective of this analysis was to control for the mutual confounding effects of TCA use during different time periods. In table 7 and table 9, we found that only the TCA use during 16-20 years preceding the index date was associated with an increased risk of colorectal cancer, but only was statistically significant for medium dose and medium duration (Table 7: RR_{low}=0.88, 95%CI=0.67-1.17, RR_{medium}=1.51, 95%CI=1.09-2.09, RR_{high}=1.09, 95%CI=0.69-1.72, p-trend=0.93; table 9: RR_{short}=0.89, 95%CI=0.69-1.15, RR_{medium}=1.60, 95%CI=1.13-2.27, RR_{high}=1.22, 95%CI=0.74-2.01, p-trend=0.60). This is not a strong supporting evidence for the primary hypothesis because of the absence of a dose response effect.

Similarly to the discussion for the association between cumulative TCA use and colorectal cancer risk (section 6.2.1.1.1), we consider that uncontrolled confounding effects by main risk factors of colorectal cancer would result in an overestimation of this association. And the multiple comparisons would increase the probability of wrongly rejecting the null hypothesis, but not result in an underestimation of the TCA-colorectal cancer association.

Hence, according to the estimation of associations between TCA use during different time period preceding the index date and colorectal cancer risk, we consider that there is no strong supporting evidence for the primary hypothesis that the use of TCAs increases the risk of colorectal cancer, as compared to non-use of TCAs.

6.2.1.2 The carcinogenic effect of genotoxic TCAs compared to non-genotoxic TCAs on colorectal cancer: no supporting evidence

Overall, there is no supporting evidence in this study for the secondary hypothesis that the use of genotoxic TCAs increases the risk of colorectal cancer, as compared to the non-genotoxic TCAs.

6.2.1.2.1 Ever exposed and cumulative exposure to genotoxic TCAs and non-genotoxic TCAs

According to the ever exposed and cumulative exposure measures (Table 4), we did not find any significant association between genotoxic TCAs and an increased risk of colorectal cancer. However, we found that cumulative exposure to non-genotoxic TCAs was associated with a significantly increased risk among high dosage and long duration groups, during a 20 years exposure history (RR_{dosage}=2.04, 95%CI=1.30-3.22, p-trend for dosage=0.32; $RR_{duration}$=1.95, 95%CI=1.17-3.25, p-trend for duration=0.32). This is against to the priori hypothesis that the use of genotoxic TCAs increases the risk of colorectal cancer, as compared to the non-genotoxic TCAs.

In the analysis for cumulative use of genotoxic TCAs and non-genotoxic TCAs during 11-20 years preceding the index date (Table 6), there is still no increased risk of colorectal cancer found for cumulative use of genotoxic TCAs. At the same time, the association between cumulative exposure to non-genotoxic TCAs and increased cancer risk became weaker and non-significant among the high dosage group (RR=1.63, 95%CI= 0.90-2.95, p-trend=0.94) and the long duration group (RR=1.23, 95%CI=0.57-2.65, p-trend=0.55). Although this association became stronger and significant among the medium cumulative duration group (RR=1.83, 95%CI=1.14-1.96), there is no dose-response effect (p-trend=0.55). These results suggest that the non-genotoxic TCAs may be not an initiator of colorectal cancer. Again, uncontrolled confounding effect or multiple comparison would only result in an overestimation of the association between cumulative exposure to genotoxic and non-genotoxic TCAs and the risk of colorectal cancer or wrongly rejecting the null hypothesis.

Therefore, we consider that cumulative use of genotoxic TCAs is not associated with the increased risk of colorectal cancer. We also consider that the evidence is not sufficient to support that cumulative use of non-genotoxic is associated with increased risk of colorectal cancer because 1) this association might be overestimated according to discussion above; and 2) there is lack of any supporting evidence from either

experimental study or other epidemiological studies for carcinogenic effect of non-genotoxic TCAs.

6.2.1.2.2 Exposure during different time periods preceding the index date

We carried out an analysis in which potential confounding between the genotoxic and non-genotoxic TCAs was controlled by restriction (Table 8 and 10). The exposure was defined during each period using mutually exclusive categories: exclusive use of TCAs from each subclass, as well as exposure to both subclasses. Since there was a common referent for each period consisting of subjects unexposed to any TCA, the ratio of the RRs associated with exclusive exposure to each subclass provided an unbiased estimate of the ratio of the incidence of colorectal cancer among subjects exposed to one class of TCAs to the incidence among subjects exposed to the other. We did not find that genotoxic TCAs were associated with a higher risk of colorectal cancer as compared to the non-genotoxic TCAs.

Contrary to the priori hypothesis, a slightly increased risk of colorectal cancer was observed for non-genotoxic TCAs among the medium and high dosage group, as well as the medium and long duration group during the 16-20 year period preceding diagnosis (Table 7-10). However, most of these associations had no statistical significance except for subjects exposed to medium duration (Table 9, RR=1.89, 95%CI=1.14-3.14). Moreover, the relatively weak association, consistent absence of a dose response, possible positive confounding effect, as well as the increased risk of falsely rejecting null hypothesis due to multiple comparisons did not support a true carcinogenic effect of non-genotoxic TCAs.

Nevertheless, we could not completely exclude the possibility that the increased risk of colorectal cancer may be associated with some agents categorized into "non-genotoxic" subclass. Firstly, the genotoxicity of TCAs determined in fluit flies may not be applicable to human beings. Secondly, the observed increased risk of colorectal cancer may due to the effect of one or more individual drugs that were classified into non-genotoxic subclass, rather than the effect of the whole non-genotoxic subclass. Tutton

and Barkla [Tutton 1989] reported that TCA desipramine (categorized into "non-genotoxic" in this study) accelerated intestinal crypt cell proliferation in intact rats, thereby enhancing colon carcinogenesis. Iishi et al [1993] confirmed this hypothesis in their study. Finally, the small number of drug users during the 16-20 year period limits the ability to detect some small, but potentially still meaningful associations between single antidepressant drugs with colorectal cancer risk.

6.2.2 The effect of SSRI class on colorectal cancer risk

6.2.2.1 Experimental evidence for anti-tumor effect of SSRI class on colorectal cancer

As discussed in Section 2.3.1, Tutton and Barkla reported [1982] that the SSRIs fluoxetine (10-20mg/kg) and citalopram (20-40 mg/kg) slowed the growth of two out of three lines of human tumors propagated as xenografts in immune-deprived mice. These two antidepressants also suppressed cell division in chemically induced colonic tumors in rats. Because serotonin is a stimulator to cell division in several tissues, the authors postulated that serotonin may be a mediator of cell proliferation in colonic tumour cells and that the inhibition of serotonin uptake by these two antidepressants results in the suppression of cell proliferation in tumors. Tutton and Barkla previously reported evidence in support of this hypothesis when they found that colonic tumors induced by dimethylhydrazine (DMH) might have a serotonin-uptake mechanism, and the serotonin-receptor antagonists could retard the growth of such tumors [Tutton & Steel 1979].

Brandes et al [Brandes 1992] reported that one SSRI with histamine-receptor activity, fluoxetine, was found to promote fibrosarcomas, melanomas, and mammary carcinogenesis in rodents at concentrations similar to the clinical treatment dose of human depression. However, several subsequent studies were not able to replicate this result [Mathews 1995, Bendele1992, Parchment 1996].

