Population-based case-control study of the effects of antidepressant drugs on the risk of development of cancer

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Abstract

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Introduction: Although mechanisms have not been identified, animal and epidemiological studies suggest that tricyclic antidepressants (TCAs) promote tumor growth in humans. Recently, a study in fruit flies differentiated between two types of TCAs: genotoxic ones, which were found to be carcinogenic, and non-genotoxic ones, which were not. Consistent results were found, in an epidemiologic study, in humans' breast cancer. We carried out a historical population-based case-control study to determine whether the use of TCAs increases the risk of developing any of four cancer types (breast, prostate, and ovarian cancers, and non-Hodgkin's lymphoma). The effects of the use of different classes of antidepressants on the risk of developing cancer were assessed as well.

Methods: The source population was the dynamic cohort defined by membership with Saskatchewan Health between the years 1981 and 2000. At least four matched controls were selected for each case identified by the Saskatchewan Cancer Registry, using incidence density sampling. The detailed drug exposure data over a minimum of 5 years before diagnosis and up to a maximum of 23 years allowed us to study for each site the respective effects of dosage, timing, and duration of antidepressant drug use.

Results: During the 20-year period, the numbers of breast, prostate, ovarian, and non-Hodgkin's lymphoma cases included in the analyses were 7330, 7767, 1090, and 1980 respectively. Exposure to genotoxic TCAs, 2-5 years prior to the date of diagnosis, was associated with an increased risk of both breast and prostate cancers (p-trend = 0.001 and 0.08 respectively). Genotoxic TCAs also increased the risk of breast cancer and non-Hodgkin's lymphoma when exposure took place 11-15 years prior to the date of diagnosis (p-trend = 0.03 and 0.02 respectively). Surprisingly, exposure to genotoxic TCAs 6-10 years prior to the index date was associated with a decreased risk of prostate cancer (p-trend = 0.01). On the other hand, exposure to non-genotoxic TCAs, 2-5 years before the index date, was associated with an increased risk of breast cancer and non-Hodgkin's lymphoma (p-trend = 0.008 and 0.002 respectively). In addition, an increased risk of ovarian cancer was associated with exposure to non-genotoxic TCAs 6-10 years before the index date (p-trend < 0.001). Finally, exposure to SSRIs (Selective Serotonin Reuptake Inhibitors), 10 years before diagnosis, was not associated with the risk of any of the 4 cancers.

Conclusion: Although our breast cancer analyses provided similar conclusions to those reported in the literature on the effects of genotoxic TCAs, we didn't find similar effects in association with the three other cancer types (prostate, ovarian, and non-Hodgkin's lymphoma). Globally, our results did not show any consistent results in favor of the a priori hypothesis stating that exposure to genotoxic TCAs increases the risk of cancer development, as compared with non-genotoxic TCAs.

Résumé

Etude cas-témoins sur l'effet des antidépresseurs sur le risque de développement de cancer

Introduction: Bien que les mécanismes n'aient pas été identifiés, plusieurs études animales et épidémiologiques suggèrent que les antidépresseurs tricycliques (ATCs) sont des promoteurs de la croissance des tumeurs chez les humains. Récemment, une étude chez les animaux a différencié deux types d'ATCs : génotoxiques- (responsables de cancer) - et non-génotoxiques (non cancérogènes). Ces résultats ont été confirmés par une étude épidémiologique sur le cancer du sein. Dans ce contexte nous avons effectué une étude **cas-témoins** à base populationnelle pour déterminer si l'usage des ATCs augmentait le risque de développement de cancer au niveau de 4 sites (cancers du sein, de la prostate, et de l'ovaire, ainsi que les lymphomes Non-Hodgkiniens). L'effet de plusieurs classes d'antidépresseurs sur le risque de cancer a été évalué.

Méthodes: La population source est une cohorte dynamique définie par l'appartenance à Santé Saskatchewan pour la période 1981 à 2000. Pour chaque cas identifié dans le Registre du Cancer de Saskatchewan au moins quatre contrôles ont été sélectionnés dans la population source en utilisant la technique d'échantillonnage de densité d'incidence. Les données détaillées sur l'exposition aux médicaments (un minimum de 5 ans avant le diagnostic et jusqu'à un maximum de 23 ans) nous ont permis d'étudier pour chaque site les effets respectifs du dosage, de la période d'exposition, et de la durée de l'usage d'antidépresseurs.

Résultats: Sur une période de 20 ans, nous avons pu observer 7330 cancers du sein, 7767 cancers de la prostate, 1090 cancers de l'ovaire et 1980 cas de lymphome Non-Hodgkinien. L'exposition aux ATCs génotoxiques dans la période de 2-5 ans avant la date du diagnostic, était associée à un risque accru des cancers du sein et de la prostate (p de tendance = 0.001 et 0.001 respectivement). Les ATCs génotoxiques ont également été trouvés associés au risque de cancer du sein et de lymphome Non-Hodgkinien quand l'exposition a eu lieu 11-15 ans avant la date du diagnostic. De manière inattendue (et contre l'hypothèse), l'exposition aux ATCs génotoxiques 6-10 ans avant la date du diagnostic a été trouvée associée avec un risque décru de cancer de la prostate (p de tendance = 0.01). De plus (contre l'hypothèse), l'exposition aux ATCs non-génotoxiques, 2-5 ans avant la date de diagnostic, a été trouvée associée à un risque accru de cancer du sein et de lymphome de Non-Hodgkinien (p de tendance = 0.008 et 0.002 respectivement). De même, un risque accru de cancer ovarien a été trouvé associé à l'exposition aux ATCs non-génotoxiques 6-10 ans avant la date de déclaration du cancer (p de tendance < 0.001). L'exposition aux IRSSs (Inhibiteurs spécifiques de recaptage de la sérotonine), 10 ans avant le diagnostic, n'a pas été trouvée associée à aucune tendance pour aucun des 4 cancers considérés.

Conclusion: Bien que l'analyse du cancer du sein ait fournie les mêmes conclusions reportées dans la littérature sur les effets des ATCs génotoxiques, nous n'avons pas trouvé d'effets similaires en association avec les trois autres sites (prostate, ovaire et lymphome Non-Hodgkinien). Nos résultats ne supportent pas l'hypothèse a priori voulant que l'exposition aux ATCs génotoxiques accroisse le risque de cancer par rapport aux ATCs non-génotoxiques.

Statement of Originality

This thesis was undertaken to determine whether the use of antidepressant drugs, genotoxic TCAs in particular, increases the risk of developing any of 4 different types of cancer (breast, prostate, ovarian, and non-Hodgkin's lymphoma). This research constitutes original scholarship and advances the knowledge in the domain of both cancer epidemiology and pharmaco-epidemiology.

This work is considered an advancement in the literature since it is the first population-based study of the effects of antidepressants on prostate and ovarian cancers and non-Hodgkin's lymphoma. Although previous work has assessed the effect of antidepressants on cancer development, this thesis represents one of the initial attempts to differentiate between two types of tricyclic antidepressants, genotoxic and non-genotoxic ones. Overall, the original findings of this research provide new insights into the effects of antidepressants in general, and tricyclics in specific, on cancer development.

This project contains no previously published material, except where reference is made in the context of this thesis. Data provided by Saskatchewan Health for this study has not been previously analyzed or reported elsewhere, ensuring the originality of the results presented in this thesis.

I personally carried out the literature review, analyses, and the write up of the thesis; with the highly appreciated guidance and contribution of the committee members recognized in the acknowledgments.

Disclaimer

This Study is based in part on de-identified data provided by the Saskatchewan Department of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Department of Health.

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To those whose names I did not specifically mention, please accept my thanks.

Dedication: I dedicate this work to my parents who made me who I am.

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Chapter 1: Introduction

Cancer develops gradually as a result of increased genetic susceptibility; environmental insults, such as chemical exposure or smoking cigarettes; lifestyle factors, including diet; and many more.

The incidence of cancer varies considerably among different geographic areas worldwide; incidence ranges from 4 to 100 times for the most common sites (Parkin et al., 1987; IARC, 1990; and Boring et al., 1994). This geographic variation, together with the results of studies of migrant populations showing that migrants tend to acquire the cancer incidence of the host countries, demonstrates the important role played by environmental factors in the development of human tumors. It has been estimated that more than 75% of cancers are the result of environmental exposures (Lenbard et al., 2001). Nevertheless, epidemiological studies show that most cancers manifest a tendency to aggregate in families. Close relatives of a cancer patient can be considered to have increased risk of that neoplasm, but not for all forms of cancer. It has been estimated that no more than 20% of cancers are based on inherited genetic predisposition.

The epidemic of cancer is receiving intense scrutiny on three different levels (Strom, 2000). On the most fundamental level, the complex dynamics of cellular growth and differentiation and their disruption during oncogenesis are being studied in laboratories around the world. On the next level up, experiments in animals are being carried out to measure carcinogenicity of agents with animal bioassays. Finally, epidemiological studies in human populations are being conducted to asses the effects of hereditary, environmental, and life-style factors on the occurrence of cancer.

Over the past fifty years, the application of increasingly sophisticated observational methods in cancer epidemiology has led to the characterization of high and low risk populations throughout the world and to the identification of multiple chemical, physical, and microbial carcinogens, as well as agents that may inhibit carcinogenesis. The notion that chemical exposures can cause cancer is well accepted. Chemicals have been found that cause genetic damage and induce neoplastic transformation of cells. Most of the recognized carcinogens are chemicals to which humans are exposed, which further supports the hypothesis that cancer is a disease predominantly related to environmental exposures.

One of the first authoritative lists of cancer-causing agents, and probably the best at that time, was prepared by a WHO expert committee in 1964 (World Health Organization, 1964). Among the recognized etiological factors susceptible to control are exposure to sunlight; tobacco smoking; chewing of betel, nass, and tobacco; consumption of alcohol; atmospheric pollution; ionizing radiation; and several specific industrial cancer hazards (Schottenfeld et al., 1996). Thus, it is not unreasonable to assume that other chemicals among the thousands to which we are exposed will be identified as carcinogenic to humans.

The attitude prevailing today is that only epidemiological studies may provide unequivocal evidence that an exposure is carcinogenic in humans. Chemicals demonstrated to be carcinogenic in animals cannot always be assumed to be human carcinogens until there is epidemiologic evidence for such an association (Rothman et al., 1998). As a consequence, experimental evidence, in particular the one obtained in long-term animal tests, has often been regarded as a secondary line of evidence. Nevertheless, past experience showed that the experimental evidence of carcinogenicity indeed preceded evidence in humans for certain chemicals, and it could have been used to discontinue exposure before confirmation from studies in humans became available. This was the case of 4-aminobiphenyl, aflatoxins, mustard gas, DES, melphalan, 8-methyoxypsoralen + UV radiation, and vinyl chloride (Tomatis et al., 1989).

Medications are deliberately ingested by or injected into people in amounts usually much greater than other chemicals found in the environment that are suspected to be carcinogenic. There is good evidence that some drugs can increase the risk of cancer, thus raising the possibility that other drugs may have similar effects. Although some drugs have been shown to be carcinogenic in animals, few have been demonstrated to initiate or promote the development of cancer in humans (Schottenfeld et al., 1996). This is true especially for drugs that are widely used over long periods of time for the treatment of chronic illnesses.

In particular, the status of antidepressant drugs as possible carcinogens in humans remains unclear. Animal and epidemiologic studies provide inconsistent results (Steingart et al., 1995). In 1993, a study in fruit flies showed that some tricyclic antidepressants (TCAs) were genotoxic (Van Schaik et al., 1991; and Van Schaik et al., 1993). Consistent results were found in humans in a large epidemiologic study which demonstrated an association between exposure to the same TCAs and the development of breast cancer (Sharpe et al., 2002). The consistency of the results of the above mentioned studies raises the question of whether the use of these antidepressants is associated with the development of other types of cancer. The relatively widespread use of these drugs makes this question important from a public health point of view.

The objective of this study was to investigate the relation between antidepressant drug use and the risk of cancer (at 4 different sites) using a multiple site-specific case-control approach. The general hypothesis tested was that people exposed to TCAs are at increased risk of developing cancer.

Chapter 2: Review of the literature

This chapter will be divided into four sections. The first section will include a brief review of cancer development as well as a description of the cancer sites under study. The second section will be devoted to reviewing depression as a disease, as well as the use of antidepressants. The results of the previous studies that assessed the association between the use of antidepressants and the development of cancer will be provided in the third section. Finally, the conclusion, as well as the rationale and the relevance of the current study, will be summarized in the fourth section.

2.1 Cancer

2.1.1 Introduction

Cancer is the second leading cause of death in the United States and Canada, exceeded only by heart disease. In 2000, in the US, approximately 1.2 million persons were expected to receive new diagnoses of cancer, and 0.55 million persons were expected to die from this disease (23% of all deaths) (American Cancer Society, 1993; Boring et al., 1994; and Greenlee et al., 2000). Since 1990, approximately 12 million new cases have been diagnosed, and nearly five million lives have been lost to cancer in the US. The National Cancer Institute estimates that more than 8 million cancer survivors are alive in the US today (Ries et al., 1999). As for Canada, an estimated 132,100 new cases and 65,000 deaths from cancer were expected in 2000.

Among Canadian children in the late 1990s, an average of 879 were diagnosed with cancer and 176 died from cancer each year.

The financial costs of cancer are great both to the individual and to the society as a whole. In the United States, the National Cancer Institute estimates overall annual costs for cancer at $107 billion; $37 billion for direct medical costs, $11 billion for morbidity costs (cost of lost productivity), and $59 billion for mortality costs (Thom, 1996).

As for the cancer sites that mainly account for the increased incidence of cancer in general, it was found that, in 1999, the most frequently diagnosed cancers were breast cancer in women and prostate cancer in men (Greenlee et al., 2000). The cancers that caused the most deaths in the United States were lung cancer (first in each sex), colorectal cancer (second in both sexes combined), breast and uterine cancers in women, and prostate cancer in men. Together they accounted for more than 55% of all deaths from cancer. As for childhood cancers, the most common cancer was leukemia, which accounted for over 30% of new cases and deaths.

Cancer is primarily a disease of older people, with 70% of new cancer cases and 80% of deaths due to cancer occurring among those who are at least 60 years of age (National Cancer Institute of Canada, 1997). As the population continues to grow in size and shifts to an older age distribution, increasing numbers of people will be affected by cancer. Cancer risk is not the same for both sexes where males develop and die from cancer with greater frequency than females. The lifetime risk of developing cancer has been estimated to be one in two men and one in three women (Ries et al., 1999).

2.1.2 Definition

Cancer refers to an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the surrounding normal tissues and persists in the same excessive manner after cessation of the stimuli which evoked the change (Willis, 1952). Cancer may also be called a malignancy, a malignant tumor, or a neoplasm, meaning "new growth". It results from the continuous and rapid production of abnormal cells that invade and destroy other tissues.

Cancer can arise from any type of tissue. Most cancers are named for the type of cell or organ in which they start. If a cancer spreads (metastasizes), the new tumor bears the same name as the original (primary) tumor. For example, if lung cancer spreads to the liver, the cancer cells in the liver are lung cancer cells. The disease is called metastatic lung cancer (not liver cancer).

Cancer is a complex family of diseases and carcinogenesis is a complex process. From a clinical point of view, cancer is a large group of diseases, perhaps up to a hundred or more, that vary in their age of onset, rate of growth, state of cellular differentiation, diagnostic detectability, invasiveness, metastatic potential, prognosis, and response to various therapeutic modalities. From a molecular and cell-biological point of view, however, cancer may be a relatively small number of diseases involving alterations to a cell's genetic apparatus. Ultimately, cancer is a disease of abnormal gene expression of the genes regulating cell division and apoptosis (programmed cell death). The cellular properties that malignant cancer cells have in common include their unregulated cellular proliferation, invasiveness, metastatic potential, and their resistance to apoptosis.

Cancers are tough opponents because they do not abide by the same regulations as the normal cells. They can multiply out of control without aging or dying. They have the ability to change quickly and to acquire mechanisms that help them resist recognition and attack by the immune system. They can even release proteins that help build a network of blood vessels to nourish themselves with nutrients and oxygen.

2.1.3 Cell division

Growth, renewal, and repair in all multicellular organisms depend on formation of new cells by repeated division of pre-existing ones. Two processes of cell division are distinguished, mitosis, which occurs in somatic cell types, and meiosis, which takes place only in the development of germ cells in the ovary and testis.

2.1.3.1 Cell cycle

A somatic cell undergoing mitosis divides to form two daughter cells each with the same chromosome complement as the parent cell. The frequency of cell division varies greatly among the many cell types in the body.

The cell cycle is defined as a repeating sequence of biochemical and morphological events taking place in the cell. The key biochemical event of the cell cycle is the replication of the DNA strands that form the chromosomes. DNA synthesis is not a continuous process from one mitosis to the next but rather occurs during a discrete period of the intermitotic time.

The cell cycle can be subdivided into four temporally distinct phases: mitosis, G_1, S, and G_2. Mitosis is the nuclear division that a cell undergoes to produce two daughter cells with identical copy of its genetic material. G_1 is the interval during which the daughter cells increase in size, and is between the end of mitosis and the initiation of DNA replication (S). The S phase is the portion of the cell cycle dedicated to fulfilling the specialized functions of a given cell type, ie DNA synthesis. G_2 is the interval between the end of the S phase and the beginning of the next mitosis and it represents the time required to organize the nucleus for the events of mitosis (Fawcet, 1986; Moossa et al., 1991).

The length of a cell cycle can vary depending on the cell type and environmental conditions. For mammalian cells, the cell cycle can be as long as several days. The entire process of cell renewal is referred to as the cell turnover, and its duration is the cell turnover time. In humans, the mucosa of the jejunum has the fastest rate of turnover of any tissue in the body, where the complete cell cycle occupies about 24 hours (Fawcet, 1986). The gastrointestinal epithelium is completely replaced in two to five days. The tissue renewal time is 15 to 30 days for skin, and 50 days for pancreas (Sell et al., 1994).

2.1.3.2 Cell differentiation

Cells in vivo can exist in a nonproliferating (quiescent) growth state in which they are inactive with regard to proliferation (do not progress through the cell cycle), but are extremely active in carrying out the specialized functions dictated by the state of differentiation (Moossa et al., 1991). Cells can also exist in a proliferating growth state, in which they progress through the cell cycle and ultimately divide. Some cells can undergo a change in growth state, whereas for others as in terminally differentiated cells, growth state transitions cannot occur (Baserga R, 1985; Pardee et al., 1978; and Prescott, 1987).