To date no epidemiological study has examined the association between the use of SSRIs and development of colorectal cancer. Several studies have examined the association between the use of the SSRIs class or individual SSRIs and the risk of all cancers

combined or breast cancer [cotterchio 2000, Kelly 1999,Coogan 2000, Dalton 1999], and no increased risk of cancer was found. The common limitation of these studies is that they were based on a very small number of SSRI users.

6.2.2.2 Anti-tumor effect of SSRI class on colorectal cancer: supporting evidence

Overall, there is a supporting evidence for the priori hypothesis that the use of SSRI class decreases the risk of colorectal cancer. Decreased risks of colorectal cancer were consistently found for SSRI users among those exposed to high cumulative dosage and long cumulative duration (Table11 and 12) as well as those exposed to high average dose and long duration during the 1-5 years preceding diagnosis (Table 13 and 14), with statistical significant dose-response effects. The anti-tumor effect was not observed for SSRI users during the 6-10 years before the diagnosis (Table 13 and 14). These results are consistent with the experimental evidence suggesting that the use of SSRIs could slow the growth of established colonic tumors. That is, SSRIs only suppressed the cell division in established colonic tumor instead of normal intestinal crypt cells [Tutton & Barkla, 1982].

The confounding by depression and other main risk factors of colorectal cancer related to unhealthy life style is not an issue in association between SSRI use and the decreased risk of colorectal cancer since the possible effects of these factors would only tend to attenuate the observed association (section 6.1.3.1).

It is possible that people would increase the use of antidepressants during the year immediately preceding diagnosis because of as-yet-undiagnosed cancer symptoms (depression or pain). However, we considered that it would only attenuate the observed anti-tumor effect of SSRIs. We checked this effect by dividing the 5 years preceding diagnosis into 0-1 year and 2-5 year periods, and including the exposure during three time periods (0-1, 2-5 and 6-10 years) into a single logistic model (Table15 and 16).

The anti-tumor effect during the 2-5 years period was still significant, after adjustment for exposure during the 0-1 year period (RR=0.51, 95%CI=0.32-0.82, p-trend=0.03).

While there was no obvious anti-tumor effect found for those exposed to SSRIs during the 0-1 year period preceding diagnosis (Table 15 and 16). There might have several explanations for this result.

Firstly, table 15 shows a slightly increased cancer risk among subjects highly exposed to SSRIs during the 0-1 year period preceding diagnosis (RR=1.22, 95%CI=0.84-1.75). This may be due to "reverse causality". For instance, some cases increased their use of antidepressant because of as-yet-undiagnosed symptoms of cancer. Moreover, there might be a delay between cancer diagnosis and cancer registration. Patients' knowledge about the diagnosis may induce or aggravate the depressive symptoms and therefore increased the use of antidepressants.

Secondly, animal studies showed that SSRIs could retard the growth of tumors by suppressing the cell division rather than reducing or curing the tumor. It is likely that, during the year immediately before diagnosis, the tumor was in a rapid progression stage and thus the rate of tumor progression overwhelmed the rate of tumor inhibition. It is possible that we were not able to find the inhibition effect of SSRIs during the year immediately preceding the diagnosis because our outcome is the detection of tumor rather than the measurement of tumor size. Only double blind randomized clinical trials could provide an answer to this question.

Furthermore, the experimental study indicated that the growth of some, but not all, colonic tumors is retarded by SSRIs. The growth of HXM2 (poorly differentiated adenocarcinoma) and HXM4 (well-differentiated adenocarcinoma), which had previously been shown to be inhibited by the serotonin-receptor antagonist [Barkla & Tutton 1982], were observed to be slowed by SSRIs. In contrast, the growth of tumour line HXM3 did not appear to be influenced by either SSRIs or serotonin antagonist. Since we did not examine the effect of SSRIs on different histological types of colorectal cancer, we cannot exclude the possibility that an anti-tumor effect of SSRIs exists only in some specific types of colorectal tumors.

Finally, the experimental study was based on two individual SSRIs, fluoxetine and citalopram, while we examined all the SSRIs together and the anti-tumor effect might be diluted. However, the small number of SSRI users in our study restricted the sub-group analysis of specificity of anti-tumor effect according to different histological types of tumor, different location of tumor, and individual SSRI agents.

In estimating the association between SSRIs use and the colorectal cancer risk, we took into account the effect of NSAIDs, estrogen and OCs. The fact that we found a trend towards lower colorectal cancer risk with use of these medications is consistent with an previously established or possible protective association, suggesting that we would have been able to detect the effect for antidepressants if such an effect truly existed.

In conclusion, our results suggested a possible anti-tumor effect of SSRIs on colorectal cancer. Since SSRIs are so commonly used and became the "first line" antidepressant for treatment of depressive disorders, their possible anti-tumor effects needs to be further examined.

Chapter 7: Conclusions

This chapter summarizes the results of this master thesis:

1) There is no sufficient supporting evidence for the primary hypothesis that the use of TCA class increases the risk of colorectal cancer, as compared to the non-use of TCA class. This conclusion is unlikely affected by uncontrolled confounding effects of main colorectal cancer risk factors.

2) There is no supporting evidence for the secondary hypothesis that the use of genotoxic TCAs increases the risk of colorectal cancer, compared to the use of non-genotoxic TCAs. On the other hand, an increased risk of colorectal cancer was found to be associated with medium or heavy use of non-genotoxic TCA during 16-20 year period preceding diagnosis. However, the weak strength of association, consistent absence of a dose response, the possible effect of positive confounding factors, as well as the risk of falsely rejecting null hypothesis in multiple comparisons do not support a true carcinogenic effect of non-genotoxic TCAs.

3) This study provides supporting evidence for the primary hypothesis that the use of SSRI class decreases the risk of colorectal cancer, as compared to non-use of SSRI class. A decreased risk of colorectal cancer was consistently found to be associated with the use of SSRIs among subjects heavily exposed during the 2-5 year period peceding diagnosis. This conclusion is unlikely affected by uncontrolled confounding factors. This interesting hypothesis needs to be further studied with proper double blind randomized clinical trials.

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Chapter 9: Tables and Figures

Table 1. Determinants of development of colorectal cancer

	Modifiable factors	Non-modifiable factors
Risk factors	Lifestyle Obesity Physical inactivity[a] Smoking[a] Diet and nutrition Animal fat[a] Red meat[a] Alcohol[a]	Age[a] Male gender[a] Race/Ethnicity[a] Family history (first-degree relative)[a] Inflammatory bowel disease[a]
Preventive factors	Diet and nutrition Multivitamins containg folate[a] Diet fruit, vegetables and fiber Calcium[a] Medication NSAIDs[a] Hormonal replacement therapy(HRT) Oral contraceptives Screening	

[a.] With fairly consistent evidence

Table 2. Name and class of antidepressants dispensed

Class		Drug name
Tricyclic antidepressants (TCAs)	Genotoxic	Amoxapine
		Clomipramine
		Desipramine
		Doxepin
		Imipramine
		Trimipramine
	Non-genotoxic	Amitriptyline
		Amitriptyline/Perphenazine
		Maprotiline
		Nortriptyline
		Protriptyline
Selective Serotonin Reuptake Inhibitors (SSRIs)		Citalopram
		Fluoxetine
		Fluvoxamine
		Paroxetine
		Sertraline
Mono-Amine Oxidase Inhibitors (MAOIs)		Isocarboxacid
		Phenelzine
		Tranylcypromine
		Moclobemide (type A)
Atypical antidepressants		Bupropion
		Nefazodone
		Nomifensine
		Trazodone
		Venlafaxine

Table 3A. Experimental studies of effects of antidepressants on colorectal cancer risk

Effect of drug	drug name and class	Model	Mechanisms	Author
Promotes tumors	Desipramine (TCAs)	Rats	Accelerates intestinal crypt cell proliferation in intact rats, suggesting it might enhance colon carcinogenesis.	Tutton and Barkla(1989)
	Desipramine (TCAs)	Rats	Increase serum norepinephrine(NE) concentration, and subsequently increasing the proliferation of colon epithelial cells in azoxymethane(AOM)-induced carcinogenesis in the rat colon	Iishi et al. (1993)
	Pargyline (MAO-B inhibitor)	Rats	Increase the norepinephrine(NE) concentration in the colon wall, and subsequently increasing the proliferation of colon epithelial cells in azoxymethane(AOM)-induced carcinogenesis in the rat colon	Iishi et al. (1994)
	Nialamide(MAOIs)	Rats	Not significantly influence cell proliferation in nonmalignant tissues but accelerated cell division in colonic tumors.	Tutton and Barkla(1976)
No effect	Clorgyline (MAO-A inhibitor)	Rats	No influence on development or histological appearance of colon tumors	Iishi et al. (1994)
Antineoplastic effect	Citalopram(SSRIs) Fluoxetine(SSRIs)	Mice+rats	Slowed the growth of two out of three lines of human colonic tumors in immune-deprived mice, and suppressed cell division in chemically induced colonic tumors in rats through suppression of cell proliferation.	Tutton and Barkla(1982)

Table 3B. Epidemiological studies of effects of antidepressants on cancer risk

Study	Drug name and class	Cancer site	Results	Study design and study population	Adjusted covariates	Limitations
Friedman et al. *	Amitriptyline and Imipramine(TCAs)	**56 cancer sites**		Cohort. N=143,574 FU=up to 15yrs Using computerized pharmacy records, the California Tumor Registry, and computer-stored hospitalization records.	No.	No adjustment of any know factors for cancer. The statistical power may not have been sufficient to detect a small effect for each cancer site. Only ever/never exposure estimation. (No consideration of the effect of dose, timing, and duration of use on cancer).
1980			No association between amitriptyline and an increased incidence of any cancer site or all sites combined.	FU=662,000person-yrs		
1983			No association between amitriptyline (RR=1.07, 95%CI=0.92-1.23) or imipramine (SMR=0.77, 95%CI=0.40-1.34) and an increased incidence in any cancer site or all sites combined	FU=868,000person-yrs		
1989			Amitriptyline was found positively associated with liver cancer, but SMR was not significantly elevated.	FU=1,370,000person-yrs		
Dalton SO, et al(2000)*	TCAs, MAOIs, SSRIs	**All possible cancer sites**	Only TCAs use associated with increased risk of Non-Hodgkin's lymphoma. (SIR=2.5, 95%CI=1.4-4.2), with the risk increasing with the number of prescriptions.	Cohort. N=30,807 (>15yrs of age) FU=average 3.2yrs(0-7yrs), 97,237person-yrs Using Prescription database of the country of north Jutland, Danmark., and Denish Cancer Registry.	Smoking	No adjustment of most of potential CFs. Relatively short FU.

Weiss SR, et al (1998)*	Antidepressant or antihistamines	**Cancer recurrentces or second primary cancers**	Typical use of antidepressant or antihistamine drugs did not increase risk for recurrent (OR=0.97,95%CI=0.52-1.78) or second primary tumors (OR=0.94,95% CI=0.50-1.77) among patients with cancer.	Nested case-control studies. N_{case}=173,$N_{control}$=865, 5:1 matched on cancer site, stage, and follow-up time.	Cancer site, stage and Follow-up time	Difficult to distinguish the effect of antidepressant and antihistamines.
Dublin S, et al(2002)	Doxepin, Amitriptyline, imipramine (TCAs)	**Ovarian cancer**	Cases were slightly less likely than controls to take antidepressant prescriptions in any 6-month period prior to a reference date set 1.5 years before diagnosis (OR=0.71, 95%CI=0.47-1.1), or to take an antidepressant continuously for 6 months or longer(OR=0.64, 95%CI=0.36-1.1)	Population-based Case-Control. N_{case}=314, $N_{control}$=790 4:1 matched on age, calendar year and the length of HMO membership, Using computerized pharmacy database, and health maintenance organization(HMO) database	Age, past medication use, and length of HMO membership	No adjustment of most of potential confounders. Relatively small sample size
Coogan PF, et al(2000)	Self-reported TCAs, SSRIs	**Ovarian cancer**	No association for regular use (at least 4 days/week for at least 1 month), at least 5 years use, or 10 or more years use previously.	Case-control Surveillance N_{case}=716 for TCAs, 739 for SSRIs, $N_{cancer\ control}$=1496, $N_{noncancer\ control}$=1496	Age,race, religion, smoking. parity, OC use, body weight, age at menarche, age at menopause, number ofphysician visits , study center, year of interview.	Recall bias Small number of cases among users of TCAs (n=29), and of SSRIs (n=9).

Harlow BL, et al.(1998)	Self-reported psychotropic medication, including antidepressants.	**Ovarian cancer**	Use of 6 months or longer was associated with a increase in risk of invasive ovarian cancer (AOR=1.6,95%CI=1.1-2.3) and in risk of epithelial ovarian caner(AOR=1.4,95%CI=1.0-2.0),compared to nonusers. First use before the cessation of menstrual periods for more than 2 years was associated with 3-fold risk of ovarian cancer(AOR=2.9,95%CI=1.3-6.6)	Population-based case-control N_{case}=563,$N_{control}$=523, Matched on age, race and residence	Age, education,parity, OC use, smoking, center, marital status, and premenstrual symptomatology	Recall bias. Impossible to separate the effect of antidepressant and other psychotropic drugs.
Harlow BL, et al.(1995)	Self-reported antidepressant	**Ovarian cancer**	increased risk for ever use (OR=2.1, 95%CI=0.9-4.8),for first use 10 years prior to index date (OR=9.7,95%CI=1.2-78.8), and for first use before age 50(OR=3.5,95%CI= 1.3-9.2)	Population-based case-control N_{case}=450, $N_{control}$=454, Matched on age, race and residence	Age, race, residence, parity, prior OC use, religion, body weight, prior hysterectomy, therapeutic abortion.	Recall bias, Possoble selection bias
Sharpe et al (2002)	TCAs	**Breast cancer**	1. Heavy exposure to TCAs was associated with an elevated risk of breast cancer 11-15 years later (RR=2.02, 95%CI=1.34-3.04). 2. Post hoc analyses showed the exclusive use of genotoxic TCAs increased risk of cancer 11-15 years later for highest dose and longest duration (RR_{dose}=1.92,95%CI=0.93-3.95 and $RR_{duration}$=1.90, 95%CI=0.93-3.90), compared with the non-genotoxic TCAs which did not (RR_{dose}=0.84,95%CI=0.36-1.93, and $RR_{duration}$=0.80,95%CI=0.40-1.61)	Population-based Case-control N_{case}=5882, $N_{control}$=23,514, Matched on age and sampling time, Using Saskatchewan Prescription Drug Program and the Sasdatchewan Cancer Registry	Age	No adjustment of any potential confounders other than age.