Stem cells are undifferentiated cells that are able to retain the ability to divide throughout life and give rise to any of the body's more than 200 cell types, that in turn can become highly specialized and take the place of cells that die or are lost. Unlike mature cells, which cannot replicate, stem cells can both renew themselves as well as create new cells of whatever tissue they belong to.

Two examples of tissues composed totally or predominantly of quiescent cells are liver and nerves (Moossa et al., 1991). Hepatocytes and neurons are both highly differentiated and very long-lived cell types that normally do not divide during the life of the adult organism. In the liver, however, after partial hepatectomy (removal of part of the organ) or injury to the liver, the remaining cells are stimulated to proliferate rapidly until the original volume of liver has been restored. Nonproliferating hepatocytes, therefore, exist in a reversible quiescent state. By contrast, there are no stimuli known to reactivate the proliferation of mature neurons. Once fully differentiated, neurons are apparently incapable of cell division. Thus, neurons exist in an irreversible quiescent state. The distinction between reversible and irreversible quiescent states has important implications for the susceptibility of cells to neoplastic transformation (Lenbard et al., 2001). In a number of epithelia, such as those of the gastrointestinal tract and the skin, there is a continual loss of fully differentiated superficial cells, and thus a population of undifferentiated stem cells retain the capacity for rapid proliferation to provide continual replacement commensurate with the rate of cell loss.

Complex tissues contain cell populations in different states of differentiation and often in different growth states. For example, skin contains terminally differentiated keratinocytes that are irreversibly quiescent, fibroblasts that are reversibly quiescent, and epithelial stem cells that proliferate regularly.

2.1.3.3 Cell division in relation to tumor cells

The increase in the number of cells is one way in which normal tissues grow in mass or replace dead cells. It is also the predominant mechanism by which tumors grow in mass. The basic biochemistry of normal and tumor cells are remarkably similar. Tumor cells do not necessarily grow faster than normal cells and they generally go through all four phases of the cell cycle when they proliferate.

Nevertheless, tumor cells are defective in one or more regulatory mechanisms that normally prevent inappropriate proliferation. Usually, the transformed malignant cells fail to stop in the G_1 or at the G_1/S boundary in the cell cycle when they are subject to metabolic restriction of growth (Moossa et al., 1991). In addition, tumor cells often modify their local environment such that it becomes more favourable for cell proliferation.

Cell proliferation is regulated by both positive and negative regulatory mechanisms that control growth state transitions and progression through the cell cycle. Neoplastic growth can be influenced by increased sensitivity to (or activation of) growth stimulatory mechanisms or from decreased sensitivity to (or inactivation of) growth inhibitory mechanisms (Moossa et al., 1991).

Tumor cells from different origins display a wide spectrum of growth control defects. However, there is strong evidence that no single defect in growth control can fully account for the tumorigenic phenotype; multiple defects are required for tumorigenesis in tumor cells from a single origin, and thus these cells are often defective in more than one growth regulatory mechanism (Moossa et al., 1991). Thus, by the time a tumor has been detected, the cells have undergone multiple changes that together allow relatively autonomous proliferation.

Apoptosis is the normal physiological process of cell death that functions to control cell populations during embryogenesis, immune responses, hormone withdrawal from dependent tissues, and normal tissue homeostasis. One of the growth control defects that tumor cells show is their resistance to apoptosis.

2.1.4 Carcinogenesis

Mutation lies at the heart of carcinogenesis, and it may be acquired by the action of both external (chemicals, radiation, and viruses) and internal (hormones, immune conditions, and inherited mutations) factors. Three classes of normal regulatory genes - the growth-promoting protooncogenes, the growth-inhibiting cancer-suppressor genes (antioncogenes), and genes that regulate programmed cell death - are the principal targets of genetic damage.

On the other hand, laboratory and human data reveal the existence of two distinct classes of cancer genes (Moolgavkar, 1986; and Cotran et al., 1999).

1- The cancer-causing genes or the oncogenes, which develop from the protooncogenes: cellular genes that regulate normal growth and differentiation. Protooncogenes and cellular oncogenes are dominantly inherited and are normal components of all cells. They code for proteins that are involved in cellular growth and development. In many cancers, it has been established that activated oncogenes mediate neoplastic transformation and uncontrolled growth. Activation during the carcinogenic process might occur through major genetic alterations, such as chromosomal translocation, transposition, major deletions, or formation of new genes, or simply by the processes of transcription, transversion, or minor deletions. It is only in the transformed cell that the oncogene proteins escape this regulation.

2- Tumor-suppressor genes (antioncogenes or regulatory genes) are another class of genes which play an important role in human carcinogenesis. These genes normally suppress cell division, stimulate terminal differentiation, and maintain genomic stability. And, in contrast to oncogenes, a mutation that inappropriately inactivates these genes increases the probability of neoplastic transformation. They are recessively inherited and require the loss of both genomic alleles to affect function. The inactivation of specific tumor-suppressor genes may be responsible for the development of specific neoplasms.

2.1.5 Cancer development

All carcinogenesis models assume that carcinogenesis is a multistage process and that cancer is the end result of a sequence of changes that began in a single cell. The multistage model of carcinogenesis was introduced by Berenblum who described the carcinogenic process of mouse epidermis induced with tetradecanolyphorbol-13-acetate (TPA) (Berenblum, 1947; and Berenblum, 1954). The model also found application to virus-induced rabbit papilloma and the spontaneous mammary neoplasia of rabbits (Greene, 1940), which further helped in the understanding of carcinogenesis.

The multistage model can be differentiated into three main stages of development: initiation, promotion, and progression. The first event in the multistage model of carcinogenesis is that there is the formation of a new cell called the "initiated cell". The initiated cell can be the beginning of cancer, if certain events follow. Once a new cell becomes "initiated" it is unlikely that the cell will revert to its former normal self, and the only way it can be removed is by an event that leads to cell death. Although the process of initiation is irreversible, it is also, by itself, relatively unimportant, compared with the stages of promotion and progression in relation to the ultimate appearance of cancer as a disease (Schottenfeld et al., 1996).

Figure 1 is a graphical representation of the 3 stages of the multistage process of carcinogenesis.

2.1.5.1 Initiation

Initiation, the first stage in the natural history of neoplastic development, is a permanent and irreversible alteration in the genetic structure of a cell that confers the potential to develop into a neoplastic clone of cells, with the capacity to become malignant. This is a characteristically rapid and irreversible event, which has been described by Berenblum (1954), resulting in the formation of a small number of latent or dormant tumor cells. The initiated cell may remain latent for long periods of time until exposure to a promoting agent and subsequent growth of the nascent tumor. Although the initiation event is difficult to observe, its presence may be inferred on the basis of its future behavior.

The mechanism of initiation by a variety of carcinogenic compounds has been widely studied and involves damage to the DNA. Cell biologists believe that the crucial event which initiated cancer usually occurs in the cellular DNA of a regenerating stem cell. This could be a break in a chromosome caused by UV irradiation or an oxidation of a DNA nucleotide base by a chemical. The neoplastic potential is a function of the strength and the duration of the carcinogen applied, as well as time from first exposure. In order for these initial lesions to affect a permanent change in the DNA structure, however, it is vital for the cell to undergo a rapid replication since most injuries are corrected by DNA repair enzymes. For example, a methylating agent might produce a point mutation resulting in the replacement of a Guanine-Cytosine base pair to an Adenine-Thymine base pair, or a chromosome breakage could result in the translocation of genes from one chromosome to another. In fact spontaneous point mutations occur frequently during cell replication. It is only when these mutations are not corrected and are transmitted to the daughter cells that a permanent mutation is created.

Initiation of a cell may be followed by the cell's death either through toxicity of the carcinogen or destruction by the host immune defense, repair by DNA repair enzymes, indolent persistence, or proliferation under the influence of promotion. After the cell is initiated it may go through a typically long phase called the promotion phase.

2.1.5.2 Promotion

Berenblum described promotion as entailing two processes, cellular proliferation and delay of cell maturation (Berenblum 1954). The characteristic of the stage of promotion that clearly distinguishes it from the stages of initiation and progression is reversibility. Unlike initiation, a variety of environmental alterations (including the frequency with which the promoting agent is administered) and the aging process can continually modulate the stage of promotion.

In contrast to the initiation stage, the mechanism of promotion is not well understood. Agents which induce this phase are called promoters, and might be exogenous or endogenous factors. Numerous actions of promoters have suggested underlying tumor promotion including stimulation of proliferation, altered gene expression, generation of oxygen free radicals, inhibition of intercellular communication, and inhibition of apoptosis (Moolgavkar, 1986).

The promotion phase is characterized by the unregulated increase in number of cells originating from the initiated cell. Therefore, the initiated proliferating stem cells express the altered genotype. They are characterized by both a behavior and a morphology that are different from the tissue in which they originate. These cells might be identified in histological slides by their atypical appearance.

Cancer cells fail to stop proliferating when cell density reaches that of a monolayer of cells in contact with one another (i.e., loss of contact inhibition). As a result, cancer cells overgrow and form multicell layers called foci. Typically, normal human cells grown in culture display a finite number of population doublings or passages in cell culture before they stop growing and die. Often, this process is termed in vitro aging or senescence. Cancer cells in culture show no restriction in their number of proliferative generations. This unlimited capacity for proliferative growth is termed immortalization.

Normal human cells in cell culture require the presence of high levels (5%) of serum for optimal proliferative growth. In the presence of low levels of sera, cells remain viable but do not proliferate readily. The lessened dependence on exogenously supplied growth factors corresponds with cancer cell ability to display autonomous growth characteristics. Malignant cells can produce growth factors and can express receptors for these same growth factors and thus, lose their dependence on exogenously supplied growth factors (Lenbard et al., 2001).

The classic experiments that allowed the distinction between initiation and promotion were performed on mouse skin and are outlined in Figure 2 (Cotran et al., 1999). The following concepts relating to the initiation-promotion sequence have emerged from these experiments:

1. Initiation results from exposure of cells to an appropriate dose of a mutagenic agent (initiator); an initiated cell is in some manner altered, rendering it likely to give rise to a tumor (groups 2 and 3). Initiation alone, however, is not sufficient for tumor formation (group 1).
2. Initiation causes permanent DNA damage (mutations). It is therefore rapid and irreversible and has "memory". This is illustrated by group 3, in which tumors were produced even if the application of the promoting agent was delayed for several months after a single application of the initiator.
3. Promoters can induce tumors in initiated cells, but they are nontumorigenic by themselves (group 5). Furthermore, tumors do not result when promoting agent is applied before, rather than after, the initiating agent (group 4). This

indicates that, in contrast to the effects of initiators, the cellular changes resulting from the application of promoters do not affect DNA directly and are reversible.

4. That the effects of promoters are reversible is further documented in group 6, in which tumors failed to develop in initiated cells if the time between multiple applications of the promoter was sufficiently extended.

2.1.5.3 Progression

The final stage is the progression to cancer. It is the stage in which malignant disease appears, and is most directly associated with the development of cancer as a disease in humans that directly involves cancer therapy. Progression is an irreversible qualitative change in the nature of the cellular lesion during its development to a malignant neoplasm (Foulds, 1964). It is an irreversible stage since it demonstrably changes the structure of the genome of the neoplastic cell, and thus it affects the structure and function of the cell. Such changes continue to progress during this stage, and are directly related to the increased unrestricted growth, metastasis, invasiveness, transplantability, loss of contact inhibition, biochemical disturbances, and autonomy of growth; however, there is no order in the development of these characteristics, and furthermore there is no one trait or set of traits that has been defined as the beginning of tumorigenesis.

Once progression has begun, the action of promoters will not be needed anymore. It is the stages of initiation and progression that involve changes in the structure of the genome of the cell (although it is only demonstrable during the stage of progression).

2.1.5.4 Carcinogenic agents

Based on the existence and characteristics of the stages of initiation, promotion, and progression during carcinogenesis in animal systems, the classification of carcinogenic agents may be related to the stage(s) at which they exert their principal effects on the carcinogenic process (Schottenfeld et al., 1996):

1- Initiating agents are capable only of initiating cells

2- Promoting agents are capable of causing the expansion of initiated cell clones

3- Progressor agents are capable of converting an initiated cell or a cell in the stage of promotion to a potentially malignant cell

4- Complete carcinogens are agents possessing the capability of inducing cancer in normal cells; usually possessing properties of initiating, promoting, and progressor agents

5- Non carcinogens do not affect any of the stages or carcinogenesis, and thus acute or chronic exposure does not lead to the development of neoplasia.

The words “initiator”, promoter”, and “progressor” were originally defined within the context of experiments on chemical carcinogenesis in animals. They had to be administered in the proper sequence (initiator followed by promoter) to produce tumors. In epidemiology, an initiator is often thought of as an early-stage carcinogen, whereas a promoter is thought of as a late-stage carcinogen (Moolgavkar, 1986). In differentiating between these two types of carcinogens, one should take into consideration factors such as: the time since the initial exposure, the duration of exposure, the time following cessation of exposure until diagnosis of cancer, and the age at first exposure to the agent, although in many cases it may not be possible to determine each of these parameters with confidence.

Current understanding of chemical carcinogenesis suggests that chemicals act at one or more stages in a process that includes initiation of previously normal cells and promotion of these cells toward malignancy. The process may require 20 years or more to produce clinically detectable cancer (Farber, 1987). For both initiation and promotion, prolonged exposure is considered important, although in some cases a single exposure may be sufficient to initiate cells.

2.1.5.5 Latency period

Cancer, like most diseases, is characterized by a period of latency between the initial etiologic insult and the clinical appearance of the disease itself (Thomas, 1988). This period, which is usually very long lasting up to 30 years, could be divided into an induction period followed by a latent period. The time between the first application of the carcinogen or exposure and development of the first tumor cell is called the induction period. When the induction period ends, the latent period begins. The latent period is the period from development of the first tumor cell to detection or diagnosis of cancer. This period is a function of not only how quickly the cancer manifests itself clinically, but also the state of diagnostic technology. Among the first to describe a latency period in human neoplasia was Ramazzini (Wright, 1964), who observed a high incidence of breast cancer in Catholic nuns and reasoned that the causative factor was the lack of parity in this population. This implied a latency period between the lack of pregnancy in the early years of life and the development of mammary carcinoma in later years.

2.1.6 Histological classification (cell of origin)

Cancer, which may arise from any type of cell in any body tissue, is not a single disease but includes a large number of diseases classified according to the tissue of origin and type of cell in which new growth occurs. Several hundred such classes exist, constituting three major subtypes:

1- Carcinomas, malignant tumors of epithelial or organ parenchymal derivation, include the most frequently occurring forms of human cancer (85% of all registered cancers). They arise from the epithelial tissue, which is made up of the cells that cover the external surface of the body (such as the skin) or that line the internal cavities and organs, plus those cells derived from the linings that form glands (such as glandular tissue of the breast and prostate). In other words, the epithelial cells include the cells that secrete or otherwise process the body's chemicals and thus, are the first point of contact of the body with environmental substances and circulating carcinogens or pre-carcinogens. In addition, epithelial cells and blood cells are the major dividing cells in adults. This is important because most cancers become invasive and clinically important only after the cells originally damaged by a carcinogen have undergone several divisions. Muscle or fat cells, with a low rate of cell division, although exposed to radiation or some other carcinogen, will be less likely than epithelium to undergo sufficient proliferation for latent malignant changes to be manifested clinically. Two types of carcinomas could be differentiated: carcinomas with a structure resembling skin are termed squamous cell carcinomas, and those that secrete mucins or hormones or at least forming gland-like structures are called adenocarcinomas.

2- Sarcomas arise from connective and supportive tissue such as fat, fibrous tissue, bone, cartilage, blood vessels, nerves, and muscles.

3- Leukemias and lymphomas include the cancers that involve blood-forming tissue and are typified by the enlargement of lymph nodes, the invasion of the spleen and bone marrow, and the overproduction of immature white cells.

Tumors are also classified as either benign or malignant. The empirically known biological behavior of the tumor, as well as its microscopical appearance are the most important features used to differentiate between these two types of tumors.

Benign tumors grow only in the tissue in which they originate and are usually separated from neighboring tissue by a surrounding capsule, or sac. Benign tumors generally grow slowly and in structure closely resemble the tissue in which they first grew. The clearest cases of benign tumors are skin moles and warts. A few benign tumors, such as polyps of the colon, may later become malignant. Benign tumors may in some cases endanger a person's health by obstructing, compressing, or displacing neighboring tissues or organs, as in the brain. Chief among these are brain tumors called gliomas, which can grow large enough to exert substantial pressure on nearby brain structures and destroy respiratory function. A liver tumor can kill by destroying the vital functions of that organ.

Malignant cells on the other hand, are unable to differentiate or mature into an adult, functioning state. As these cells multiply, they may form a mass called a tumor, which enlarges and continues to grow without regard to the function of the tissue in which it originated. Cells in malignant tumors are sometimes said to have lost their characteristic function. The most important property rendering a tumor malignant is the ability to invade nearby or distant tissues; this spread to distant tissues is called metastasis, and it usually occurs by means of the blood or lymph vessels.

2.1.7 Metastasis

Metastasis is the spread or movement of cancer cells from the primary cancer site to another area of the body. Malignant cells are characterized by their capacity to metastasize (i.e., to invade surrounding normal tissues through the bloodstream, lymphatic systems, or other fluids to distant organs). Other than certain white blood cells, this is something most normal cells cannot do, and it is the most deadly characteristic of cancer.

The routes and sites of metastases vary with different primary cancers. One route of metastasis is when a cancer extends through the surface of the cancerous organ into the space surrounding the organ where tumor cells may break away from the surface and penetrate the fibrous boundaries that normally separate one tissue from another and grow on the surface of the adjacent organs.

The tumor cells can also infiltrate the walls of the lymph vessels and be carried to the lymph nodes and pass into the lymphatic circulation. Tumor cells shed into the lymph system often proliferate in the nearest cluster of lymph nodes, where they grow before spreading to more distant parts of the body.

Many cancers directly shed cells into the bloodstream early in their growth. Most of these cells die in the bloodstream, but some lodge against the surface and pass through blood vessel walls into the tissue to grow into a tumor, a process called vascular invasion. Others may divide only a few times, forming a small nest of cells that remain dormant as a micrometastasis. They may remain dormant for many years, only to grow later for reasons not yet known. Fewer than 1 in 10,000 cells shed from the primary tumor are thought to survive, but these are enough to spawn secondary tumors elsewhere in the body.