Wang PS, et al(2001)	TCAs, SSRIs, MAOIs, Atypical	**Breast cancer**	1. No association between use of any antidepressant and cancer risk (Adjusted HR=1.04, 95%CI=0.87-1.25) 2. No association for specific antidepressants (for TCAs, Adjusted HR=1.09, 95%CI=0.92-1.31) 3. No significantly increased risk for any quartile of duration, nor any trend toward increased risk for longer durations of use.	Retrospective Cohort , $N_{exposed}$=38,273, $N_{unexposed}$=32,949 FU= maximum of 7.5 yrs, Using New Jersey Cancer Registry, New Jersey Medicaid program database, and New Jersey Pharmaceutical Assistance to the aged and Idsabled(PAAD) program database.	Demographic, clinical, and health care utilization.	No adjustment for some known risk factors: reproductive history, family history, socioeconomic status, alcohol use, etc. Relatively short FU
Cotterchio M, et al.(2000)	Self-reported TCAs, SSRIs, MAOIs, Atypical.	**Breast cancer**	Non-significantly increased risk in subgroups of patients who used TCAs for more than 2 years (OR=3.1,95%CI=0.9-5.0) and for those who used one of the SSRIs, paroxetine(OR=7.2,95%CI=0.9-58.3)	Population-based Case-control. N_{case}=701, $N_{control}$=702, Using Ontario Cancer Registry and Ontario Ministry of Finance database.	Age, clinical depression, benign proliferative breast disease.	Recall bias
Kelly JP, et al.(1999)	Self-reported TCAs, SSRIs, other antidepressant (no definition).	**Breast cancer**	No elevated risk of cancer compared with both cancer-controls and noncancer-controls with any antidepressant class for at least 4 days per week for duration of at least 4 weeks.	Hospital-based Case-control N_{case}=5814, $N_{cancer\ control}$=5095, $N_{noncancer\ control}$=5814	Age,region, race, religion, year of interview, age at menarche, age at first birth, body weight, history of benign breast disease, menopausal status, family history, alcohol, and number of hospitalization.	Recall bias Selection bias related to different exposure pattern in hospital control.

Wallace RB, et al.(1982)	Self-reported Amitriptyline, nortriptyline, desipramine(TCAs) and phenelzine(MAOIs)	**Breast cancer**	Adjusted RR=2.84(P<0.04) for any antidepressant use. Significant interaction between antidepressant use and socioeconomic status.	Case-control $N_{case}=N_{control}=151$ Matched on age	Menstrual, reproductive and family history of breast cancer.	Recall bias Only ever/never use was considered. Small sample size
Danielson DA(1982)	TCAs	**Breast cancer**	Reduced risk for TCAs use in the six months prior to diagnosis relative to nonusers (RR=0.5,90%CI=0.3-0.8).	Retrospective Cohort. $N_{case}=302$, FU =184,438 women-years Using Group Health Cooperative of Puget Sound, Seattle, a prepaid health care organization with computerized information on diagnosed and outpatient drug use.	Age	No adjustment of any important confounders other than age. Small sample size Only ever/never use was considered. The inappropriate exposure period(exposure histories limited to 6 months before diagnosis)

* Studies including assessment of association between antidepressant use and development of colorectal cancer

Figure 1. Annual incidence of colorectal cancer (1981-2000)

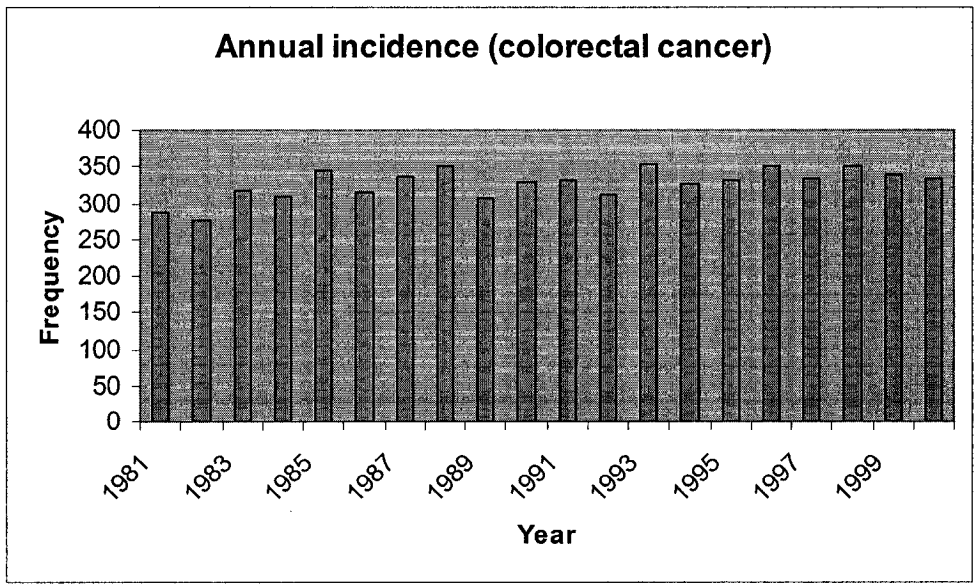

Figure 2. Gender distribution in study population

	Sample size	Male	Female
Cases (%)	6544	3742 (57.18%)	2802 (42.82%)
Controls(%)	26176	14968 (57.18%)	11208 (42.82%)

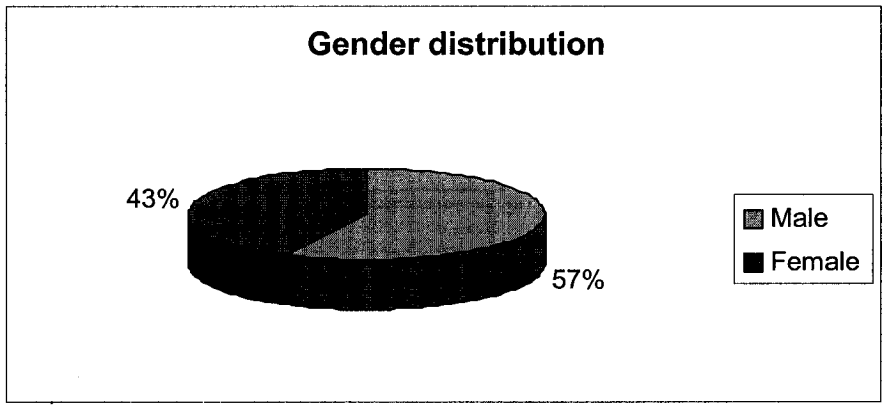

Figure 3. Age distribution of study population

	Mean	Std Dev	Minimum	Maximum
Study population	66.8(yrs)	10.2	24.0	82.5
Case	66.8	10.1	24.6	81.0
Control	66.8	10.2	24.0	82.5