Tumor cells shed from colon cancer, for example, are carried by the portal and lymphatic circulation to the liver, where secondary tumors then arise. Tumor cells from other areas of the body travel by the blood through the heart and on to the lungs, where they start metastatic lung tumors, before being carried to other organs. The lungs and liver are therefore the most common sites of metastases.

2.1.8 Staging

Microscopic examination of tissue is used to determine tumor grade and stage, which together offer important prognostic information. Tumor grading is based primarily on the degree of differentiation of the malignant cells, their nuclear features, and an estimate of the rate of growth as indicated by the mitotic rate. Tumor staging is based on features of the untreated primary lesion (including size and extent of tissue invasion) and on the presence of lymph node or hematogenous metastasis as determined by microscopic examination. Four stages have been defined, each stage being progressively more serious. Stage one tumors are small and local, stage two and stage three tumors are larger and usually involve lymph nodes, and stage four tumors have metastasized to other areas of the body.

2.1.9 Description of the cancer sites under study

In the absence of specific knowledge about etiology of some of the cancer sites, they can only be described in terms of risk factors and statistical associations. In the following section, a description of the cancer sites considered in this study is given, along with some information on the known risk factors.

2.1.9.1 Female breast cancer

Breast cancer (ICD-O: C50-C50.9) (Percy et al., 1990) is a malignant tumor in the glandular tissues of the breast. It is the most common cancer in women (184,200 in 2000), accounting for almost 30% of all newly diagnosed cancers, and the second leading cause of cancer death (41,200 in 2000) in US women (Greenlee, 2000).

Carcinoma of the breast develops as a neoplasm of the ductal epithelium in over 90% of the cases, with the remainder developing as lower grade neoplasms from lobular epithelium (Schottenfeld et al., 1996).

A substantial body of experimental, clinical, and epidemiologic evidence indicates that estrogens play a major role in the etiology of breast cancer. Prolonged estrogen stimulation may increase the risk of developing breast cancer (early menarche, late menopause, postmenopausal obesity). Risk of breast cancer increases with age (women in their 40's), nulliparity, and age at first birth. Other factors that were found to be associated with an increased risk of breast cancer include use of postmenopausal estrogen replacement therapy, oral contraceptive use, diet, and alcohol intake. Other factors, such as physical activity, were found to be protective ones against the development of breast cancer. In addition, Inherited, or familial, breast cancer accounts for 5 to 10% of all breast cancers. The importance of family history is reflected in the nine-fold greater risk if a first-degree relative has had bilateral premenopausal breast cancer.

2.1.9.2 Prostate cancer

Prostate cancer (ICD-O: C61.9) (Percy et al., 1990) is a malignant tumor in the prostate, a gland in a man's reproductive system, which encircles the bladder outlet. In the United States, prostate cancer is expected to be the most common cancer in men (180,400 cases in 2000) and the second leading cause of cancer death in men (31,900 in 2000) (Greenlee, 2000). Prostate cancer accounts for approximately 29% of new cancer cases in men and 11% of cancer deaths.

It has been shown that risk of prostate cancer increases with age (especially among those older than 55 years) and family history of prostate cancer.

2.1.9.3 Ovarian cancer

Ovarian cancer (ICD-O: C56.9) (Percy et al., 1990) is the malignancy that occurs in one or both of a woman's ovaries. Ovarian cancer is the sixth leading cause of cancer and fifth leading cause of cancer death in US women; in 2000, an estimated 23,100 women are expected to receive a new diagnosis of this cancer, and 14,000 are expected to die from this disease (Greenlee, 2000).

Women older than 50 years old are at higher risk of developing ovarian cancer. Other risk factors for ovarian cancer include diet, history of ovarian cancer in the family, number of pregnancies, age at first birth, breast-feeding and use of oral contraceptives.

2.1.9.4 Non-Hodgkin's lymphoma

Non-Hodgkin's lymphomas (ICD-O Morphology code: 959*, and 967*-972*) are cancers that start in the lymphatic system. These lymphomas occur both in children and in adults. These lymphomas are the third most frequent type of cancer in children. An expected 7,400 new cases and 1,400 deaths are expected in the United States in 2000 (Greenlee, 2000). Non-Hodgkin's lymphoma is the fifth leading cause of cancer and cancer death in US men and the fifth leading cause of cancer and the sixth leading cause of cancer death in US women (Greenlee, 2000).

These types of cancer occur most often in people between 15 and 34 and in people over the age of 55. Brothers and sisters of those with these cancers have a higher-than-average chance of developing this disease. People with certain medical conditions are at higher risk of developing Hodgkin's disease. Slightly higher rates of the disease occur among people with reduced immunity.

2.2 Antidepressants

2.2.1 Depression

A number of large-scale studies indicate that depression rates have increased worldwide over the past several decades. At least 8% of adults in the United States and Canada experience serious depression at some point during their lives; estimates of life-time incidence range as high as 19.5% (Angst et al., 1992; and Sellick et al., 1999). The total number of health related visits for depression in the United States increased from 11 million in 1985 to 20.4 million in 1994 (Pincus et al., 1998). A WHO report projects that by the year 2020 depression will rank second only to cardiovascular disease in terms of its disability-associated burden (Murray et al., 1996). The illness affects all people, regardless of sex, race, ethnicity, or socioeconomic standing. Furthermore, younger generations are experiencing depression at an earlier age than did previous generations (Weissman et al., 1995).

2.2.1.1 Definition

Depression, one of the most common mental illnesses among people of different ages, is characterized by intense sadness or loss of interest in usual activities, accompanied by poor appetite, insomnia or hypersomnia, psychomotor agitation or retardation, decreased sexual drive, fatigue, feelings of worthlessness, decreased concentration, or thoughts of death or suicide.

While everyone experiences episodes of sadness at some point in their lives, depression is distinguished from this sadness when symptoms are present most days for a period of at least two weeks. Severe depression, also called major depression, can considerably impair a person's ability to function in social situations and at work. As many as 10 to 15% of individuals with this disorder display suicidal behavior during their lifetime.

Depression can take several other forms. In bipolar disorder, sometimes called manic-depressive illness, a person's mood swings back and forth between depression and mania. People with seasonal affective disorder typically suffer from depression only during autumn and winter, when there are fewer hours of daylight. In dysthymia, people feel depressed, have low self-esteem, and concentrate poorly most of the time - often for a period of two years - but their symptoms are milder than in major depression. Some people with dysthymia experience occasional episodes of major depression. Mental health professionals use the term "clinical depression" to refer to any of the above forms of depression.

The illness may come on slowly then deepen gradually over months or years. On the other hand, it may erupt suddenly in a few weeks or days. A person who develops severe depression may appear so confused, frightened, and unbalanced that observers speak of a "nervous breakdown". Symptoms of depression can vary by age. In younger children, depression may include physical complaints, such as stomachaches and headaches, as well as irritability, "moping around," social withdrawal, and changes in eating habits. Children may feel unenthusiastic about school and other activities. In adolescents, common symptoms include sad mood, sleep disturbances, and lack of energy. Elderly people with depression usually complain of physical rather than emotional problems, which sometimes leads doctors to misdiagnose the illness.

2.2.1.2 Causes of depression

Some depressions seem to come without any apparent reason. Others seem to have an obvious cause: a marital conflict, financial difficulty, or some personal failure. Yet many people with these problems do not become deeply depressed. Psychologists believe depression results from an interaction between stressful life events and a person's biological and psychological vulnerabilities.

Psychological theories of depression focus on the way people think and behave. In a 1917 essay, Austrian psychoanalyst Sigmund Freud explained melancholia, or major depression, as a response to loss - either real loss, such as the death of a spouse, or symbolic loss, such as the failure to achieve an important goal. Freud believed that a person's unconscious anger over loss weakens the ego, resulting in self-hate and self-destructive behavior. It is proposed that depressed people tend to view themselves, their environment, and the future in a negative light because of errors in thinking. These errors include focusing on the negative aspects of any situation, misinterpreting facts in negative ways, and blaming themselves for any misfortune. People learn these self-defeating ways of looking at the world during early childhood. This negative thinking makes situations seem much worse than they really are and increases the risk of depression, especially in stressful situations.

Psychologists agree that stressful experiences can trigger depression in people who are predisposed to the illness. Stressful experiences may include the death of a loved one, divorce, pregnancy, the loss of a job, and even childbirth. About 20% of women experience an episode of depression, known as postpartum depression, after childbirth. In addition, people with serious physical illnesses or disabilities often develop depression.

By studying twins, researchers have found evidence of a strong genetic influence in depression. Genetically identical twins raised in the same environment are three times more likely to have depression than fraternal twins. Moreover, women are two to three times more likely than men to suffer from depression (Weissman et al., 1995).

Depression is considered to be a long-term, often lifelong, disorder. Results of a study of 431 patients treated within a community showed that after 5 years, 55% of patients had suffered at least one recurrence of the illness, 12% had been chronically depressed all the time, and only 33% had recovered and were in continued good health (Keller et al., 1992). After 15 years, the majority of patients had suffered at least one recurrence (82%), 6% had been depressed the entire time, and only 12%

had recovered and stayed well. Risk factors for recurrence include history of frequent of multiple episodes, onset after the age of 60 years, long duration for episodes, severe index episode, seasonal pattern, family history of depression, and comorbid anxiety disorder or substance abuse.

2.2.1.3 Depression and cancer

Throughout the 1980's, the relationship between depression and cancer risk was studied by several investigators. Some of the studies conducted to assess this association found that depressed patients were at increased risk of developing cancer, whereas other studies did not find an association.

Shekelle et al. (Shekelle et al., 1981) and Persky et al. (Persky et al., 1987) conducted 17- and 20-year follow-up studies to assess the association between depression at baseline and mortality from cancer in a sample of 2020 men. The authors found an increase in the risk of death from cancer associated with depression [OR = 2 (95% CI = 1.38 - 3.54)]. The association persisted after adjusting for the effects of age, cigarette smoking, alcohol consumption, and family history of cancer.

Linkins et al. (Linkins et al., 1990) conducted a 12-year follow-up study to assess the association between the presence of depression at baseline in 2264 subjects, and the development of cancer. The authors found a strong association between depression and the development of cancer which was limited to smokers.

Compared with non depressed people who never smoked, depressed mood at the highest level of smoking was associated with relative risks of 4.5 (95% CI = 1.9 - 10.6) for total cancer, 2.9 (95% CI = 0.9 - 9.3) for cancer at sites not associated with smoking, and 18.5 (95% CI = 4.6 - 74.4) for cancer at sites associated with smoking. The major disadvantage of this study was the lack of control for any of the major confounding factors.

More recently, in 1998, Penninx et al. (Penninx et al., 1998) conducted a population-based cohort study to examine the association between depressive symptoms and cancer. The authors used the Center for Epidemiologic Studies Depression scale to assess depression in 4825 subjects aged 71 years or older who were followed for a mean follow-up of 3.8 years. After adjustment for possible confounding variables, the hazard ratio for cancer associated with chronically depressed mood was 1.88 (95% CI: 1.13 – 3.14). This analysis was based on a small sample size, 146 chronically depressed persons (3% of the cohort), a feature which was one of the limitations of this study. Lack of adequate control for the effect of antidepressant drug use was another limitation, since information on antidepressant drug use was obtained only for the 2 weeks period prior to the inception of the cohort.

Other studies conducted to assess the same relation did not find any association between depression and the development of cancer. A cohort study conducted by Hahn et al. (Hahn et al., 1988) did not find any statistically significant association between depression and the subsequent development of breast cancer in a sample of 8932 women. In a study conducted by Kaplan et al. (Kaplan et al., 1988), the authors did not find an association between the presence of depressive symptoms and cancer incidence and mortality in a cohort of 6848 persons free of cancer. Zonderman et al. (Zonderman et al., 1989) did not find any significant risk for cancer morbidity or mortality in association with the presence of depressive symptoms in a 10-year follow-up study.

In 1994, Friedman (Friedman, 1994) conducted a follow-up study of up to 19 years, to assess the association between depression and incidence of cancer. The study population consisted of 923 patients with some form of depression diagnosed in a psychiatric clinic. The authors found that depressed patients showed a slightly elevated risk of developing cancer in comparison with the other members of a cohort of 143,574 persons who received prescriptions from a pharmacy [Standardized morbidity ratio = 1.21 (95% CI: 0.95 - 1.53)]. The risk of developing cancer increased when cancers diagnosed in the first 2 years after the diagnosis of depression were ignored [Standardized morbidity ratio = 1.38 (95% CI: 1.06 - 1.76)].

More recently, Gallo et al. conducted a 13-year follow-up study in which they assessed the association between depression at baseline and development of cancer among 2017 persons (Gallo et al., 2000). After adjustment for the effect of age, gender and tobacco and alcohol use, major depression was not found to be significantly associated with increased risk of cancer at follow-up. However, among women with major depression, the risk of breast cancer was increased [adjusted RR = 3.8 (95% CI: 0.6 - 2.8)], based on 25 breast cancer cases.

In summary, the evidence for an association between depression and cancer occurrence from the prospective cohort studies conducted to date is inconclusive, with finding either a lack of association or a weak positive association (McGee et al., 1994; Spiegel, 1996; Penninx et al., 1998; and Croyle, 1998). Such an association could have been a result of reverse causality bias in which the depressed mood is the consequence rather than the cause of the undiagnosed cancer (Linkins et al., 1990). Lack of control for the effect of confounding could have affected the results of these studies. Specifically, the effect of treatment of depression, such as antidepressant drug use, is an important factor that most of the studies failed to adequately control for.

2.2.2 Antidepressants

About 70% of patients with depression respond to antidepressant drug therapy and can experience a complete recovery from their depression (Richelson, 1994). However, relapses occur very frequently and patients must often take antidepressants to either prevent or treat relapses. Consequently, prolonged exposure to antidepressant drugs over extended periods is frequent.

Antidepressants are also used to treat other disorders such as anxiety disorders, agoraphobia (fear of open spaces), panic attacks, obsessive-compulsive neurosis, migraine headaches, and chronic pain (Hardman et al., 1996). These drugs are also used to treat enuresis (urinary incontinence) in children. Antidepressants are also frequently prescribed to cancer patients to treat pain, a fact that makes the association under study of specific importance.

Treatment of depression with antidepressants can be divided into two types: continuation and maintenance treatment. Continuation treatment begins after acute remission is achieved, and is intended to prevent relapses back into the depressive episodes. Most antidepressants take about two to three weeks of treatment before beneficial effects occur. Maintenance treatment attempts to prevent a recurrence of depression following completion of continuation therapy. It has been recommended that continuation therapy of 3-6 months after acute stabilization should be considered for all depressed patients, and maintenance therapy should be considered for many severely depressed patients of (Hirschfeld, 2000).

Thousands of neuronal signals are transmitted to an individual's brain each moment, controlling his breathing, movements, thoughts, and emotions. Neuronal circuits provide the basic "road map" for brain signals, and chemical neurotransmitters transmit signals from one neuron to another. Neurotransmission in the brain utilizes several chemicals and peptides. Neurotransmitters involved in depression include norepinephrine, dopamine, and serotonin.

Treatable neurotransmission diseases fall into two categories, those caused by too much neurotransmission and those caused by too little. The biogenic amine hypothesis suggests that depression is caused by impaired neurotransmission due to abnormally low levels of neurotransmitters in certain parts of the brain. Antidepressants are thought to work by increasing the levels of neurotransmitters in the brain. Specifically, antidepressants work by interacting with neurotransmitters at three different points: they can change the rate at which the neurotransmitters are either created or broken down by the body; they can block the process in which a neurotransmitter is recycled by a presynaptic neuron and used again, called reuptake; or they can interfere with the binding of a neurotransmitter to neighboring cells.

2.2.3 Specific description of antidepressants

Currently used antidepressant drugs fall into four classes (tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and atypical antidepressants). The following is a specific description of each of the antidepressants assessed in this study, categorized according to their classes. The chemical names, chemical structures, empirical formulae, and molecular weights of the antidepressant drugs used in the US and Canada are presented in appendix A (A.1 - A.4).

2.2.3.1 Tricyclic antidepressants

Tricyclic antidepressants (TCAs), named for their three-ring chemical structure (figure 3), were the first antidepressants to be discovered in the 1950s. TCAs block the reuptake of neurotransmitters into the presynaptic neurons, keeping the neurotransmitter in the synapse longer and making it more available for action on the postsynaptic cell. TCAs can be categorized according to their chemical structure into two groups: one having a carbon atom at position 5 in the central ring, and the other having a nitrogen atom at that position. Molecules with a carbon atom at position 5 (5-C) include amitriptyline, doxepin, maprotiline, nortriptyline, and protriptyline. Molecules with a nitrogen atom at that position (5-N) include imipramine, desipramine, clomipramine, lofepramine, and trimipramine. The TCA amoxapine is atypical and is included in neither group. Figure 3 shows the structural formula of amitriptyline and imipramine drugs representing the 5-C and 5-N groups, respectively. Undesirable effects of TCA use may include anticholinergic effects, cardiotoxicity, sedation, orthostatic hypotension, mania, hypomania, weight gain, impotence, or obstructive jaundice.

2.2.3.2 Monoamine oxidase inhibitors

Monoamine oxidase inhibitors (MAOIs) decrease the rate at which neurotransmitters are metabolized, thus increasing their synaptic concentration. This class includes isocarboxazid, moclobemide, phenelzine, and tranylcypromine.

Undesirable effects of MAOI use may include hepatotoxicity, excessive CNS stimulation, or orthostatic hypotension.

2.2.3.3 Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) became available in 1987; they block the reuptake of the neurotransmitter serotonin into presynaptic neurons, thereby prolonging its activity. Drugs in this class include citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline.

2.2.3.4 Atypical antidepressants

The atypical antidepressants are those which do not fall in any of the previously described categories, and thus are grouped into a separate category. Drugs in this category include nefazadone, trazodone, and venlafaxine.

2.2.4 Frequency of use of different antidepressants

Antidepressant medications in general are widely prescribed. In the United States, the number of depression visits during which an antidepressant medication was prescribed increased from 10.99 million in 1988 to 20.43 million in 1993 and 1994 ($p<0.01$) (Pincus et al., 1998).

Most of the currently used TCAs began to see broad use in psychiatry in the early 1950's and were the most-used antidepressant medications until mid 1990's (Voirol et al., 1999). Recently, prescribing patterns of antidepressant drugs have changed. Because of their equivalent efficacy and more favorable side-effect profile, prescribing of SSRIs has increased over time (Peretti et al., 2000; Mendlewicz et al., 2000). Despite this trend, TCAs are still being widely used (Potter et al., 1998). For example, a personal or family history of responsiveness to TCA pharmacotherapy may favor a TCA trial earlier rather than later in the treatment plan. Mamdani et al. found that the prescriptions for SSRIs accounted for 9.6% of antidepressant prescriptions dispensed in 1993 and 45.1% in 1997 in a population-based study of more than 1.4 million Ontario residents aged 65 years or older (Mamdani et al., 2000). In the same population prescriptions for tricyclic antidepressants fell from 79.0% in 1993 to 43.1% in 1997.

Although the prevalence of use of antidepressants among children and adolescents under the age of 18 is relatively low, it has significantly increased during the last few decades, particularly in the last 15 years. Younger generations are experiencing depression at an earlier age than did previous generations (Weissman et al., 1995). Social scientists have proposed many explanations, including changes in family structure, urbanization, and reduced cultural and religious influences. Antidepressants have been used to treat depression, anxiety, and attention deficit/hyperactivity disorders in children and adolescents.

Most of the studies that have assessed the prevalence of antidepressant drug use among very young children (younger than 5 years old), have found an increase in prescriptions for this age group over time. An analysis was carried out in 2000 to estimate the prevalence of antidepressant drug use among children aged 2 through 4 years in the US (Magno Zito et al., 2000). The prevalence was calculated using three large computerized data sources, for three different times (1991, 1993, and 1995). The prevalence (per 1000) of the use of antidepressants in general among the participants (almost 158,060 children) was found to be 1.4 in 1991, 2.1 in 1993, and 3.2 in 1995; whereas the numbers for tricyclic antidepressants were 1.3, 1.8 and 2.4 respectively. Another report described a 10-fold increase in prescriptions for an SSRI in the United States for children 5 years and younger between 1993 and 1997 (Minde K, 1998).

In the United States, around 20 million people have problems with accidental urination, when they are developmentally able to have control of their bladders (5 to 7 million are children 6 to 12 years old). This loss of urinary control is called "urinary incontinence" or enuresis. Although it affects many young people, it usually disappears naturally over time, which suggests that incontinence, for some people, may be a normal part of growing up. About 10% of 5-year olds, 5% of 10-year olds, and 1% of 18-year olds experience episodes of enuresis, and it is twice as common in boys as in girls. Antidepressant drugs (such as imipramine, amitriptyline, clomipramine and desipramine) are used to treat enuresis in children on a chronic basis (Rapoport et al., 1980). It acts on both the brain and the urinary bladder.

Unfortunately, total dryness with either of the medications available is achieved in only about 20% of patients.

2.2.5 Selection of antidepressants

Individual antidepressants have unique profiles of psychopharmacologic effects, and individual patients have unique profiles of depressive symptoms (Stahl, 1998). The initial choice of antidepressant drug therapy from among the wide variety of drugs available is based on both the pharmacologic characteristics of the antidepressant and each patient's characteristics (such as age, pregnancy status, smoking and drinking habits, psychosocial factors, and whether the patient has a prior history of response or non-response to a particular drug) (Kaplan et al., 1993; Richelson, 1994; and Flint, 1998).

None of the antidepressants has been proven more effective than the others in treating depression. Thus, the grounds for the choice among these antidepressants depends on the onset of action, elimination half-life, therapeutic blood level, side effects, drug interactions, toxicity associated with overdose, efficacy, and cost (Kaplan et al., 1993; Richelson, 1994; Rudorfer et al., 1997, and Flint, 1998).

The mechanism of action of antidepressants allows prediction of both adverse effects and therapeutic effects (Stahl, 1998). Because numerous pathways in the brain use the same neurotransmitter, manipulating transmission in a diseased pathway simultaneously affects synapses of normal neurons. For this reason, antidepressant drugs are notorious for causing a variety of side effects. These CNS drugs are considered as neurotransmitter modulators. And thus, some tricyclic side effects relate to the fact that these medications have similar effects on other neurotransmitters in the CNS, notably histamine and acetylcholine. In some cases, side effects, such as the sedating properties of some TCAs, might be advantageous for the treatment of specific diseases, such as comorbid anxiety and insomnia.

Doctors determine which antidepressant to prescribe according to the type of side effects an individual can tolerate. It is believed that many of the antidepressant-responsive conditions have a hereditary component. Thus, starting with the same agent to which a genetically related family member with the same disorder has responded favorably in the past may be likely to produce a beneficial effect.

Taking the TCAs as an example, there are two broad chemical classes of these drugs. The tertiary amines (amitriptyline, imipramine, trimipramine and doxepin), which have proportionally more effect in boosting serotonin than norepinephrine, produce more sedation, anticholinergic effects and orthostatic hypotension. Amitriptyline and doxepin are especially sedating. Secondary amines (nortriptyline, desipramine, and protriptyline) tend more toward enhancement of norepinephrine levels and hence toward irritability, overstimulation and disturbance of sleep. The tertiary amines, thus, are more useful where depression is accompanied by sleep disturbance, agitation and restlessness; whereas the secondary amines may be preferable where the depressed patient is fatigued, withdrawn, apathetic and inert. The psychiatrist's initial evaluation, therefore, must go into extensive detail about the pattern of depressive symptoms a person has experienced, in order to select the most appropriate drug. An impression about which side effects a person would best tolerate or benefit from will enter into the physician's choice of tricyclic as well. Overall, desipramine and nortriptyline are the most benign in terms of patient tolerance, and are often the initial TCA of choice.

However, these are just the broadest guidelines, and in practice, treatments are individualized in terms of agent and dose in a trial-and-error fashion. Since there is no way to predict with certainty which drugs will benefit any given patient, depressed patients may need to try several different antidepressants before a suitable one can be found.

2.3 Antidepressants and cancer

One implication of the chemical carcinogenesis theory is that drugs taken for long intervals may be more suspect as possible carcinogens than those used only briefly. Initial suspicion of drug-cancer associations often results from theoretical considerations of the chemical and pharmacokinetic properties of the compound, from results of in vivo or in vitro tests for mutagenicity or other genetic effects, or from reports of experiments in animals (Schottenfeld et al., 1996). In the following sections, the experimental and the epidemiological studies of the association between antidepressant drug use and cancer development are summarized.

2.3.1 Experimental studies of the effects of antidepressants on cancer risk

The main source of evidence for tumor promotion by antidepressant drugs was a Canadian study that received considerable attention when it was published because of the quality of the study and its disturbing implications (Brandes et al., 1992; Miller, 1993). Brandes et al. studied whether antidepressant drugs could promote tumor growth and development in rodents at concentrations relevant to the treatment of human depression (equivalent human dose range: 100-150 mg/day for amitriptyline, and 20-80 mg/day for fluoxetine) (Brandes et al., 1992; Brandes, 1992; Brandes et al., 1995; and Labella et al., 1996). The rationale behind carrying out this study was the structural similarity between antidepressants (amitriptyline, and fluoxetine) and N,N-diethyl-2-[4-(phenylmethyl)phenoxy] ethanamine HCL (DPPE), a derivative of tamoxifen that increases DNA synthesis in malignant cells and stimulates tumor growth in rodents. Three tumor models were studied: i) tumors transplanted via subcutaneous injections of C-3 fibrosarcoma cells in mice; ii) tumors transplanted via subcutaneous injections of B16f10 melanoma cells in mice; and iii) dimethylbenzanthracene (DMBA) induced mammary cancers in female rats. The results showed that both amitriptyline and fluoxetine promoted tumor growth in all of the 3 rodent models.

A similar study, however, conducted by the Food and Drug Administration's Division of Research and Testing was not able to replicate the results of Brandes et al. (Mathews, 1995; and Parchment et al., 1996). The authors studied the effect of the drugs considered in Brandes et al. (Brandes et al., 1992) on the promotion of tumor growth using the same published study design and methodology. Both TCAs and SSRIs were studied; no evidence was found that these drugs increased tumor growth in vitro or in laboratory rodents.

Wright et al., in 1994, tested the hypothesis that inhibition of cell death through apoptosis may underlie the mechanism of tumor promotion in chemical carcinogenesis (Wright et al., 1994). They found that amitriptyline and fluoxetine, along with 8 other known and suspected tumor promoters, blocked apoptosis (through inhibition of DNA fragmentation) in a variety of cell types including fibroblasts, myeloid and moncytic leukemias, and carcinomas derived from the prostate, breast, and liver. In addition, amytriptyline inhibited DNA fragmentation at a concentration even lower than serum levels in patients receiving a typical dose (100 mg/day) of this antidepressant. The cells gradually acquired resistance to apoptosis upon treatment with these drugs. The kinetics of this phenomenon was dose-related: cells cultured in the highest concentration of amitriptyline acquired resistance more rapidly than cells cultured in the lowest concentration.

In two studies, Iishi et al. investigated the effects of different antidepressants on the incidence and multiplicity of colon tumors, as well as on the serum norepinephrine concentration and the labeling index of colon mucosa in Wistar rats (Iishi et al., 1993; and Iishi et al., 1994). The colon tumors, which were induced by treating the rats with azoxymethane, were classified histologically as adenomas, carcinomas in situ, and adenocarcinomas. Rats were treated with azoxymethane in NaCl solution once a week for 10 weeks. In their first study (Iishi et al., 1993), desipramine hydrochloride dissolved in a saline solution was injected daily into the rats for 35 weeks. Treatment with desipramine significantly increased the incidence but not the number of colon tumors in week 35. In their second study (Iishi et al., 1994), pargyline (a monoamine oxidase B inhibitor) and clorgyline (a monoamine oxidase A inhibitor) were dissolved in a saline solution and injected in the rats each day for 35 weeks. Pargyline was found to enhance colon carcinogenesis in rats by week 35, whereas no effect was detected in relation to clorgyline. Two explanations for finding an effect of pargyline but not of clorgyline were considered: i) treatment with pargyline increased significantly the dopamine concentration in the nucleus more than treatment with clorgyline, or ii) treatment with pargyline resulted in a significant increase of vesicular norepinephrine in whole brain homogenates. These studies concluded that the antidepressants (desipramine and pargyline) enhanced experimental colon carcinogenesis by their effect of increasing the norepinephrine concentration in the colon wall and subsequently increasing the proliferation of colon epithelial cells.

Bendele et al. (Bendele et al., 1992) tested fluoxetine hydrochloride for carcinogenicity in three studies in Fischer rats and C57BL/6 x C3H F_1 mice. Each study consisted of a control group and three treatment groups to which fluoxetine was administered for 24 months at three different dietary daily doses. The three different doses administered to rats and mice were approximately 1-25 times the equivalent daily human dose for depression (20 mg/day). The authors did not find any statistically significant increase in incidence of any individual type of neoplasm in either rats or mice.

In 1991, Van Schaik and Graf assessed the genotoxicity of different tricyclic antidepressants using a test in Drosophila melanogaster (Van Schaik et al., 1991; and Van Schaik et al., 1993). Drosophila has been used in mutagenesis studies and also in short-term assays for identifying carcinogens. An array of known genotoxins that require bioactivation were detected by the wing spot test (also known as the wing-mosaic system), attesting to the validity of the assay (Vogel et al., 1999). The wing spot test allows detection of several genetic end-points such as mutation and recombination. Three-day-old larvae, trans-heterozygous for 2 linked recessive wing hair mutants (multiple wing hairs and flare), were fed the test compounds in water mixed with a standard dry food for 48 hours. Wings of the emerging adult flies were scored for the presence of spots of mutant cells which can be the consequence of either somatic mutations or mitotic recombination events. Imipramine, desipramine, clomipramine, and lofepramine, which have a nitrogen atom at position 5 in the central ring of their chemical structure, were clearly genotoxic. Three out of the 4 drugs showed a dose-response relationship. Figure 4 shows the dose-response relationships for amitriptyline, desipramine and imipramine with total spots per wing considered as the response. An explanation as to why lofepramine did not show any dose-response relationship might be related to its chemical structure. Lofepramine is a compound similar to imipramine and clomipramine with the difference being a longer and more complex side chain attached to the nitrogen atom. Amitriptyline, protriptyline, and nortriptyline, which have a carbon atom at position 5 in their central ring, were not genotoxic. The authors suggested that the nitrogen atom at position 5 in the 7-membered central ring of the tricyclic molecule was responsible for the genotoxicity of the compounds in Drosophila. This genotoxicity assay (wing spot test) using Drosophila was further tested by an epidemiological study, discussed in the next section (Sharpe et al., 2002).

2.3.2 Epidemiological studies of the effects of antidepressants on cancer risk

Epidemiologic studies have provided inconsistent results regarding associations between antidepressant drug use and the risk of cancer. The following section summarizes all the studies, identified through an extensive literature review, assessing the underlying association (starting with the earliest and ending up with the most recent ones). A tabulated summary of all these studies is also provided in appendix B.

Friedman et al. carried out a systematic screening of medical drugs for possible carcinogenic effects with a maximum follow-up period of 15 years of exposure (Friedman et al., 1980; Friedman et al., 1983; Selby et al., 1989; and

Friedman, 1992). The cohort consisted of 143,574 outpatients who had at least one prescription recorded in a drug-dispensing database during the period between July 1969 and August 1973 in San Francisco. They reported results for 215 drugs or drug groups in relation to 56 primary cancer sites and combinations of sites. Each drug was screened for associations with each cancer site and all sites combined by comparing the number of new cases that developed among the users of that drug (i.e. persons to whom it was dispensed at least once) with the number expected among the same group on the basis of age- and sex -specific incidence rates for all pharmacy users. Neither of the two antidepressants assessed (amitriptyline and imipramine) was found to be significantly associated with the development of cancer at any site. Among the 1,957 amitriptyline users, 195 developed cancer, when 182.7 were expected [Standardized Mortality Ratio (SMR) = 1.07 (95% CI: 0.92 - 1.23)]. Among the 308 imipramine users, 12 developed cancer, when 15.6 were expected [SMR = 0.77 (95% CI: 0.40 - 1.34)] (Friedman, 1992). This study, however, had several important limitations including the small number of exposed cases and the fact that dosage, duration of use, and timing of exposure were not specified. Moreover, exposure status was incomplete because only 78% of the prescriptions were filled at the facility pharmacy. Surveillance also missed 15% of the cancers diagnosed in subjects who had left their medical center but remained in the area.

A retrospective cohort study of nonestrogenic drugs and risk of breast cancer was conducted by Danielson et al. (Danielson et al., 1982). Data from a prepaid health care organization with computerized information on diagnoses and outpatient drug use (since July 1976) were used. The study included 302 women aged 35-74 years diagnosed with breast cancer between 1977 and 1980. Exposure to any of the nonestrogenic drugs was defined by having a study drug dispensed to a woman within the six-month period before the breast cancer was diagnosed. An age-adjusted risk ratio of 0.5 for the use of tricyclic antidepressant drugs relative to nonusers was found (90% CI: 0.3 – 0.8). This protective effect is difficult to interpret because the sample size was small and the study had limitations such as selection bias, no control of confounding, crude assessment of exposure without any consideration of dosage or duration of use, and short exposure histories limited to 6 months before diagnosis (Danielson et al., 1982).

Wallace et al. conducted a case-control study in which they studied psychotropic drugs in relation to the development of cancer (Wallace et al., 1982). The study population consisted of 151 breast cancer patients and 151 hospital controls matched on age, with no prior history of cancer. Information on past antidepressant drug use was obtained from subjects through interviews. A subject was considered to be exposed to antidepressants if she specified that she was taking antidepressant medication for an interval longer than 1 month. The crude relative risk for prior use of antidepressants was 1.77, which was not statistically significant. After adjustment for menstrual, reproductive, and family history of breast cancer, the relative risk was 2.84 (p-value < 0.04). Controlling for the effect modification by socioeconomic status decreased the RR to a non-significant 1.62 (p-value > 0.2). Dosage and timing of drug use before diagnosis were not specified. Another weakness of this study was the possibility of recall bias.

An analysis using data from two population-based case-control studies was conducted by Harlow et al. to assess the association between self-reported use of antidepressants and epithelial ovarian cancer (Harlow et al., 1995). The study included 450 cases and 454 controls matched on age, race, and residence. Prior use of antidepressants exceeding one to six months was associated with an increased risk of ovarian cancer [adjusted OR = 2.1 (95% CI: 0.9 - 4.8)]. The association was stronger in women who initiated treatment before age 50 [adjusted OR = 3.5 (95% CI: 1.3 - 9.2)]. A significant association was found for using antidepressants 10 or more years prior to diagnosis [adjusted OR = 9.7 (95% CI: 1.2 - 78.8)]. The same authors assessed this association, in a second analysis, using data from another population based case-control study (Harlow et al., 1998). The analysis included 563 women diagnosed with malignant or borderline epithelial ovarian tumors, and 523 controls. Women who reported using any psychotropic medication for 6 months or longer had a significantly greater risk of epithelial ovarian cancer [adjusted OR = 1.4 (95% CI: 1.0 - 2.0)] and invasive ovarian cancer [adjusted OR = 1.6 (95% CI: 1.1 - 2.3)] than nonusers, after adjustment for potential confounding variables. First use of psychotropic medication before the cessation of menstrual periods for more than 2 years was associated with a 3-fold increase in risk of ovarian cancer relative to non exposed women [adjusted OR = 2.9 (95% CI: 1.3 - 6.6)]. One of the strengths of this study was the consideration of timing and duration of exposure. The weaknesses included small sample size, failure to consider dosage, as well as possible recall bias.

Kelly et al. examined the association between use of antidepressants (TCAs and SSRIs, and other antidepressants) and development of breast cancer in a hospital-based case-control study (Kelly et al., 1999). The study included 5,814 women with primary breast cancer and two control groups: 5,095 women with primary malignancies of other sites, and 5,814 women with other conditions. Data on medical history, as well as lifetime history of medication use, were collected by interviewing the subjects. The authors did not find any association between the use of antidepressant drugs and the risk of breast cancer, and the results were very similar using both control groups. An effect could have been missed in this study because of the misclassification that might have resulted from basing drug exposure on subjects' recall. Because this was a hospital-based case-control study, the prevalence of antidepressant exposure among the hospitalized controls may have been greater than the prevalence among the general population; this could have resulted in estimates biased towards the null.