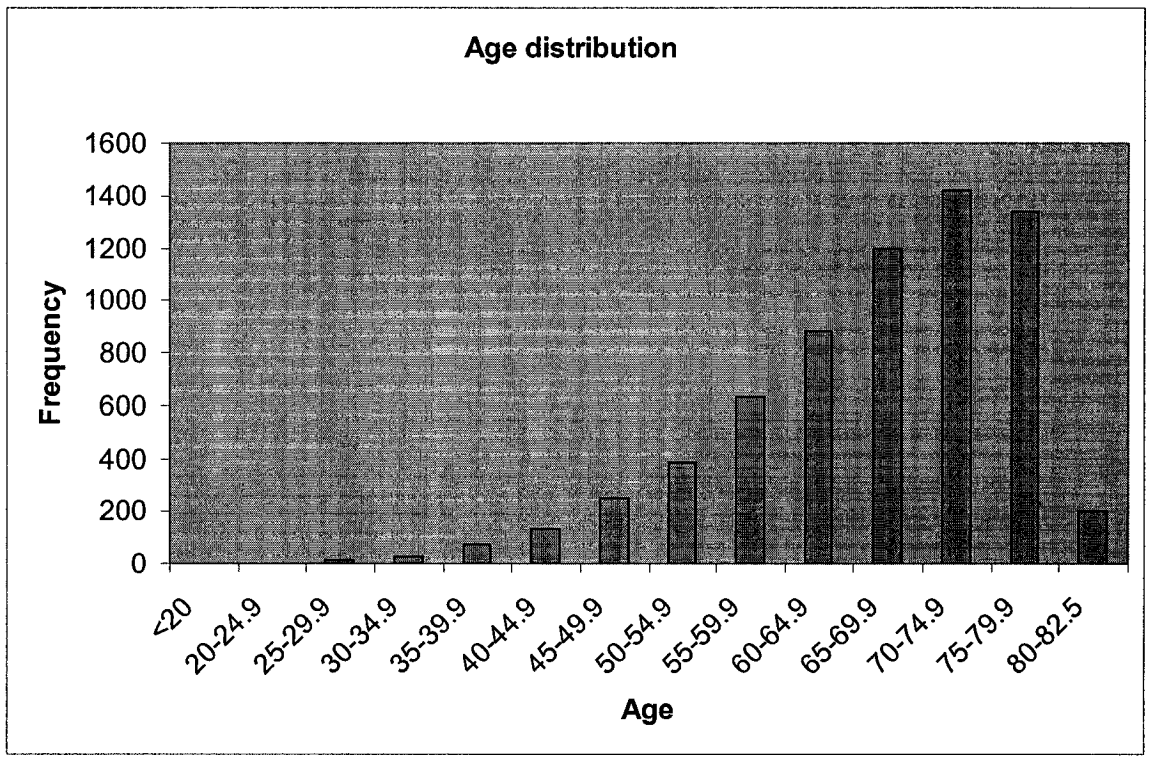

Table 4. RRs for colorectal cancer according to **TCAs** exposure**(ever,cumulative dosage,cumulative duration)** for subjects who had completed **15 years** exposure history

Ever exposure

Subclass of TCAs	Exposure to TCAs*	Cases N=3226	Controls N=12835	Adjusted RRs**	95%CI
Genotoxic or Nongenotoxic	Never	2697	10525	1	referent
	Ever_geno	191	838	0.87	0.74-1.03
	Ever_nongeno	214	917	0.91	0.78-1.07
	Both	124	555	0.83	0.68-1.02
Any TCAs	Never	2697	10525	1	referent
	Ever_any	529	2310	**0.89**	**0.80-0.99**

Cumulative dosage

Subclass of TCAs	Exposure to TCAs*	Cases N=3226	Controls N=12835	Adjusted RRs***	95%CI
Genotoxic	Unexposed	2697	10525	1	referent
	Low	94	374	1.00	0.79-1.27
	Medium	56	264	0.81	0.60-1.09
	High	41	200	0.86	0.61-1.22
	P-trend			0.42	
Non-genotoxic	Low	101	480	0.84	0.67-1.05
	Medium	71	282	1.06	0.81-1.40
	High	42	155	1.24	0.86-1.77
	P-trend			0.79	
	Both	124	555	0.89	0.73-1.10
Any TCAs	Unexposed	2697	10525	1	referent
	Low	211	889	0.95	0.81-1.12
	Medium	175	735	0.94	0.79-1.12
	High	143	686	0.89	0.73-1.07
	P-trend			0.07	

Cumulative duration

Subclass of TCAs	Exposure to TCAs*	Cases N=3239	Controls N=12885	Adjusted RRs***	95%CI
Genotoxic	Unexposed	2973	11717	1	referent
	Short	73	331	0.88	0.68-1.14
	Medium	26	121	0.86	0.56-1.33
	Long	13	78	0.64	0.35-1.19
	P-trend			0.13	
Non-genotoxic	Short	70	283	0.99	0.76-1.30
	Medium	28	90	1.25	0.81-1.92
	Long	14	62	0.92	0.51-1.66
	P-trend			0.87	
	Both	42	203	0.86	0.61-1.21
Any TCAs	Unexposed	2973	11717	1	referent
	Short	156	640	0.98	0.81-1.17
	Medium	71	316	0.92	0.70-1.20
	Long	39	212	0.74	0.52-1.06
	P-trend			0.11	

* Cutoff point for cumulative dosage: (0.01,0.07)moles, for cumulative duration:(6,27)months

** Adjusted for age and gender

*** Adjusted for age, gender, and cumulative exposure to NSAIDs

Table 5. RRs for colorectal cancer according to **TCAs** exposure **(ever,cumulative dosage, cumulative duration)** for subjects who had completed **20 years** exposure history

Ever exposure

Subclass of TCAs	Exposure to TCAs*	Cases N=1609	Controls N=6299	Adjusted RRs**	95%CI
Genotoxic or Nongenotoxic	Never	1272	4934	1	referent
	Ever_geno	95	456	0.79	0.63-1.01
	Ever_nongeno	143	538	1.01	0.83-1.24
	Both	99	362	1.02	0.80-1.30
Any TCAs	Never	1272	4943	1	referent
	Ever_any	337	1356	0.96	0.84-1.10

Cumulative dosage

Subclass of TCAs	Exposure to TCAs*	Cases N=1609	Controls N=6299	Adjusted RRs***	95%CI
Genotoxic	Unexposed	1272	4943	1	Referent
	Low	45	214	0.83	0.59-1.17
	Medium	33	127	0.93	0.62-1.40
	High	17	105	0.74	0.43-1.26
	P-trend			0.65	
Non-genotoxic	Low	67	311	0.86	0.65-1.15
	Medium	43	159	1.06	0.73-1.52
	High	33	68	**2.04**	**1.30-3.22**
	P-trend			0.32	
	Both	99	95	1.16	0.90-1.48
Any TCAs	Unexposed	1272	4943	1	referent
	Low	121	549	0.89	0.72-1.10
	Medium	114	416	1.03	0.82-1.29
	High	102	391	1.20	0.94-1.53
	P-trend			0.55	

Cumulative duration

Subclass of TCAs	Exposure to TCAs*	Cases N=1625	Controls N=6373	Adjusted RRs***	95%CI
Genotoxic	Unexposed	1287	5000	1	Referent
	Short	56	284	0.75	0.55-1.02
	Medium	27	98	1.21	0.76-1.91
	Long	13	78	0.75	0.41-1.39
	P-trend			0.37	
Non-genotoxic	Short	74	364	0.84	0.64-1.10
	Medium	43	125	1.36	0.94-1.98
	Long	26	57	**1.95**	**1.17-3.25**
	P-trend			0.32	
	Both	99	367	1.16	0.90-1.48
Any TCA	Unexposed	1287	5000	1	referent
	Short	144	689	0.83	0.68-1.01
	Medium	116	363	**1.29**	**1.02-1.62**
	Long	78	321	1.14	0.87-1.50
	P-trend			0.61	