Dalton et al. conducted a population-based cohort study to assess the association between the use of antidepressant medications and the risk of cancer using a county's prescription database in Denmark (Dalton et al., 2000). The study included 30,807 adult antidepressant drug users (older than 15 years of age) who were followed for an average of 3.2 years between 1989 and 1995. The authors assessed the association between antidepressant drug use and the incidence of four groups of cancer: Non-Hodgkin's lymphoma, smoking related cancers, other cancer sites, and total cancer. An increased risk of non-Hodgkin's lymphoma among people with five or more TCA prescriptions was found [Standardized Incidence Ratio = 2.5 (95% CI: 1.4 - 4.2)]. Limitations of this study included the short follow-up period, and the rough estimation of drug exposure, with no consideration of dosage, timing and duration of exposure.

Coogan et al. conducted a case-control study to examine the association between ovarian cancer and the use of tricyclic antidepressants and selective serotonin reuptake inhibitors (Coogan et al., 2000). The analysis included 748 women diagnosed with epithelial ovarian cancer, between 1976 and 1997, who were compared with cancer controls (n = 1496) and non-cancer controls (n = 1496). A lifetime history of medication use was obtained by asking about drug use, where for each episode of drug use reported, information on drug name, starting date, frequency of use, and duration of use were recorded. Odds ratios derived with cancer and non-cancer controls were not significantly increased for regular use of any of the antidepressants under study. For the TCAs, the odds ratio was found to be 0.8 (95% CI: 0.4 – 1.5) when compared with cancer controls, and 0.7 (95% CI: 0.4 – 1.3) when compared with non-cancer controls. When the analysis was restricted to those who started using TCAs regularly 10 years before the index date, the odds ratio was found to be 1.6 (95% CI: 0.6 – 4.6) when compared with cancer controls and 1.5 (95% CI: 0.5 – 4.10) when compared with non-cancer controls. These estimates are questionable mainly because these analyses were based on a very small sample size, with the number of cases not exceeding 16 cases in any of separate analyses. Another limitation of the study was the fact that they collected information on drug exposure through interviews; it would have been hard for the participants to remember information on the 40 indication categories which were recorded.

A population-based case-control study was conducted by Cotterchio et al. to evaluate the association between the use of various antidepressant medications and breast cancer risk (Cotterchio et al., 2000). The study included 701 primary breast cancer cases diagnosed during 1995 and 1996, who were matched on age with 702 randomly selected population controls. The duration of antidepressant medication use for more than 25 months was associated with an increased risk of breast cancer when only age was adjusted for [Age-adjusted Odds Ratio = 1.6 (95% CI: 0.9 - 2.8)]. On the other hand, both the age-adjusted and multivariate-adjusted odds ratio estimates for more than 25 months of tricyclic antidepressant medication use were associated with an increased risk of breast cancer [Age-adjusted Odds Ratio = 2.5 (95% CI: 1.2 - 5.1); and multivariate-adjusted Odds Ratio = 2.1 (95% CI: 0.9 - 5.0)]. None of the other associations for durations of less than 5 months and between 6 and 24 months of antidepressant use was found to be larger than unity. Limitations of this study included the short follow-up period, small sample size, and the rough estimation of drug exposure, with no consideration of dosage and timing. The observed association could have been biased because of the recall of the participants because data were collected through mailed, self-administered questionnaires (Lawlor, 2000; and Beebe et al., 2000).

Another study, which assessed the association between antidepressant use and the risk of breast cancer, was conducted by Wang et al. in 2001 (Wang et al., 2001). This retrospective cohort included 38,273 women who filled a prescription for any of a number of antidepressants and 32,949 who filled a prescription for any other medication during the 1989 to 1991 period. After adjustment for potential confounders, there was no significantly elevated risk of developing breast cancer for any antidepressant use [Adjusted Hazard Ratio = 1.04 (95% CI: 0.87 - 1.25)]. No significantly increased risk was observed for any of the four quartiles of either the cumulative dosage or the duration of antidepressant (ranging from short to long) and hazard of developing breast cancer, and neither there was any suggestion of a trend towards an increasing risk with higher cumulative dosages or longer durations of use. One of the strengths of this study was the consideration of the dosage and duration of antidepressant use, whereas the lack of accounting for the timing of use, as well as the short follow-up period (2 and a half years), were among the limitations of this study.

Dublin et al. carried out a population-based case-control study to assess the association between antidepressant use and risk of ovarian cancer (Dublin et al., 2002). The study included 314 ovarian cancer cases diagnosed between 1981 and 1997 and 790 matched controls. Antidepressant exposure was obtained by reviewing the computerized pharmacy database, established in 1977. Cases were less likely than controls to have filled two antidepressant prescriptions in any 6-month period prior to the date of diagnosis (OR = 0.71, 95% CI: 0.47 - 1.1), or to have used an antidepressant continuously for 6 months or longer (OR = 0.64, 95% CI: 0.36 - 1.1). The authors concluded that women who have taken antidepressants in the past are not at an increased risk of ovarian cancer. Limitations of this study included the rough estimation of drug exposure, with no consideration of dosage, timing and duration of use.

Recently, Sharpe et al. (Sharpe et al., 2002) conducted a large population-based case-control study to test the hypothesis that exposure to TCAs increased the incidence of invasive female breast cancer. Data from the Saskatchewan health services databases and the Saskatchewan Cancer Registry (SCR) were used in their study which included 5,882 cases and 23,517 controls. The authors found that exposure to TCAs 11-15 years before diagnosis was associated with an increased risk of breast cancer with a dose-response trend and a rate ratio of 2.02 (95% CI: 1.34 – 3.04) for those highly exposed to TCAs relative to those unexposed in that time period (Sharpe et al., 2002). Higher exposure to the genotoxic TCAs (amoxapine, clomipramine, desipramine, doxepin, imipramine, or trimipramine) was associated with a trend towards an increasing rate ratio 11-15 years later (p-trend = 0.0009), where at the highest exposure level the rate ratio was 2.47 (95% CI: 1.37 - 4.40). On the other hand, exposure to non-genotoxic TCAs (amitriptyline, maprotiline, nortriptyline, and protriptyline) was not found to be associated with an increased risk of breast cancer, where at the highest exposure level, the rate ratio was 0.99 (95% CI:

0.49 – 1.99). The design of this study could be considered quasi-experimental: drugs with different chemical structures were prescribed without consideration of risk factors for breast cancer development. Thus, the differences observed in the risk of breast cancer are very likely to be related to the difference in chemical structures of the antidepressant drugs rather than confounding factors (other determinants of breast cancer risk).

2.4 Conclusion, rationale, and relevance

In summary, combining the two groups of TCAs in previous epidemiological studies might partly explain the inconsistencies in the reported results. Most epidemiologic studies that focused on the association between antidepressants and cancer incidence were limited because of rough estimates of exposure, with no specification of dosage, duration of use, or timing of use in relation to diagnosis, and in most instances, self-reporting of use (Thomas, 1988). Other important limitations included small sample sizes, short periods of follow-up, and lack of adequate control of confounding variables, such as the effect of depression on the development of cancer. However, the recent study by Sharpe et al. (Sharpe et al., 2002) strongly suggests that some TCAs may be carcinogenic (increasing risk of breast cancer). Their results were consistent with experimental studies in fruit flies (Van Schaik et al., 1991; and Van Schaik et al., 1993) which demonstrated genotoxicity (implying the relation could be due to tumor initiation) and raise important concerns given the widespread use of these agents.

Breast cancer, the site studied by Sharpe et al., might not be the only cancer site affected by exposure to antidepressants. The carcinogenicity process of antidepressants is not believed to be site specific, and thus a similar effect could exist in other cancer sites.

We studied the association between antidepressant drug use and the development of cancer at 4 different sites. The cancer sites chosen for this thesis were selected from 19 different sites available for a bigger project which aimed at assessing this association. The choice of the four cancer sites was based on their high prevalence, as well as the fact that they show variability in terms of their cell turnover rate.

We studied the association between antidepressant drug use and the risk of cancer by means of multiple site-specific nested case-control studies using data compiled from the databases of the Saskatchewan Cancer Agency and Saskatchewan Health, specifically the cancer registry and the outpatient prescription drug and health insurance registration databases, respectively. A cancer registry was established in Saskatchewan in 1932; complete computerized data for all cancer sites are available since 1967 (Downey et al, 2000). The Saskatchewan Prescription Drug Plan (SPDP) was introduced in September 1975 and provides benefits to about 91% of the population covered by Saskatchewan Health (Downey et al, 2000).

These databases provide a unique opportunity to study the association between exposure to antidepressant drugs and cancer (Downey et al, 2000). This fact has been recognized and exploited by the scientific community, as evidenced by the numerous studies that have already been conducted with either or both of these databases (Ernst et al., 1992; Strom 2000; Risch et al., 1994; Csizmadi et al., 1998; Csizmadi et al., 2000; Csizmadi et al., 2000; Csizmadi et al., 2003; Collet et al., 1999; Sharpe et al., 2000; and Sharpe et al., 2002). In addition, this project is part of a research program in onco-pharmacoepidemiology that has already studied the effects of prescribed drugs on the risks of colon cancer (Collet et al., 1999) and breast cancer (Sharpe et al., 2000; and Sharpe et al. 2002).

With the increase in incidence and mortality rates of cancer, identifying preventable causes should be a priority for research. Depression is a frequently occurring, serious illness, which seems to be occurring more frequently over time, at younger ages. Because depression is a relapsing illness, many people must use antidepressants over extended periods of time, both to prevent and treat relapses. Since many different antidepressants are available, it is important to determine which ones are safe and which ones are not with respect to the development of cancer. By relating risk to the chemical structure of the drugs, we may be able to provide physicians with new information to make better treatment decisions and the pharmaceutical industry with information that will enable chemists to modify drug structure to improve drug safety.

Chapter 3: Objectives

3.1 General objective

The general objective of this study was to determine whether the use of antidepressant drugs, in particular the genotoxic TCAs, increases the risk of developing any of the 4 different types of cancers (breast, prostate, and ovarian cancer; and non-Hodgkin's lymphoma).

The cancer sites considered in this study included three that had been studied in relation to antidepressant exposure in previous studies (breast, ovarian, and non-Hodgkin's lymphoma), and one that has never been considered in previous studies that assessed this association (prostate cancer).

TCAs were categorized into two groups, based on their genotoxicity in Drosophila: the non-genotoxic TCAs (amitriptyline, maprotiline, nortriptyline, and protriptyline), and the genotoxic TCAs (amoxapine, clomipramine, desipramine, doxepin, imipramine, and trimipramine). Accordingly, we tested the hypothesis that exposure to genotoxic TCAs increases the risk of developing cancer at one or more of the sites under study, relative to exposure to non-genotoxic ones.

The inclusion of these cancer sites in this study allowed us to test the hypothesis of whether the carcinogenic effect of the genotoxic antidepressants vary according to rates of cell turnover. The frequency of cell division varies greatly among the many cell types in the body. Some cells, such as in the prostate and the lymph nodes, are long-lived and there is no cell division in postnatal life to replace those lost through age or injury. Other cells, such as in the breast and the ovary, are short-lived and cell division in postnatal life occurs frequently to replace cells lost. This entire process of cell renewal is referred to as cell turnover (Fawcet, 1986; and Damajanov et al., 1996). Hyperplasia (an increase in the number of cells in a tissue or organ) can place an organ at an increased risk of neoplasia, especially if there is chronic stimulation of cell division. An increased percentage of cells in the cell cycle increase the possibility of spontaneous chromosomal abnormalities and thus altering oncogene structure and function and inducing mutations or rearrangements (Damajanov et al., 1996). Thus, the effect of antidepressants may be more apparent when cell division is high and the turnover is rapid, whereas, the effect may be less obvious when the multiplication is low and turnover is slow (Fawcet, 1986; and Damajanov et al., 1996).

3.2 Specific objectives

Specific objectives include:

- Testing the hypothesis that people exposed to TCAs, relative to those unexposed to antidepressants, are at increased risk of developing cancer at any of the sites under study,

- Testing the hypothesis that exposure to genotoxic TCAs increases the risk of developing cancer at any of the sites under study relative to exposure to non-genotoxic ones,
- Determining if the carcinogenic effect of the genotoxic antidepressants vary according to rates of cell turnover,
- Studying the effects of the use of other antidepressant drugs (MAOIs and SSRIs) on the risk of developing cancer at the sites under study,
- Studying for each class of drug and each site under study the respective effects of level of exposure, timing of use, and duration of use.

Chapter 4: Methods

4.1 Introduction

The approach adopted to study the association between antidepressant drug use and risk of cancer at different sites was the multiple site-specific case-control design. In case-control studies, persons with the disease of interest, and a suitable control group (reference), who are disease free, are identified within a defined population (Last, 1995).

Saskatchewan, one of the ten provinces in Canada, has a population of about one million people (or 4% of the total population of Canada). The Saskatchewan Prescription Drug Plan (SPDP) has been operating since September 1975, and provides outpatient prescription drug benefits to about 91% of the Saskatchewan population covered by the Saskatchewan Health (Downey et al., 2000). The covered population ineligible for outpatient prescription drug benefits is primarily registered Indians, who receive drug benefits under a federal program. Immigrants become eligible for health benefits three months after arriving, which is recorded as the coverage initiation date. Emigrants lose their eligibility three months after leaving. All residents of the province of Saskatchewan, except members of the Canadian Forces or Royal Canadian Mounted Police and federal penitentiary inmates, are entitled to receive benefits through the health care system once they have established residence and registered with Saskatchewan Heath for a Health Services Card. There is no distinction based on socioeconomic status. Each resident is assigned a unique personal identification number. Information including name, address, sex, date of birth, and date of effective coverage are maintained in the registry database, which is used by all Saskatchewan Health programs. This permits the electronic linkage of information contained in different databases (Downey et al., 2000).

Computerized data for all cancer cases diagnosed since 1967 (Downey et al., 2000) are maintained in the Saskatchewan Cancer Registry (SCR). Registration of cases in Saskatchewan is virtually complete because the reporting of cases is required by the law. In addition, there is a high level of diagnostic specificity as the majority of diagnoses are confirmed by pathological reports which are components of the database. Through this mechanism, approximately 98% of all new cancer cases are covered (Parkin et al., 1997).

4.2 Design

We carried out four site-specific population-based nested case-control studies using the population eligible to receive outpatient prescription drug benefits from Saskatchewan Health. Data routinely recorded by Saskatchewan Health and the SCR were used to obtain information on antidepressant use and cancer occurrence.

The source population was the dynamic cohort defined by registration with Saskatchewan Health from January 1, 1981 to December 31, 2000. All incident cases of each type of cancer diagnosed in the study population during the specified period were ascertained through the Saskatchewan Cancer Agency. Incidence density sampling, with matching on age, gender, and calendar time, was used to select controls from the dynamic study population. Controls were sampled with replacement and therefore could have been sampled again as controls, or if diagnosed with any of the listed cancers, sampled as cases. Drug exposure data for the period between 1976 and 2000 were compiled from the Saskatchewan outpatient prescription drug database.

4.3 Source population

The source population consisted of all people aged between 5 and 82.5 years, living in Saskatchewan and registered with Saskatchewan Health for at least 5 years during the period January 1, 1981 to December 31, 2000 and eligible for outpatient prescription drug benefits, with no prior history of cancer (except for non-melanoma skin cancer and carcinoma in situ of the cervix, because of inconsistent reporting to cancer registries). Excluded from this study were children younger than 5 years of age, since antidepressants are rarely prescribed before that age, as well as individuals older than 82.5 years. Individuals entered the source population at the beginning of the study (January 1, 1981) if they were aged between 5 and 82.5 years, on their 5th birthday, or on the date of the earliest health coverage initiation if their age was between 5 and 82.5 years, whichever occurred latest. They left the source population at the end of the study (December 31, 2000), on the date of diagnosis with any cancer, on the date of death, on the date when they reached 82.5 years, or on the latest date of coverage termination, whichever occurred first.

4.4 Identification of cases

The SCR identified cases of the 19 different cancer sites included in the original project. The cases were defined as all individuals in the SCR diagnosed between January 1, 1981 and December 31, 2000 with one of the cancers addressed by this study. The date of diagnosis for each cancer case, as recorded in the cancer registry, was recorded as the index date.

The specific cancer sites considered in this thesis (with the ICD-O codes) (Percy et al., 1990) were: female breast cancer (C50-C50.9), prostate cancer (C61.9), ovarian cancer (C56.9), and non-Hodgkin's lymphoma (C95.9, C96.7-C97.2). The remaining 15 cancer sites were: colorectal cancer, liver cancer, cancer of the pancreas, myeloid leukemia, skin melanoma, renal cell carcinoma, bladder cancer, uterus cancer, testicular cancer, stomach cancer, Hodgkin's disease, central nervous system tumors, retinoblastoma, nueroblastoma, and osteoscarcoma.

The choice of the 4 types of cancer was based on their high incidence, as well as the fact that they show variability in terms of their cell turnover rate.

4.5 Selection of controls

To be considered as a potential control for a specific case, the person should have been eligible to become a case, and should have been eligible to receive outpatient prescription drug benefits for at least five years prior to the date of diagnosis of the case.

For each case diagnosed with cancer in any of the 19 anatomic sites identified by the original project, the risk set in the source population was identified by age, gender, and calendar time for the purpose of selecting matched controls. Controls had to fall within the same age category as the case (at the time of diagnosis); age was divided into intervals of 2.5 years; from 5 to 82.5 years. Potential controls had to be of the same gender as the case. Finally, the controls had to be alive and free of cancer in the month that the case was diagnosed (index date). The date of diagnosis for the case was assigned to each of the potential controls as their index date, thereby matching cases and controls on sampling time as well.

Cases were categorized in one of the different "cells" defined by the 3 matching variables. In most of these "cells", there were cases of different cancer sites. One set of controls was selected for each "cell". To ensure at least 4 controls per case of each type of cancer in a "cell", a sufficient number of controls were randomly selected from the "cell" to have 4 controls for each case of the MOST

FREQUENT cancer site in that "cell". The selected controls were then used as controls for all the cases (of the 19 different sites) in the specified "cell".

Figure 5 provides an illustration of how controls were selected for female cancers according to the two other matching variables (age and time of diagnosis). For example, the cell defined by "females, 70-72.5 years of age in October 2000" included 10 breast cancer cases, 5 ovarian cancer cases, and fewer cases of uterus cancer, non-Hodgkin's lymphoma, and stomach cancer. Forty controls were selected from this "cell" based on a 4 controls per each breast cancer case (the most frequent cancer site). Thus, considering ovarian cancer in this specified cell, there were 8 potential controls available for each ovarian cancer case.

For a specific site of the four cancer sites studied, different cells would have different ratios of controls to cases, with a 4 controls per each case as a minimum. In the analyses for each cancer site, the smallest control: case ratio among all the different cells was used for all the other cells. For instance, in the example described above, the number of controls per case, in the ovarian cancer analyses, might range from 4 to 10 controls per each ovarian cancer case for different cells. Thus, 4 controls were randomly selected from the cells where the ratio was 5:1 or bigger resulting in a consistent 4:1 control: case ratio for all the ovarian cancer cases.

4.6 Exposure

4.6.1 Exposure assessment

Exposure to antidepressants data for both cases and controls was compiled from the outpatient prescription drug database for the period between January 1, 1976 or the first ever coverage initiation date (whichever came first) and the index date. For each antidepressant prescription the following data were made available: a unique subject study identification number, the dispensing date, the drug category (i.e., active ingredient for drugs of interest or the drug group for covariates), the number of units dispensed, (e.g., number of tablets), the dosage form (e.g, tablet or oral liquid), and the strength (e.g., mg/tablet). The daily dose and treatment duration pertaining to each prescription are not captured by the database. Using this information, for each subject, a profile of drug usage was constructed for up to 20 years in the past.

Data on drugs prescribed during hospitalizations or given as samples in physicians' offices are not captured in the database. They should, however, represent a small fraction of antidepressant exposure. Moreover, patients who receive antidepressants in hospitals or as samples in physicians' offices are very likely to continue treatment, and thus be identified as "exposed".

During the period of July 1, 1987 and December 31, 1988, information on drug prescriptions was incomplete because of administrative changes. As a consequence, we considered all the cases and controls to be unexposed during this one and a half year period.

4.6.2 Exposure definition

Four different exposure definitions were used to assess the association between antidepressant drug use and the risk of cancer development at the four sites under study: ever/never exposure, cumulative exposure, average daily exposure, and duration. The first two use all available history and the third and fourth are based on predefined exposure windows.

Exposure to antidepressants in the year immediately preceding the date of diagnosis was excluded from the analyses. The first reason for doing so was the fact that most cancers have an average latency period of 10 years, and thus the effect of exposure to a carcinogen could not be detected a year later. Another reason for excluding the year prior to diagnosis was to avoid protopahtic bias (also called reverse causality bias). This type of bias is introduced into a study when an error is made in the time sequence between exposure and outcome. One might wrongly conclude that exposure to a certain drug is a risk factor for a specific outcome, when in fact the drug was prescribed because of the presence of the outcome. In our study, the early symptoms of the undiagnosed cancer (during the year prior to diagnosis) could have been the reason for the use of antidepressant drugs (because of depression).

Likewise, although some subjects had exposure histories of more than 20 years, the numbers of such patients were very small, and thus the period was not considered in the analyses.

4.6.2.1 Exposure during full period

The first two exposure definitions considered the full period of history available for each subject. Because of the variability in the length of history of each subject in the database (ranging between 5 and 20 years), we assessed the association between exposure to TCAs and risk of cancer development in four groups of subjects based on their available drug history prior to the index date (those having 5, 10, 15, or 20 years of history) (figure 6).

As for the SSRIs, the association was assessed in only two different groups of subjects (5 and 10 years of history prior to index date), since the first SSRI was listed in the Saskatchewan Formulary in 1989, and thus we could not assess the association for those having 15 and 20 years of history. For this same reason, in the analyses on SSRIs, we also excluded all the cases who were diagnosed before 1989.

4.6.2.1.1 Ever/never exposed

The first exposure index used to assess the association between antidepressants use and risk of development of cancer was "ever/never exposed" to the drugs being studied. A subject was categorized as exposed if he/she filled *at least one prescription* of the drugs under study (index medication), and was categorized as unexposed if he/she did not fill any prescription of the index medication during the studied period.

4.6.2.1.2 Cumulative dosage exposure

The second exposure index used to assess the association between exposure to antidepressants and development of any of the four cancer sites was the cumulative exposure to antidepressants expressed in daily dose (moles). The aspect of drug dosage that we consider most pertinent to the development of cancer is the number of molecules that reach the target organ, which must be related to the number of molecules of each drug that was ingested. Because we had no information about which drugs were actually ingested, exposure was characterized in terms of amount of drug dispensed, calculated from the amount dispensed over the specified time period prior to the index date.

The effect of cumulative dosage was studied by calculating a measure of exposure from the number of moles of each drug dispensed (calculated from the molecular weight given in the Merck Index) (Budavari et al., 1989) and the quantity of units dispensed.

Cumulative exposure was used as a continuous variable and as a categorical one (low and high). Subjects who did not fill any prescription of the index antidepressants during the specified period were categorized as unexposed.

In addition, to assess whether exposure to antidepressants, in a specific time period prior to the index date, had an effect on the development of cancer we calculated the same cumulative dosage measures when restricting the follow-up period by five-year increment. For example, for those who had 20 years of follow-up, we calculated the cumulative dosage measures for the windows 2-20, 6-20, 11-20, and 16-20 years prior to the index date.

4.6.2.2 Exposure by time period

In order to study the effect of timing of exposure to antidepressants, the third and fourth exposure definitions represented exposure in different time periods preceding the diagnosis of cancer. Exposure history was divided into 4 successive periods (while excluding the prior year): 2-5 years, 6-10 years, 11-15 years, and 16-20 years (figure 6). The duration of these periods was decided a priori.

4.6.2.2.1 Average daily dose of exposure

The third exposure index used to assess the association between antidepressants use and risk of cancer development was also related to dosage of the drugs dispensed. In this exposure index, as in the cumulative dosage exposure index, we considered the number of moles of each drug and the quantity of units prescribed. We used the duration of the imposed time periods to calculate the average daily dose of exposure in each of these 4 successive time periods.

In other words, we expressed the average daily dosage in terms of the average number of moles (gram molecular weights) of each drug per day. Because we analyzed drug exposure as classes of drugs, the number of moles dispensed of each drug in each class was summed and divided by the number of days in each time period to give the average number of moles dispensed/day for each class of drugs. For example, if a subject received imipramine for the first 6 months during the period 11-15 years before the index date, followed by clomipramine for the next 12 months, followed by amitriptyline for the next 36 months, followed by no antidepressant for the next 6 months, we added the numbers of moles of imipramine and clomipramine dispensed during the 5-year period and divided by 1,825 days to give the average moles/day of genotoxic TCAs dispensed during the period. Similarly, we would calculate the number of moles of amitriptyline dispensed and divide by 1,825 days to give the average moles/day of non-genotoxic TCAs dispensed during the period.

Within each time period, the average daily dose was represented by continuous and categorical variables: low, medium, and high. Subjects who did not fill any prescription of the index medication during the specified period were categorized as unexposed.

4.6.2.2.2 Duration of exposure

To estimate the duration of drug use, each time period before the index date was divided into 3-months intervals (91 days) and then the number of intervals during which a prescription was dispensed was counted. For example, a person who had a drug dispensed during 11 of 20 intervals of a specific time period (5 years) was considered to be exposed 55% of the time. This method of characterizing drug exposure was considered to be appropriate for antidepressants which are prescribed for continuous daily use over extended periods of time.

Similarly, within each time period duration of use was represented by continuous variables, as well as categorical variables: unexposed, short, medium, and long.

4.7 Adjusting for covariates

Matching at the design stage and carrying out matched analyses at the analysis stage were used to control for the effect of age and sex. We also controlled for the confounding effects of other drugs that may be related to the occurrence of cancer. In each of the four cancer sites analyses, the drugs which we controlled for were the ones thought to be associated with an increased or decreased risk of the cancer site under study. The drugs we controlled for were specific to each cancer site and information on their use was compiled from the outpatient prescription drug database.

These drug groups included estrogens, oral contraceptives, major and minor tranquilizers, systemic adrenal corticosteroids, disease modifying anti-rheumatoid drugs (e.g., azathioprine, methotrexate, etc.), gastro-protective agents (e.g., proton pump inhibitors, histamine 2 antagonists, etc.), anticoagulants, drugs used over the long term in treating cardiovascular disease (e.g., beta blockers, ACE inhibitors, etc.), and nonsteroidal anti-inflammatory drugs (NSAIDs).

In the breast and ovarian cancer analyses, we controlled for the possible confounding effect of estrogens and oral contraceptives (which are known to increase the risk of these cancers) and NSAIDs (which are thought to be protective) (Schottenfeld et al., 1996). As for the analyses carried out on prostate cancer and non-Hodgkin's lymphoma, NSAIDs was the only drug group that was controlled for in the analyses, since they could to decrease the risk of these cancers.

The level of detail compiled for the drug groups identified as possible covariates was less than that provided for the antidepressants. For each prescription dispensed to the subject as an outpatient before the index date, the following information was reported: the subject's unique study number, the date of dispense, and the drug category (e.g., NSAID, oral contraceptive, etc.). The number of units dispensed and the strength (e.g., mg/tablet) were not reported.

4.8 Statistical analysis

The OR was used as the estimator of the incidence density ratio of each cancer site in the exposed versus the unexposed. We analyzed exposure to antidepressants as classes of drugs (TCAs and SSRIs). Moreover, we analyzed exposure to TCAs as subclasses of drugs (genotoxic and non-genotoxic). The third class of antidepressants (MAOIs) was not analyzed since the number of exposed subjects was not adequate to carry out the analyses.

The following sections describe the analyses that were carried out for each of the cancer sites studied.

4.8.1 Exposure during full period

The association between exposure to antidepressants, as represented by the ever/never exposure and cumulative dosage exposure indices, and risk of cancer development was assessed for each of the TCAs and the SSRIs as a class of drugs. The reference group for these analyses included those who were not exposed to the index medication during the period under study. Moreover, another set of analyses was carried out when TCAs were categorized into genotoxic and non-genotoxic TCAs.

These analyses took the matching on gender, age at diagnosis, and index date into account but ignored the fact that the length of the exposure histories varied.

4.8.2 Exposure by time period

The risk of cancer development in association with the average daily dose and the duration of exposure was assessed for TCAs (genotoxic, non-genotoxic, and combined) and SSRIs. The same type of analyses were also carried out for exclusive exposure to either genotoxic or non-genotoxic TCAs, in reference with those who were not exposed to any of these drugs, in relation to cancer development, for each of the 4 periods prior to index date.

Two types of analyses (crude and adjusted) were carried out on each of the index medications. The crude analyses assessed the association between the exposure index and the development of each cancer site in each period independently of the other periods under study, i.e. taking into account the matching variables for that specific period only.

On the other hand, the adjusted analyses accounted for the effect of the matching variables as well as exposure during the other three time periods. This was done since successive time periods of exposure can be viewed as separate determinants of the outcome that can be mutually confounded, thus requiring separate representation in the same statistical model (Miettinen, 1985). The principles proposed by Miettinen relating to temporal dimensions of drug exposure derive from the fact that duration of therapy, time between discontinuation of therapy and outcome, as well as previous use of the drug generally all affect the incidence of adverse events. We cannot assume that current users are first-time users, neither that subjects not currently exposed have never been exposed to the drug under study; previous use of the same drug should be considered as a potential confounder (Miettinen, 1985).

If the drug exposure history for a period was missing or incomplete due to the coverage initiation date (i.e. the patient entered the study during this period), the subject was assigned to a separate exposure category designated as "other" (Haberman et al., 1999; and Breslow et al., 1980). Since one of the inclusion criteria was that the subject having at least 5 years of Saskatchewan Health coverage prior to the index date, all the available cases of a specific cancer, along with their controls, were available for the analyses in the first period before diagnosis (2-5 years). The sample size used for the analyses in the other three periods decreased because of the categorization of some of the subjects in the "other" category. For example, for a specific cancer site, a case or a control that was categorized as "other" in the second period before diagnosis (6-10 years) would also be categorized as "other" in the third and fourth period (11-15, and 16-20 years respectively).

4.8.3 Statistical methods used

4.8.3.1 Descriptive analyses

Descriptive analyses were carried out on cases and controls, of each of the cancer sites, to identify the distribution of the subjects in terms of age and yearly incidence. The results were summarized either in the text or as histograms.

4.8.3.2 Multivariate analyses

To assess the effect of exposure to TCAs and SSRIs, as classes, on the risk of development of cancer, we calculated an incidence density ratio for the exposure to the index medication relative to those unexposed to any antidepressant. On the other hand, when we compared the effect of exposure to genotoxic TCAs with that of non-genotoxic TCAs, we calculated two incidence rate ratios: one for the exposure to genotoxic TCAs relative to those unexposed to any antidepressant, and another one for the exposure to non-genotoxic TCAs relative to those unexposed to any antidepressant.

Odds ratios were calculated, with 95% confidence intervals, to estimate incidence density ratios (Rate Ratios). Matched analyses were carried out to control for the potentially confounding effect of age, gender, exposure in other periods, and use of other drugs. This was achieved by using the conditional logistic regression approach, by means of the SAS PHREG procedure (SAS, 1999).

The statistical model that we used to represent the drug exposure history by time periods was:

$$\text{Log}\,(p/1\text{-}p) = \beta_0 + \beta_1 X_{2\text{-}5\text{ years}} + \beta_2 X_{6\text{-}10\text{ years}} + \beta_3 X_{11\text{-}15\text{ years}} + \beta_4 X_{16\text{-}20\text{ years}}$$

where p represented the probability of being diagnosed with the cancer under study, the values of β_i represented regression coefficients, and the values of X_i represented drug exposure during the successive periods of time preceding the index date.

Drug confounders were also represented by categorical variables describing their dispensing rates during successive periods of time.

Exposure measures calculated on a continuous scale were categorized into 2 or more categories. For each cancer site-specific analyses, the cut-off points used for categorizing the continuous variables were selected based on their distributions. This was done to increase the power by ensuring that the different categories have enough subjects.

Whenever continuous exposure was categorized into 2 or more categories (such as low, medium, high), we tested for linear trends, of the continuous variable itself, by examining the significance of the coefficients with a chi-squared test (p-trend).

We carried out the data management and analyses using SAS (version 8.0) statistical software (SAS, 1999).

4.9 Ethical issues

The ethics committee at the Sir Mortimer B. Davis-Jewish General Hospital, Montreal, Canada, approved the design and conduct of the study. The extraction of the data from the electronic databases pertaining to disease status and drug exposure was carried out by employees of the SCR and the Saskatchewan Health respectively, with the linkage between the two sources done by Saskatchewan Health. The data provided for analysis were devoid of any nominal information or any other information that could be used to identify any subject and were limited to only variables required for this analysis. Subjects were identified to the investigators by a study identification number only, which was assigned by Saskatchewan Health and is unique to this study and bears no resemblance to the health services number or any other personal identifier.

Chapter 5: Results

This chapter summarizes the results of the analyses carried out to assess the association between exposure to antidepressant drugs (TCAs and SSRIs) and the development of each of the four types of cancer under study (breast, prostate, ovarian, and non-Hodgkin's lymphoma). Because of the complexity of the results obtained from the analyses carried out on the different TCA exposure indices, in association with the four cancer types, the major results are summarized in tables 33 - 37.

The chapter is divided into four sections, each one covering the results pertaining to one of the types of cancer under study. Each section is then divided into two subsections covering the association between either TCAs or SSRIs and the development of each of the specific cancers. In each of these subsections, the four exposure indices (ever/never, cumulative dosage, average daily dose, and duration) are assessed separately. Appendix C summarizes the cut off points used for categorizing the 3 continuous exposure indices into categorical variables.

5.1 Female breast cancer

Between the years 1981 and 2000, 7330 breast cancer cases were identified among the eligible study population. Each breast cancer case was matched by age, gender, and time of diagnosis to four controls, resulting in 29,320 controls available for these analyses.

Figure 7 shows the yearly incidence of breast cancer cases from year 1981 till year 2000. The average number of cases accrued per year was 367 cases (sd = 54 cases). The lowest incidence during the 20-year period was in 1982 where 280 cases were identified, whereas the highest incidence was in year 1999 (433 cases) (figure 7).

The mean age at diagnosis was 61.0 years for both the breast cancer cases and their controls (sd = 12.4 and 12.3 years respectively). The youngest breast cancer case was 20.4 years old, whereas the oldest one was 82.5 years old. The age distribution of the breast cancer cases is also represented by a histogram shown in figure 8.

5.1.1 Tricyclic antidepressants

5.1.1.1 Effect of ever/never and cumulative dosage exposure

5.1.1.1.1 20-year history

Table 1 presents the results of assessing the association between breast cancer development and the two TCA exposure indices (ever/never and cumulative dosage exposure) for those having at least 20 years of history. Of the 7330 breast cancer cases, 1876 (25.6%) had at least 20 years of provincial health coverage prior to diagnosis, and thus were included in these analyses. As for the controls, 25.1% were included in these analyses (7362 out of 29320) (table 1).

The RRs for the development of breast cancer were close to 1 for the ever/never exposure index when all TCAs were combined and when the genotoxic and non-genotoxic TCAs were separated (table 1).

The RRs calculated when the cumulative dosage exposure index, of all TCAs combined, was used were not different, even when 5, 10, and 15 years were excluded from the 20-year period (table 1).

When exposure to genotoxic and non-genotoxic TCAs was categorized, a higher RR was found for the genotoxic TCAs at the high level of exposure (RR = 1.20, 95% CI = 0.91 - 1.57) as compared with that for the non-genotoxic ones (RR = 1.11, 95% CI = 0.86 - 1.43) for the 2-20 year period of cumulative dosage exposure prior to the index date (table 1). When the exposures in the 10 years prior to the index date were excluded from the analyses, the RR was higher for the non-genotoxic TCAs at the high level (RR = 1.21, 95% CI = 0.88 - 1.67) as compared with the genotoxic ones (RR = 1.02, 95% CI = 0.76 - 1.38) (table 1).