* Cutoff point for cumulative dosage: (0.01,0.07)moles, for cumulative duration:(6,27)months

** Adjusted for age and gender

*** Adjusted for age, gender, and cumulative exposure to NSAIDs

Table 6. RRs for colorectal cancer according to **TCAs** exposure **(cumulative dosage, cumulative duration)** during **11-20 years** preceding the index date

Cumulative dosage

Subclass of Antidepressants	Exposure to TCAs*	Cases N=1609	Controls N=6299	Adjusted RRs**	95%CI
Genotoxic	Unexposed	1388	5415	1	referent
	Low	32	171	0.77	0.52-1.14
	Medium	35	118	1.14	0.76-1.70
	High	12	74	0.76	0.40-1.44
	P-trend			0.60	
Non-genotoxic	Low	41	167	0.93	0.65-1.32
	Medium	25	95	0.99	0.63-1.57
	High	17	35	1.63	0.90-2.95
	P-trend			0.94	
	Both	59	220	1.16	0.85-1.58
Any TCA	Unexposed	1388	5415	1	referent
	Low	77	386	0.85	0.66-1.10
	Medium	83	258	1.11	0.86-1.44
	High	61	240	1.13	0.83-1.52
	P-trend			0.58	

Cumulative duration

Subclass of Antidepressants	Exposure to TCAs*	Cases N=1625	Controls N=6373	Adjusted RRs**	95%CI
Genotoxic	Unexposed	1403	5477	1	referent
	Short	49	240	0.82	0.59-1.13
	Medium	23	78	1.24	0.75-2.03
	Long	7	50	0.69	0.30-1.55
	P-trend			0.48	
Non-genotoxic	Short	47	220	0.83	0.60-1.15
	Medium	27	57	**1.83**	**1.14-1.96**
	Long	9	28	1.23	0.57-2.65
	P-trend			0.55	
	Both	60	223	1.18	0.87-1.61
Any TCA	Unexposed	1403	5477	1	referent
	Short	106	489	0.85	0.68-1.07
	Medium	80	236	**1.41**	**1.07-1.85**
	Long	36	171	0.95	0.65-1.39
	P-trend			0.67	

* Cutoff point for cumulative dosage: (0.01,0.07)moles, for cumulative duration:(6,27)months

** RRs were adjusted for age, gender, and cumulative exposure to NSAIDs

Table 7. Adjusted RRs for colorectal cancer according to **TCA** exposure **(average datily dosage)** by time periods preceding the index date

		Non-genotoxic TCA				Genotoxic TCA				Any TCA			
Time period preceding the index date	**Average daily dose#**	**Cases N=6544**	**Controls N=26176**	**Adjusted RRs***	**95%CI**	**Cases N=6544**	**Controls N=26176**	**Adjusted RRs***	**95%CI**	**Cases N=6544**	**Controls N=26176**	**Adjusted RRs****	**95%CI**
2-5 years	Unexposed	6235	24781	1	Referent	6219	24909	1	Referent	5990	23838	1	Reference
	Low	150	647	0.94	0.79-1.13	138	533	1.09	0.90-1.33	237	962	1.02	0.88-1.19
	Medium	84	392	0.87	0.68-1.11	96	382	1.08	0.85-1.36	156	682	0.96	0.80-1.15
	High	75	356	0.89	0.66-1.19	91	352	1.13	0.86-1.48	161	694	0.98	0.80-1.22
	P-trend			0.32				0.85				0.64	
	Other	0	0	-	-	0	0	-	-	0	0	-	-
6-10 years	Unexposed	4665	18528	1	Referent	4658	18496	1	Referent	4492	17719	1	Reference
	Low	126	537	0.97	0.79-1.19	105	493	0.89	0.71-1.10	171	824	0.85	0.72-1.01
	Medium	76	316	1.05	0.80-1.37	85	355	1.02	0.79-1.31	140	582	1.01	0.83-1.24
	High	44	216	0.93	0.62-1.40	63	253	1.07	0.76-1.52	108	472	1.02	0.78-1.35
	P-trend			0.22				0.9				0.52	
	Other	1633	6579	-	-	1633	6579	-	-	1633	6579	-	-
11-15 years	Unexposed	3071	12198	1	Referent	3072	12103	1	Referent	2960	11669	1	Referent
	Low	87	315	1.16	0.91-1.49	75	340	0.88	0.68-1.14	127	527	0.98	0.80-1.20
	Medium	40	203	0.83	0.58-1.19	48	234	0.83	0.60-1.16	82	364	0.90	0.70-1.14
	High	28	119	1.04	0.64-1.70	31	158	0.76	0.48-1.20	57	275	0.83	0.58-1.18
	P-trend			0.27				0.44				0.16	
	Other	3318	13341	-	-	3318	13341	-	-	3318	13341	-	-
16-20 years	Unexposed	1518	5987	1	Referent	1520	5934	1	Referent	1464	5723	1	Referent
	Low	50	176	1.20	0.87-1.67	41	180	0.91	0.64-1.29	63	295	0.88	0.67-1.17
	Medium	26	88	1.33	0.84-2.12	36	107	1.34	0.89-2.01	54	158	**1.51**	**1.09-2.09**
	High	15	48	1.43	0.75-2.73	12	78	0.69	0.36-1.34	28	123	1.09	0.69-1.72
	P-trend			0.78				0.65				0.93	
	Other	4935	19877	-	-	4935	19877	-	-	4935	19877	-	-

cutoff point (0.000008,0.00005)moles/day

* Adjusted for age, gender and exposure to NSAIDs; exposure to genotoxic TCAs and non-genotoxic TCAs during each time period were included in a single logistic model

** Adjusted for age, gender, exposure to NSAIDs, and exposure to TCAs during other time periods

Table 8. Adjusted RRs for colorectal cancer according to **exclusive exposure** to **genotoxic and non-genotoxic TCAs (average daily dosage)** by time period preceding the index date