5.1.1.1.2 15-year history

The results of the analyses assessing the association between breast cancer and the two TCA exposure indices (ever/never and cumulative dosage exposure), among those having at least 15 years of history, are presented in table 2. Of the 7330 breast cancer cases, 3883 (53.0%) were included in these analyses, whereas 52.5% of the controls were included (15389 out of 29320) (table 2).

The RRs for the ever/never exposure index, when all TCAs were combined and when genotoxic and non-genotoxic TCAs were separated, ranged between 1.01 and 1.08 (table 2).

When the cumulative dosage exposure index of all TCAs combined was used, the RRs for the high level of exposure (ranging from 1.02 to 1.11) were higher than for the low levels of exposure (ranging from 0.91 to 0.98) when the last 1, 5, and 10, years were excluded from the 15-year period respectively (table 2).

The cumulative dosage exposure to genotoxic TCAs, during the period 2-15 years prior to the index date, was significantly associated with the incidence of breast cancer (RR = 1.20, 95% CI = 1.04 - 1.51). Although the RR remained higher for the cumulative dosage exposure to genotoxic TCAs as compared with the non-genotoxic ones, the RRs decreased when 5 and 10 years were excluded from the 15-year period (table 2). Another point to be noted is that the cumulative dosage exposure to TCAs (both genotoxic and non-genotoxic) at the high level showed a higher RR as compared with those at the low level.

5.1.1.1.3 10-year history

Table 3 presents the results of the analyses assessing the association between breast cancer and the two TCA exposure indices (ever/never and cumulative dosage exposure) for those having at least 10 years of provincial health coverage history. Of the 7330 breast cancer cases, 5689 (77.6%) were included in these analyses, whereas 77.7% of the controls were included (22775 out of 29320) (table 3).

When the ever/never exposure index was used, the RR of the association between exposure to genotoxic TCAs, 2-10 years prior to the index date, and breast cancer was significantly greater than 1 (RR = 1.12, 95% CI = 1.00 - 1.26), whereas that for exposure to the non-genotoxic TCAs was not significant (RR = 1.09, 95% CI = 0.98 - 1.22) (table 3).

The RRs at the high level of cumulative dosage of TCA exposure were significantly higher than those unexposed to any TCA when the 2-10 year period prior to index date was considered (RR = 1.13, 95% CI = 1.02 - 1.24) (table 3). When the 5 years prior to diagnosis were excluded from the analyses, the RR at the high level of cumulative dosage of TCA exposure was greater than 1, non-significant (RR = 1.07, 95% CI = 0.96 - 1.20).

The last section of table 3 presents the results of the analyses on the cumulative dosage exposure to genotoxic and non-genotoxic TCAs in association with the incidence of breast cancer. The RR for the association between exposure to high levels of genotoxic TCAs, 2-10 years prior to the index date, and breast cancer was significantly greater than 1 (RR = 1.23, 95% CI = 1.04 - 1.44), as compared with that of the non-genotoxic TCAs (RR = 1.12, 95% CI = 0.96 - 1.32) (table 3). When the prior 5 years were excluded from the 10-year period, the RRs for both genotoxic and non-genotoxic TCAs were greater than 1 but were not significant (table 3).

5.1.1.1.4 5-year history

Finally, table 4 presents the results of the analyses, assessing the risk of breast cancer in relation to the two TCA exposure indices (ever/never and cumulative dosage exposure), carried out on those having at least 5 years of history. Since one of the inclusion criteria was that subjects must have at least 5 years of provincial health coverage prior to the index date, all of the 7330 breast cancer cases and the 29320 controls were included in these analyses (table 4).

The RR for the association between ever being exposed to any TCA, during the 2-5 year period preceding the index date, and the development of breast cancer was significantly greater than 1 (RR = 1.15, 95% CI = 1.07 - 1.24) (table 4). Although the association between ever being exposed to genotoxic or non-genotoxic TCAs and incidence of breast cancer were significant, the RR for the genotoxic TCA exposure (RR = 1.20, 95% CI = 1.06 - 1.35) was higher than that for the non-genotoxic ones (RR = 1.15, 95% CI = 1.03 - 1.28) (table 4).

Those with high cumulative exposure to any TCA in the 2-5 years before the index date had a significantly higher incidence of breast cancer than those who had no exposure to any TCA in this period (RR = 1.19, 95% CI = 1.08 - 1.31). Those who had low cumulative exposure during the same period also had a higher, but non-significant, incidence of breast cancer as compared with those who had no exposure to any TCA in that period (RR = 1.10, 95% CI = 0.98 - 1.23) (table 4).

Finally, a higher incidence of breast cancer was associated with the cumulative dosage exposure to genotoxic TCAs at the high level (RR = 1.29, 95% CI = 1.10 - 1.50), as well as with the cumulative dosage exposure to non-genotoxic TCAs at the high level (RR = 1.19, 95% CI = 1.02 - 1.38) (table 4). Nevertheless, the p-trend for the association between exposure to genotoxic TCAs and breast cancer was 0.02 for the 2-5 year period prior to the index date, as compared with 0.22 for exposure to non-genotoxic TCAs (table 4).

5.1.1.2 Effect of average daily dose of exposure by time period

The sample size used in the analyses to assess the effect of the average daily dose of exposure was different for the 4 different time periods. For the first period before diagnosis (2-5 years), all of the cases and the controls (7330 and 29320 respectively) were utilized in the analyses (tables 5-7). As for the second period (6-10 years), 1641 cases and 6545 controls were excluded from the specific analysis (categorized in the "other" category) and thus 5689 cases and 22775 controls were utilized in the analyses for this period (tables 5-7). The numbers of cases and controls included in the analyses of the third and fourth period before the index date were 3883 and 1876 cases matched to 15389 and 7362 controls respectively (tables 5-7).

5.1.1.2.1 All TCAs combined

Table 5 presents the results of the analyses pertaining to the association between the estimated dosage of exposure to all TCAs and the development of breast cancer, for the 4 periods prior to the index date.

When the 2-5 years time period was considered, the adjusted RR for the association between breast cancer and exposure to any TCA, as compared with those unexposed to any TCA, increased from the low dosage level (adjusted RR = 1.12, 95% CI = 1.00 - 1.26) to the medium dosage level (adjusted RR = 1.20, 95% CI = 1.04 - 1.39) to the highest dosage level (adjusted RR = 1.19, 95% CI = 1.01 - 1.40), with a p-trend of 0.21 (table 5). On the other hand, the p-trend for the same association in the 11-15 years period was 0.05, although none of the adjusted RRs for the low, medium, and high dosage levels of exposure was significant (adjusted RR = 0.90, 1.02, and 1.10 respectively).

5.1.1.2.2 Genotoxic and non-genotoxic TCAs

The results of the analyses of the association between the estimated dosage of genotoxic and non-genotoxic TCAs, in each of the four time periods, and breast cancer are presented in table 6.

In the first period prior to the index date (2-5 years), the adjusted RRs calculated for the exposure to genotoxic TCAs and breast cancer were higher than those calculated for the non-genotoxic ones for the medium and high dosage level of exposure, but not for the low dosage level (table 6). The adjusted RRs for the genotoxic TCAs ranged between 1.06 and 1.19, whereas the ones for the non-genotoxic TCAs ranged between 1.06 and 1.11.

Considering the period 11-15 years before the index date, the p-trend for the association between exposure to genotoxic TCAs and incidence of breast cancer was 0.002 for an increase in the adjusted RR from 0.91 at the low dosage level to 1.04 at the medium level to 1.27 at the high level (table 6). The adjusted RRs for the association between exposure to non-genotoxic TCAs and breast cancer were as follows: 0.91 at the low dosage level, 1.07 at the medium level, and 0.91 at the high level.

5.1.1.2.3 Exclusive genotoxic and non-genotoxic TCAs

Table 7 presents the results of the analyses of the dosage of exclusive genotoxic or non-genotoxic TCA exposure, during the four periods before the index date, and incidence of breast cancer. A p-trend of 0.03 was found for the association between the incidence of breast cancer and the exclusive exposure to genotoxic TCAs during the first period before index. The adjusted RR at the medium dosage level of this association was 1.34 (95% CI = 1.07 - 1.68) and that at the high dosage level of exposure was 1.32 (95% CI = 1.04 - 1.67) (table 7).

When considering the third period (11-15 years prior to index date), a p-trend of 0.03 was calculated for the association between incidence of breast cancer and exclusive exposure to genotoxic TCAs, with a highest adjusted RR of 1.17 at the high dosage level of exposure (95% CI = 0.79 - 1.74) (table 7).

5.1.1.3 Effect of duration of exposure by time period

The sample size used for the estimated duration analyses was different for the 4 different time periods. Because the time periods in the duration analyses were not exactly the same as those constructed for the dosage analyses, the number of subjects excluded in each period were not identical to those excluded in the previous analyses. For the first period before diagnosis (2-5 years), all of the cases and the controls (7330 and 29320 respectively) were utilized in the analyses (tables 8 - 10). As for the second period (6-10 years), 1637 cases and 6535 controls were excluded from these analyses (categorized in the "other" category), and thus 5693 cases and 22785 controls were kept for the analyses (tables 8 - 10). The number of cases used in the analyses of the third and fourth period was 3893 and 1899 respectively, whereas the number of controls was 15437 and 7450 respectively (tables 8 - 10).

5.1.1.3.1 All TCAs combined

Table 8 presents the results of the analyses carried out to assess the association between the estimated duration of TCA use, during the four time periods prior to the index date, and the incidence of breast cancer.

The p-trend for the exposure to TCAs during the first period (2-5 years prior to index date) was 0.0004, which reflected the following increase in the adjusted RRs; 1.06 at the short duration level (95% CI = 0.93 - 1.20), 1.22 at the medium duration level (95% CI = 1.07 - 1.39), and 1.32 at the long duration level (95% CI = 1.12 - 1.54) (table 8).

5.1.1.3.2 Genotoxic and non-genotoxic TCAs

The same trend was reflected in table 9, which shows the results of the analyses of the estimated duration of genotoxic and non-genotoxic TCA exposure, during the four periods prior to the index date, and incidence of breast cancer. The p-trend for the association between genotoxic TCAs and breast cancer during the first period before index date (2-5 years) was 0.01 with a significant adjusted RR at the long duration level of exposure (adjusted RR = 1.30, 95% CI = 1.04 - 1.63). On the other hand, the p-trend for the association with the non-genotoxic TCAs was 0.03, with a significant adjusted RR at the medium duration level of exposure (adjusted RR = 1.21, 95% CI = 1.03 - 1.43) (table 9).

Similar to what was found with the average daily dose analyses, the RR for the association with the genotoxic TCAs during the third period (11-15 years before index date) increased from 0.90 at the short duration level to 1.34 at the long duration level (p-trend = 0.10) (table 9).

5.1.1.3.3 Exclusive genotoxic and non-genotoxic TCAs

The results of the analyses assessing the association between the estimated duration of exclusive genotoxic and non-genotoxic TCA exposure, during the four periods before the index date, and the incidence of breast cancer are shown in table 10. The p-trend for the estimated duration of exclusive exposure to both genotoxic and non-genotoxic TCAs during the first period (2-5 years) was found to be significant (0.001 and 0.008 respectively) (table 10). The adjusted RR for the association with the genotoxic TCAs was higher than that of the non-genotoxic TCAs, although both showed significant adjusted RR at the medium and long duration levels of exposure (table 10).

5.1.2 SSRIs

The sample size used for the analyses to assess the association between exposure to SSRIs and development of breast cancer was much smaller for that used in the TCA exposure analyses. Of the 7330 breast cancer cases, 4682 (63.9%) were included in the following analyses (since having an index date after the date when the first SSRI was introduced). Similarly, 18728 out of the 29320 (63.9%) controls were included in these analyses (tables 11 - 14).

5.1.2.1 Effect of ever/never and cumulative dosage exposure

5.1.2.1.1 10-year history

The observed associations between the two SSRI antidepressants exposure indices (ever/never and cumulative dosage exposure) and breast cancer development, for those having at least 10 years of history, are presented in table 11.

The association between ever being exposed to SSRIs, in the 2-10 year period prior to the index date, and incidence of breast cancer was not significant (RR = 1.09, 95% CI = 0.93 - 1.27) (table 11).

When the cumulative dosage exposure index was used, the association between the low level exposure to SSRIs and the incidence of breast cancer (RR =

1.14) was lower than that of the high level of exposure (RR = 1.02) when the 2-10 year period was assessed (table 11).

5.1.2.1.2 5-year history

The results of the association between breast cancer development in association with the two SSRI antidepressants exposure indices (ever/never and cumulative dosage exposure), for those having 5 years of history, are presented in table 12.

The ever use of SSRI drugs, during the 2-5 year period prior to the index date, was associated with an elevated incidence of breast cancer (RR = 1.13, 95% CI = 0.95 - 1.33) (table 12).

The cumulative dosage exposure to SSRI drugs, at the low level, was of borderline significance, when the 2-5 year period was considered (RR = 1.23, 95% CI = 0.99 - 1.54) (table 12).

5.1.2.2 Effect of average daily dose of exposure by time period

Table 13 presents the results of the analyses of the estimated dosage of exposure to SSRIs and the incidence of breast cancer for the 2 periods prior to the index date (2-5 years and 6-10 years).

The only significant association found in these analyses was for the association between exposure to SSRIs at the low dosage level 2-5 years prior to the index date and the incidence of breast cancer (adjusted RR = 1.26, 95% CI = 1.01 - 1.57). Exposure to SSRIs at the high level, during the 2-5 years period, yielded an adjusted RR of 1.24, which was not significant (95% CI = 0.78 - 1.98) (table 13).

5.1.2.3 Effect of duration of exposure by time period

The results of the analyses of the estimated duration to SSRI drugs and the incidence of breast cancer for the 2 periods prior to the index date (2-5 years and 6-10 years) are presented in table 14. Exposures to the SSRIs at the short and long duration levels, during the first period before diagnosis, were associated with an non-significant increase in the incidence of breast cancer (adjusted RR = 1.22 and adjusted RR = 1.22 respectively) (table 14).

5.2 Prostate cancer

The results of the analyses carried out to assess the association between antidepressant drug exposure and the incidence of prostate cancer are summarized in this section. The study data set included 7767 prostate cancer cases, and thus 31068 matched controls were selected based on a 4 controls per each case.

For the 20-year study period, the average number of prostate cancer cases accrued per year was 388 cases (sd = 108 cases). The yearly incidence of prostate cancer is presented in figure 9. The year 1984 was characterized with the lowest incidence of prostate cancer (247 cases), whereas the year 1993 was characterized with the highest incidence (577 cases) (figure 9).

The mean age at diagnosis for the prostate cancer cases and controls was 70.5 years (sd = 6.7 and 6.8 years respectively). Age of the prostate cancer cases ranged between 36.8 years and 82.5 years. Figure 10 shows the age distribution of the prostate cancer cases in the form of a histogram.

For reasons of brevity, the results of assessing the association between prostate cancer development and the two exposure indices of TCAs and SSRIs (ever/never and cumulative dosage exposure) are included in appendix E (E.1 - E.4).

5.2.1 Tricyclic antidepressants

5.2.1.1 Effect of average daily dose of exposure by time period

The number of cases used in the analyses on the effect of average daily dose of exposure, during the four periods prior to the index date, in association with prostate cancer development was: 7767, 6308, 4693, and 2234 respectively. As for the controls, there were 31068, 25143, 18655, and 8799 available controls for the four periods respectively (tables 15 and 16).

The results of the analyses of the average daily dose of exposure to all TCAs, during the 4 periods prior to the index date, and the development of prostate cancer are summarized in appendix E.5. The results of the analyses of the association between the average daily dose of exposure to genotoxic and non-genotoxic TCAs, as well as the exclusive exposure to these drugs, in each of the four time periods and incidence of prostate cancer are presented in this section (tables 15 and 16 respectively).

5.2.1.1.1 Genotoxic and non-genotoxic TCAs

In the first period prior to index date (2-5 years), exposure to low average daily dosage levels of the non-genotoxic TCAs was associated with a significant increase in the incidence of prostate cancer (adjusted RR = 1.25, 95% CI = 1.05 - 1.49), whereas it was exposure to medium levels of genotoxic TCAs that was associated with a significant increase in the incidence (adjusted RR = 1.33, 95% CI = 1.02-1.74) (table 15).

The other period that showed some differences between the two types of TCAs was the second period before diagnosis (6-10 years). Exposure to genotoxic TCAs at the low average daily dose level was associated with a borderline significant p-trend (0.06) for a decrease in the adjusted RR of prostate cancer from 1.28 (95% CI = 1.06 - 1.56) to a RR of 0.66 (95% CI = 0.44 - 0.98) (table 15).

5.2.1.1.2 Exclusive genotoxic and non-genotoxic TCAs

Results of the analyses assessing the association between the average daily dose of exclusive genotoxic or non-genotoxic TCA exposure and the incidence of prostate cancer, presented in table 16, were similar to those in table 15.

When considering the first period prior to the index date (2-5 years), the adjusted RR was significantly higher for those exposed to exclusive low average daily dose levels of non-genotoxic TCAs as compared with those who were not exposed to any TCAs during that period (RR = 1.34, 95% CI = 1.12 - 1.62) (table 16). The p-trend for exclusive exposure to genotoxic TCAs was 0.08 which was reflected in an increase in the adjusted RR from 1.25 at the low average dose level of exposure (95% CI = 1.00 - 1.55), to 1.39 at the medium level (95% CI = 1.02 - 1.89), to 1.47 at the high level (95% CI = 1.06 - 2.03).

Higher average daily dose of exclusive genotoxic TCAs, during the period 6-10 years prior to diagnosis, was associated with a significant decreasing trend in incidence of prostate cancer (p-trend = 0.01) (table 16). The adjusted RRs decreased from 1.36 (95% CI = 1.10 - 1.68) to 0.48 (95% CI = 0.30 - 0.77) for the low to high average dose levels.

5.2.1.2 Effect of duration of exposure by time period

The number of cases used in the analyses to assess the effect of duration of TCA exposure, during the four periods prior to the index date, in association with the incidence of prostate cancer were: 7767, 6310, 4713, and 2251 respectively. As for the controls, there were 31068, 25153, 18734, and 8865 available controls for the four periods respectively (tables 17 and 18).

Appendix E.6 presents the results of the analyses of the exposure duration to all TCAs combined, during the 4 periods prior to the index date, and the incidence of prostate cancer.