Time period prceding the index date	Subclass of TCAs	Exposure to TCAs#	Cases N=6544	Controls N=26176	Adjusted RR*	95%CI	RR(geno)/ RR(nongeno)**
2-5 years	**Genotoxic**	Unexposed	5990	23838	1	Referent	
		Low	116	420	1.14	0.93-1.41	1.23(1.14/0.93)
		Medium	67	259	1.07	0.81-1.41	1.23(1.07/0.87)
		High	62	264	0.95	0.69-1.30	1.06(0.95/0.90)
		P-trend			0.66		
	Non-genotoxic	Low	113	508	0.93	0.75-1.14	
		Medium	58	282	0.87	0.65-1.16	
		High	58	281	0.90	0.65-1.25	
		P-trend			0.36		
		Both	80	324	1.01	0.78-1.31	
		Other	0	0	-	-	
6-10 years	**Genotoxic**	Unexposed	4492	17719	1	Referent	
		Low	74	379	0.80	0.62-1.03	0.87(0.80/0.92)
		Medium	52	244	0.90	0.66-1.23	1.03(0.90/0.87)
		High	47	186	1.18	0.80-1.74	1.53(1.18/0.77)
		P-trend			0.67		
	Non-genotoxic	Low	92	406	0.92	0.73-1.16	
		Medium	44	212	0.87	0.62-1.22	
		High	30	159	0.77	0.48-1.26	
		P-trend			**0.05**		
		Both	80	292	1.16	0.89-1.52	
		Other	1633	6579	-	-	
11-15 years	**Genotoxic**	Unexposed	2960	11669	1	Referent	
		Low	55	267	0.83	0.62-1.12	0.80(0.83/1.04)
		Medium	37	162	0.94	0.65-1.36	0.94(0.94/1.00)
		High	19	100	0.76	0.44-1.33	0.61(0.76/1.25)
		P-trend			0.33		
	Non-genotoxic	Low	61	237	1.04	0.78-1.39	
		Medium	31	125	1.00	0.67-1.50	
		High	20	72	1.25	0.70-2.23	
		P-trend			0.71		
		Both	43	203	0.86	0.60-1.23	
		Other	3318	13341	-	-	
16-20 years	**Genotoxic**	Unexposed	1464	5723	1	Referent	
		Low	27	143	0.79	0.52-1.20	0.80(0.79/0.99)
		Medium	22	69	1.38	0.84-2.26	1.27(1.38/1.09)
		High	5	52	0.44	0.17-1.14	0.23(0.44/1.87)
		P-trend			0.33		
	Non-genotoxic	Low	33	136	0.99	0.67-1.45	
		Medium	13	53	1.09	0.58-2.02	
		High	10	22	1.87	0.85-4.12	
		P-trend			0.46		
		Both	35	101	1.59	1.06-2.39	
		Other	4935	19877	-	-	

Cutoff point (0.000008,0.00001) moles/day

* The variable representing exposure to the non-genotoxic TCAs, to the genotoxic TCAs, and to NSAIDs were all included in a single logistic model.

** Ratios between RRs for genotoxic TCAs and RRs for non-genotoxic TCAs in the same time periods and dosage categories

Table 9. Adjusted RRs for colorectal cancer according to estimated **duration** of **TCA** exposure by time period preceding the index date

		Nongenotoxic TCAs				Genotoxic TCAs				ALL TCAs			
Time period preceding the index date	**Duration of exposure#**	**Cases N=6544**	**Controls N=26176**	**Adjusted RRs***	**Adjusted 95%CI**	**Cases N=6544**	**Controls N=26176**	**Adjusted RRs***	**Adjusted 95%CI**	**Cases N=6544**	**Controls N=26176**	**Adjusted RR****	**Adjusted 95%CI**
2-5 years	Unexposed	6235	24782	1	Referent	6220	24912	1	Referent	5991	23842	1	Referent
	Short	131	588	0.91	0.75-1.10	125	521	1.00	0.82-1.23	204	863	0.98	0.84-1.14
	Medium	104	443	0.96	0.77-1.21	116	421	1.16	0.94-1.44	188	774	1.03	0.86-1.22
	Long	74	363	0.89	0.66-1.19	83	322	1.09	0.81-1.46	161	697	0.96	0.78-1.17
	P-trend			0.30				0.63				0.41	
	Other	0	0	-	-	0	0	-	-	0	0	-	-
6-10 years	Unexposed	4667	18542	1	Referent	4660	18506	1	Referent	4494	17729	1	Referent
	Short	150	606	1.02	0.84-1.23	123	623	0.83	0.68-1.01	198	977	**0.84**	**0.71-0.98**
	Medium	57	264	0.92	0.67-1.24	78	272	1.22	0.93-1.60	124	481	1.10	0.88-1.37
	Long	38	193	0.95	0.62-1.47	51	204	1.18	0.80-1.75	96	418	1.10	0.83-1.45
	P-trend			0.56				0.33				0.89	
	Other	1632	6571	-	-	1632	6571	-	-	1632	6571	-	-
11-15 years	Unexposed	3085	12247	1	Referent	3085	12152	1	Referent	2973	11717	1	Referent
	Short	100	390	1.08	0.86-1.36	99	428	0.92	0.73-1.16	156	640	0.98	0.82-1.18
	Medium	35	144	1.04	0.70-1.54	32	183	0.66	0.44-1.98	67	293	0.90	0.68-1.21
	Long	19	104	0.77	0.44-1.34	23	122	0.71	0.41-1.21	43	235	0.70	0.47-1.02
	P-trend			0.58				0.10				0.08	
	Other	3305	13291	-	-	3305	13291	-	-	3305	13291	-	-
16-20 years	Unexposed	1531	6055	1	Referent	1535	6002	1	Referent	1479	5786	1	Referent
	Short	61	219	1.19	0.88-1.61	55	225	0.98	0.72-1.34	75	354	0.89	0.69-1.15
	Medium	24	58	**1.89**	**1.14-3.14**	27	91	1.23	0.78-1.95	52	140	**1.60**	**1.13-2.27**
	Long	9	41	1.21	0.56-2.62	8	55	0.68	0.30-1.54	19	93	1.22	0.74-2.01
	P-trend			0.18				0.61				0.60	
	Other	4919	19803	-	-	4919	19803	-	-	4919	19803	-	-

Cutoff point (10%,40%) of time

* Adjusted for age, gender and exposure to NSAIDs; exposures to genotoxic and non-genotoxic TCAs during different time periods were included in the single logistic model

** Adjusted for age, gender, exposure to NSAIDs, and exposures to TCAs during other time periods

Table 10. Adjusted RRs for colorectal cancer according to **exclusive exposure to genotoxic and non-genotoxic TCA (duration)** exposure by time periods preceding the index date

Time period preceding the index date	Subclass of TCAs	Duration of exposure#	Cases N=6544	Controls N=26176	Adjusted RRs*	95%CI	RR(geno)/ RR(nongeno)**
2-5 years	**Genotoxic**	Unexposed	5991	23842	1	Referent	
		short	104	404	1.05	0.85-1.31	1.17(1.05/0.90)
		Medium	79	288	1.12	0.87-1.45	1.17(1.12/0.96)
		Long	61	248	0.96	0.69-1.34	1.05(0.96/0.91)
		P-trend			0.81		
	Non-genotoxic	short	98	453	0.90	0.72-1.12	
		Medium	70	311	0.96	0.73-1.25	
		Long	61	306	0.91	0.66-1.25	
		P-trend			0.37		
		Both	80	324	1.01	0.78-1.30	
		Other	0	0	-	-	
6-10 years	**Genotoxic**	Unexposed	4494	17729	1	Referent	
		short	83	476	**0.72**	**0.57-0.92**	0.77(0.72/0.94)
		Medium	46	170	1.14	0.81-1.60	1.28(1.14/0.89)
		Long	44	167	1.28	0.85-1.95	1.83(1.28/0.70)
		P-trend			0.41		
	Non-genotoxic	short	103	448	0.94	0.75-1.17	
		Medium	37	171	0.89	0.62-1.29	
		Long	26	158	0.70	0.42-1.16	
		P-trend			0.13		
		Both	79	286	1.18	0.90-1.54	
		Other	1632	6571	-	-	
11-15 years	**Genotoxic**	Unexposed	2973	11717	1	Referent	
		short	73	331	0.89	0.69-1.16	0.90(0.89/0.99)
		Medium	24	116	0.80	0.51-1.26	0.57(0.80/1.41)
		Long	15	83	0.66	0.35-1.24	0.73(0.66/0.90)
		P-trend			0.08		
	Non-genotoxic	short	70	283	0.99	0.75-1.29	
		Medium	28	82	1.41	0.91-2.20	
		Long	14	70	0.90	0.46-0.75	
		P-trend			0.71		
		Both	42	203	0.80	0.55-1.15	
		Other	3305	13291	-	-	
16-20 years	**Genotoxic**	Unexposed	1479	5786	1	Referent	
		short	31	176	0.75	0.51-1.11	0.84(0.75/0.89)
		Medium	16	57	1.25	0.71-2.21	0.72(1.25/1.74)
		Long	5	36	0.66	0.25-1.80	0.38(0.66/1.72)
		P-trend			0.29		
	Non-genotoxic	short	35	162	0.89	0.61-1.29	
		Medium	14	35	1.74	0.92-3.28	
		Long	7	19	1.72	0.69-4.31	
		P-trend			0.29		
		Both	38	102	1.79	1.20-2.66	
		Other	4919	19803	-	-	

Cutoff point (10%,40%) of time

*The variable representing exposure to the nongenotoxic TCAs, to the genotoxic TCAs, and to NSAIDs were all included in a single logistic model.

** Ratios between RRs for genotoxic TCAs and RRs for nongenotoxic TCAs in same time periods and duration categories

Table 11. Adjusted RRs for colorectal cancer according to **SSRI exposure (ever, cumulative dosage, cumulative duration)** during **10 years** overall exposure history

Ever exposure

Exposure to SSRIs	Cases N=3787	Controls N=15113	Adjusted RR**	95%CI
Never	3694	14664	1	referent
Ever	93	449	0.85	0.70-1.04

Cumulative dosage

Exposure to SSRIs*	Cases N=3787	Controls N=15113	Adjusted RR***	95%CI
Unexposed	3666	14555	1	referent
Low	78	313	1.01	0.78-1.30
High	43	245	**0.69**	**0.50-0.97**
P-trend			**0.04**	

Cumulative duration

Exposure to SSRIs*	Cases N=3787	Controls N=15113	Adjusted RR***	95%CI
Unexposed	3666	14555	1	referent
Short	72	312	0.93	0.71-1.21
Long	49	246	0.80	0.59-1.09
P-trend			0.08	

* Cutoff point for cumulative dosage:0.015moles, for cumulative duration:6months
** Adjusted for age and gender
*** Adjusted for age, gender and cumulative exposure to NSAIDs

Table 12. Adjusted RRs for colorectal cancer according to **SSRI exposure (ever, cumulative dosage, cumulative duration)** during **5 years** overall exposure history

Ever exposure

Exposure to SSRIs	Cases N=3859	Controls N=15436	Adjusted RR**	95%CI
Never	3755	14936	1	referent
Ever	104	500	0.83	0.67-1.02

Cumulative dosage

Exposure to SSRIs*	Cases N=3859	Controls N=15436	Adjusted RR***	95%CI
Unexposed	3755	14936	1	referent
Low	68	279	0.98	0.75-1.29
High	36	221	**0.64**	**0.45-0.92**
P-trend			**0.02**	

Cumulative duration

Exposure to SSRIs*	Cases N=3859	Controls N=15436	Adjusted RR***	95%CI
Unexposed	3755	14936	1	referent
Short	63	274	0.93	0.70-1.23
Long	41	226	**0.71**	**0.51-1.00**
P-trend			**0.02**	

* Cutoff point for cumulative dosage: 0.015moles, for cumulative duration:6months
** Adjusted for age and gender
*** Adjusted for age, gender and cumulative exposure to NSAIDs

Table 13. Adjusted RRs for colorectal cancer according to **average daily dosage** of **SSRI** exposure by time periods preceding the index date

Time period preceding the index date	**Average daily dose***	**Cases N=3859**	**Controls N=15436**	**Adjusted RRs (95%CI)****
1-5 years	Unexposed	3755	14936	1(Referent)
	Low	68	274	0.99 (0.75-1.30)
	High	36	226	**0.62 (0.43-0.90)**
	P-trend			**0.01**
	Other	0	0	_
6-10 years	Unexposed	3750	14969	1(Referent)
	Low	25	96	1.18 (0.76-1.85)
	High	12	48	1.29 (0.67-2.50)
	P-trend			0.24
	Other	72	323	_

* Cutoff point: 0.000008 moles/day

** Adjusted for SSRI exposure during other time period and exposure to NSAIDs

Table 14. Adjusted RRs for colorectal cancer according to estimated **duration** of SSRI exposure by time period preceding the index date

Time period preceding the index date	**Duration of exposure***	**Cases N=3859**	**Controls N=15436**	**Adjusted RRs** (95%CI)**
1-5 years	Unexposed	3755	14936	1 (reference)
	Short	63	274	0.92 (0.70-1.22)
	Long	41	226	**0.71 (0.50-1.00)**
	P-trend			**0.008**
	Other	0	0	_
6-10 years	Unexposed	3750	14969	1 (reference)
	Short	24	96	1.12 (0.71-1.77)
	Long	13	48	1.38 (0.72-2.64)
	P-trend			0.26
	Other	72	323	_

* Cutoff point: 10% of time for each period

** Adjusted for SSRI exposure during other time period and exposure to NSAIDs

Table 15. Adjusted RRs for colorectal cancer according to **average daily dosage** of **SSRI** exposure by time period preceding the index date

Time period preceding the indx date	**Average daily dose***	**Cases N=3859**	**Controls N=15436**	**Adjusted RRs (95%CI)****
0-1 year	Unexposed	3799	15168	1(Referent)
	Low	11	56	0.84 (0.44-1.62)
	High	49	212	1.22 (0.84-1.75)
	P-trend			0.08
	Other	0	0	–
2-5 years	Unexposed	3785	15052	1(Referent)
	Low	45	188	0.93 (0.66-1.30)
	High	29	196	**0.51 (0.32-0.82)**
	P-trend			**0.03**
	Other	0	0	–
6-10 years	Unexposed	3750	14969	1(Referent)
	Low	25	96	1.22 (0.78-1.92)
	High	12	48	1.32 (0.68-2.59)
	P-trend			0.23
	Other	72	323	–

* Cutoff point: 0.000008 moles/day

** Adjusted for SSRI exposure during other time period and exposure to NSAIDs

Table 16. Adjusted RRs for colorectal cancer according to estimated **duration** of SSRI exposure by time periods preceding the index date

Time period preceding the indx date	**Duration of exposure***	**Cases N=3859**	**Controls N=15436**	**Adjusted RR* (95CI)**
0-1 year	Unexposed	3799	15168	1 (reference)
	Short	44	152	1.28 (0.90-1.82)
	Long	16	116	0.76 (0.41-1.39)
	P-trend			0.57
	Other	0	0	–
2-5 years	Unexposed	3785	15052	1 (reference)
	Short	37	143	1.02 (0.70-1.48)
	Long	37	241	**0.61 (0.40-0.94)**
	P-trend			**0.056**
	Other	0	0	–
6-10 years	Unexposed	3750	14969	1 (reference)
	Short	24	96	1.15 (0.72-1.81)
	Long	13	48	1.54 (0.80-2.96)
	P-trend			0.12
	Other	72	323	–

* Cutoff point: 50% of time for 0-1 year; 10% of time for 2-5 years and 6-10 years

* Adjusted for SSRI exposure during other time period and exposure to NSAIDs