5.2.1.2.1 Genotoxic and non-genotoxic TCAs

The same trend seen in the previous two tables was reflected in table 17, which shows the results of the analyses of the estimated duration of genotoxic and non-genotoxic TCA exposure, during the four periods prior to the index date, and the incidence of prostate cancer. Exposure to short and medium duration levels of non-genotoxic TCAs, during the 2-5 years period prior to index date, was associated with a significant increase in the adjusted RR of prostate cancer development (1.24 and 1.31 respectively) (table 17).

5.2.1.2.2 Exclusive genotoxic and non-genotoxic TCAs

As in the previous analyses, the incidence of prostate cancer was affected by exposure to TCAs, 2-5 years and 6-10 years prior to the date of diagnosis (table 18). Higher duration of genotoxic TCA exposure was associated with an increase in the adjusted RRs (p-trend = 0.01) in the 2-5 years period prior to index, whereas it was associated with a decrease in the adjusted RRs (p-trend = 0.09) in the 6-10 years period.

5.2.2 SSRIs

Out of the total sample size, 5346 cases (69%) and 21384 controls (69%) were included in the following analyses pertaining the exposure to SSRIs and incidence of prostate cancer.

5.2.2.1 Effect of average daily dose of exposure by time period

The results of the analyses carried out on the estimated dosage of exposure to SSRIs and the incidence of prostate cancer are summarized in table 19. The prevalence of exposure to SSRIs among cases and controls, in the two periods studied (2-5, and 6-10 years), was relatively small. The number of exposed cases ranged from 50 at the low exposure level to 9 at the high exposure level for the 2-5 years prior to the index date, whereas the numbers were 24 and 1 for the 6-10 years prior to the index date (table 19). Exposure to SSRIs in the two periods, as compared with those unexposed to any SSRI, was not found to have a significant effect on the incidence of prostate cancer.

5.2.2.2 Effect of duration of exposure by time period

The results of the analyses carried out on the estimated duration of exposure to SSRIs and the incidence of prostate cancer, presented in table 20, were similar to those of the estimated dosage.

5.3 Ovarian cancer

The following section of this chapter covers the results of the ovarian cancer analyses in association with antidepressant exposure. The number of cases and matched controls used for the following analyses were 1090 and 4360 respectively (based on a 4 controls per each ovarian cancer case).

The distribution of the yearly incidence of the ovarian cancer cases is plotted in figure 11. The average number of ovarian cancer cases accrued per year, during the 20-year period, was 55 cases per year (sd = 9 cases). The minimum number of ovarian cancer cases accrued was 38, whereas the maximum number was 68 which corresponded to the years 1983 and 1994 respectively.

The mean age at diagnosis was 59.4 years (sd = 15.0 years) for the ovarian cancer cases, and 59.3 years (sd = 15.0 years) for the matched controls. Age of the ovarian cancer cases and controls ranged between 5.2 years and 82.5 years. The histogram summarizing the age distribution of the ovarian cancer cases is presented in figure 12.

For reasons of brevity, although the same analyses which were carried out on the breast cancer cases were carried out on the ovarian cancer cases, only the major tables are presented in this section, while the others are included in appendix F.

5.3.1 Tricyclic antidepressants

5.3.1.1 Effect of average daily dose of exposure by time period

The number of cases available for the analyses assessing the association between the average daily dose of exposure to TCAs and the incidence of ovarian cancer was 1090, 813, 553, and 241 cases, corresponding to the four periods prior to the index date (tables 21 and 22). The corresponding number of controls was 4360, 3268, 2216, and 1008 for the four periods respectively.

5.3.1.1.1 Genotoxic and non-genotoxic TCAs

The results of the analyses of the association between the average daily dose of genotoxic and non-genotoxic TCAs, in each of the four time periods, and incidence of ovarian cancer are presented in table 21.

Exposure to medium levels of the average daily dose of genotoxic TCAs, 2-5 years prior to diagnosis, was associated with the incidence of ovarian cancer with an adjusted RR of 1.66 (95% CI = 1.02 - 2.72). On the other hand, higher exposure to non-genotoxic TCAs 6-10 years prior to diagnosis was associated with an increase in the incidence of ovarian cancer with a p-trend of 0.0001 reflecting an increase up to an adjusted RR of 3.72 (95% CI = 1.79 - 7.75), at the high dosage level (table 21).

5.3.1.1.2 Exclusive genotoxic and non-genotoxic TCAs

Table 22 summarizes the results of the analyses assessing the association between the average daily dose of exclusive genotoxic or non-genotoxic TCA exposure and the incidence of ovarian cancer. An increased incidence of ovarian cancer was associated with exposure to TCAs, during the period 6-10 years prior to index date. Higher exposure to non-genotoxic TCAs was associated with an increase in incidence of ovarian cancer (p-trend of 0.0005) reflecting an increase in the adjusted RR up to 3.01 (95% CI = 1.34 - 6.77) at the high average daily dosage level of exposure (table 22).

5.3.1.2 Effect of duration of exposure by time period

The number of cases available for the estimated duration analyses of TCA exposure, during the four periods prior to the index date, and incidence of ovarian cancer was 1090, 813, 554, and 243 respectively (tables 23 and 24). The corresponding number of controls for the four periods was 4360, 3268, 2221, and 1015 respectively.

5.3.1.2.1 Genotoxic and non-genotoxic TCAs

In the analyses pertaining the duration of exposure to the two different types of TCAs and the incidence of ovarian cancer, higher duration of exposure to the non-genotoxic TCAs, during the second period prior to the index date, was associated with a p-trend of 0.01 (table 23). In the same period, exposure to a long duration of non-genotoxic TCAs was associated with a non-significant increase in incidence of ovarian cancer (RR of 3.00).

5.3.1.2.2 Exclusive genotoxic and non-genotoxic TCAs

Along the same line of what was found in the previous analyses for the risk of ovarian cancer, exclusive exposure to the non-genotoxic TCAs, 6-10 years prior to the index date, was associated with a p-trend of 0.04 with a significant adjusted RR of 2.47 (95% CI = 1.04 - 5.89) at the long duration level of exposure (table 24).

5.3.2 SSRIs

The analyses pertaining the average daily dose and duration of exposure to SSRIs, for the two periods prior to the index date (2-5, and 6-10 years), in relation to the incidence of ovarian cancer are presented in tables 25 and 26. The sample size used for carrying out these analyses was 62% (672 cases and 2688 matched controls) of the original sample size. Although the results are presented in the two tables, the number of exposed cases and controls in the 2 periods prior to the index date was very small to rely on the found associations.

5.4 Non-Hodgkin's lymphoma

The last section of this chapter summarizes the results of the analyses on the non-Hodgkin's lymphoma cases. During the 20-year study period, the 1980 non-Hodgkin's lymphoma cases identified were matched to 7920 controls (4 controls per each case).

During the 20-year period, the yearly average number of non-Hodgkin's lymphoma cases accrued, during the 20-year period, was 99 cases (sd = 17 cases). The yearly incidence of non-Hodgkin's lymphoma was lowest in 1982 (59 cases) and highest in 1997 (130 cases) (figure 13).

The mean age at diagnosis was 61.3 years (sd = 14.6 years), for both the non-Hodgkin's lymphoma cases and their matched controls. The youngest case identified in this group was 5.4 years old and the oldest was 82.5 years. Males accounted for 54% of the non-Hodgkin's lymphoma cases and their matched controls. The histogram summarizing the age distribution of the non-Hodgkin's lymphoma cases is presented in figure 14.

The results that are not presented in this section are summarized in appendix G.

5.4.1 Tricyclic antidepressants

5.4.1.1 Effect of average daily dose of exposure by time period

The number of cases available for the analyses carried out to assess the association between average daily dose of TCA exposure and incidence of non-Hodgkin's lymphoma was 1980 for the first period before diagnosis, and 1541, 1030, and 502 for the second, third, and fourth periods respectively (tables 27 and 28). The number of controls was 7920, 6200, 4054, and 1970 for the four periods respectively.

5.4.1.1.1 Genotoxic and non-genotoxic TCAs

Table 27 presents the results of the analyses of the association between the average daily dose of exposure to genotoxic and non-genotoxic TCAs, in each of the four time periods, and the incidence of non-Hodgkin's lymphoma.

Exposure to the two types of TCAs considered in this study, during the third period before diagnosis (11-15 years), was found to have opposite effects on the incidence of non-Hodgkin's lymphoma (table 27). A p-trend of 0.01 was found for higher average daily dose of exposure to genotoxic TCAs during this period, with an adjusted RR of 3.01 at the high level (95% CI = 1.42 - 6.36). On the other hand, a significant protective effect was found for the exposure to non-genotoxic TCAs at the high average daily dose level with an adjusted RR of 0.29 (95% CI = 0.09 - 0.93) (table 27).

5.4.1.1.2 Exclusive genotoxic and non-genotoxic TCAs

Those with exposure to low and medium average daily dose levels of exclusive non-genotoxic TCAs, during the first period before diagnosis (2-5 years), had a significantly higher incidence of non-Hodgkin's lymphoma (adjusted RR = 1.41 and 1.71 respectively) (table 28). Moreover, an elevated incidence of non-Hodgkin's lymphoma (RR = 2.76, 95% CI = 1.15 - 6.61) was found for the high average daily dose level of genotoxic exposure during the 11-15 year period before the index date.

5.4.1.2 Effect of duration of exposure by time period

The results of the analyses of the association between the estimated duration of genotoxic and non-genotoxic TCAs, as well as the exclusive exposure to these drugs, in each of the four time periods and incidence of non-Hodgkin's lymphoma are presented in this section (tables 29 and 30). After excluding those with incomplete drug information, the number of available cases was 1980, 1541, 1033, and 508 for the four periods prior to the date of index, respectively. The number of controls available for the four periods was 7920, 6201, 4067, and 1993 respectively.

5.4.1.2.1 Genotoxic and non-genotoxic TCAs

The same results that were found in the analyses pertaining to the estimated average daily dose of TCAs and the incidence of non-Hodgkin's lymphoma were also found when the estimated duration of exposure was studied (table 29).

In the first period before diagnosis (2-5 years), higher average daily dose of exposure to non-genotoxic TCAs was associated with the incidence of non-Hodgkin's lymphoma (p-trend = 0.01), with the adjusted RR at the long duration level being 1.95 (95% CI = 1.23 - 3.10) (table 29).

Exposure to genotoxic and non-genotoxic TCAs during the third period (11-15 years prior to index date) was characterized with opposite effects on the incidence of non-Hodgkin's lymphoma (table 29). Higher duration of exposure to genotoxic TCAs in this period was associated with an increasing trend in incidence rates of non-Hodgkin's lymphoma (p-trend = 0.003), with a significant adjusted RR of 3.77 at the long duration level (95% CI = 1.61 - 8.85). On the other hand, higher duration of exposure to non-genotoxic TCAs in this period was associated with a decreasing trend in incidence rates of non-Hodgkin's lymphoma (p-trend = 0.03), with a significant adjusted RR of 0.19 at the long duration level (95% CI = 0.04 - 0.84) (table 29).

5.4.1.2.2 Exclusive genotoxic and non-genotoxic TCAs

Once again, the same effect of exposure to genotoxic and non-genotoxic TCAs, in the first and third period before the index date, on the incidence of non-Hodgkin's lymphoma was found when duration of exclusive exposure was studied (table 30).

Higher exclusive exposure to non-genotoxic TCAs, during the first period before diagnosis (2-5 years), was associated with an increasing trend in incidence rates of non-Hodgkin's lymphoma (p-trend = 0.002) (adjusted RR at long duration level =2.28, 95% CI = 1.40 - 3.72) (table 30).

In the third period before diagnosis (11-15 years), higher exclusive exposure to genotoxic TCAs was associated with a significant trend towards an increasing incidence of non-Hodgkin's lymphoma (p-trend = 0.02) (adjusted RR at long duration level =3.72, 95% CI = 1.36 - 10.2), whereas higher exposure to exclusive non-genotoxic TCAs was associated with a trend towards a decreasing incidence of non-Hodgkin's lymphoma (p-trend = 0.06) (table 30).

5.4.2 SSRIs

The analyses pertaining the estimated average daily dose and duration of exposure to SSRIs, for the two periods prior to the index date (2-5, and 6-10 years), in relation to non-Hodgkin's lymphoma are presented in tables 31 and 32. The sample size used for carrying out these analyses was 1243 cases and 4972 matched controls. Neither the estimated average daily dose of exposure to SSRIs, nor the estimated duration of exposure to these drugs was significantly associated with the incidence of developing non-Hodgkin's lymphoma.

Chapter 6: Discussion

Antidepressants are used to treat depression (a common illness) and other diseases (such as anxiety disorders, agoraphobia, panic attacks, obsessive-compulsive neurosis, migraine headaches, and chronic pain), and thus prolonged exposure to these drugs over extended periods of time is frequent. Cancer is the second leading cause of death, exceeded only by heart disease.

Although mechanisms have not been confirmed, animal and epidemiological studies suggest that antidepressants promote tumor growth in humans. In 1991, a study in fruit flies showed that some tricyclic antidepressants (TCAs) were genotoxic, as compared with others which were not found to be genotoxic (Van Schaik et al., 1991; and Van Schaik et al., 1993). Consistent results were found in humans in a large epidemiologic study on breast cancer (Sharpe et al., 2002).

It was based on these latest results that we developed our study to investigate the relationship between antidepressant drug use and the risk of cancer. The general hypothesis tested was that people exposed to genotoxic TCAs, relative to those exposed to non-genotoxic TCAs or unexposed to any antidepressants, were at increased risk of developing any of four different cancer types.

The following chapter summarizes and interprets the results, as well as addresses strengths and limitations of the study. The final conclusion is presented at the end of the chapter.

6.1 Summary of the results

Study results for the association between antidepressants exposure and cancer occurrence are summarized and discussed in this section. In the first subsection, results on the exposure to TCAs in association with each of the four cancer sites, as well as an overall summary, are presented. In the second subsection, effects of exposure to SSRIs, on each of the four cancer sites, are summarized.

6.1.1 TCA exposure

6.1.1.1 Female breast cancer

There was a tendency for those who had more exposure to any TCA, in the 2-5 year period prior to the index date, to have higher incidence rates relative to those unexposed to any TCA in this period (tables 33 and 34). Moreover, higher exposure to either genotoxic or non-genotoxic TCAs, during the same period, was also associated with a significant trend of increasing incidence rates of breast cancer (tables 35 and 36). The results of the analyses restricted by age did not show any different effects (appendices D.1 - D.3).

Exposure to TCAs in general, during the period 6-10 years prior to the index date, was not associated with any trend in incidence rates of breast cancer (tables 33 and 34). Similarly, higher exposure to either genotoxic or non-genotoxic TCAs, during the same period, was not associated with an elevated incidence of breast cancer, even when age restriction was applied (tables 35 and 36; appendices D.1 - D.3).

Higher exposure to any TCA (as a class), as well as to genotoxic TCAs, 11-15 years before the index date, was associated with a significant trend of increasing incidence of breast cancer (tables 33 - 36), whereas higher exposure to non-genotoxic TCAs, during the same period, was not associated with any trend in the incidence of breast cancer. Similar results were found when age restriction was done on the analyses (appendices D.1 - D.3).

Finally, higher exposure to any of the three groups of TCAs (TCAs as a class, genotoxic TCAs, and non-genotoxic TCAs), during the period 16-20 years before the index date, was not associated with elevated incidence of breast cancer (tables 33 - 36). Similarly, there was no observable trend in incidence in any of the age subgroups (appendices D.1 - D.3).

6.1.1.2 Prostate cancer

Exposure to TCAs in general, during the period 2-5 years prior to the index date, was not associated with any trend in incidence rates of prostate cancer (tables 33 and 34). On the other hand, it was exposure to genotoxic TCAs, during the same period, which was associated with a significant increasing trend (p-value = 0.01) in incidence of prostate cancer (tables 35 and 36).

Exposure to TCAs in general, during the period of 6-10 years prior to the index date, was not associated with an elevated incidence of prostate cancer (tables 33 and 34). On the other hand, during this period, and against the hypothesis, higher exposure to *genotoxic TCAs* was associated with a significant decreasing trend towards incidence of prostate cancer (p-trend = 0.01) (tables 35 and 36).

Finally, higher exposure to any of the three groups of TCAs (TCAs as a class, genotoxic TCAs, and non-genotoxic TCAs), during the periods 11-15 years and 16-20 years before the index date, was not associated with any trend in the incidence of prostate cancer (tables 33 - 36; and appendices E.1, E.2, E.5, and E.6).

6.1.1.3 Ovarian cancer

Those with higher exposure to any of the three groups of TCAs (TCAs as a class, genotoxic TCAs and non-genotoxic TCAs), during the period 2-5 years before the index date, were not at higher risk of ovarian cancer (tables 33 - 36).

Those with higher exposure to TCAs in general, during the 6-10 years prior to the index date, had significantly higher incidence rates of ovarian cancer (tables 33 and 34). Nevertheless, the increased risk was confined to exposure to the *non-genotoxic* TCAs during this period (p-trend less than 0.04) (tables 35 and 36).

Finally, higher exposure to any of the three groups of TCAs (TCAs as a class, genotoxic TCAs, and non-genotoxic TCAs), during the periods 11-15 years and 16-20 years before the index date, was not associated with any trend in the incidence of ovarian cancer (tables 33 - 36; and appendices F.1, F.2, F.5, and F.6).

6.1.1.4 Non-Hodgkin's lymphoma

Another unexpected association was found between exposure to TCAs, during the period 2-5 years prior to the index date, and the incidence of non-Hodgkin's lymphoma (tables 33 - 36). Among the three groups of TCAs, it was exposure to the *non-genotoxic* TCAs that was associated with a significant trend towards an increasing incidence of non-Hodgkin's lymphoma (p-trend = 0.002).

The incidence of non-Hodgkin's lymphoma was not related to the amount of exposure to any of the three groups of TCAs, during the period 6-10 years prior to the index date (tables 33-36).

Along the same line of the proposed hypothesis, higher exposure to genotoxic TCAs, during the period 11-15 years before the index date, was associated with a significant increasing trend in the incidence rate of non-Hodgkin's lymphoma, with a p-trend of 0.02 (tables 33 - 36).

Finally, none of the three groups of TCAs, during the period 16-20 years before the index date, was associated with any trend in the incidence of non-Hodgkin's lymphoma (tables 33-36; and appendices G.1, G.2, G.5, and G.6).

6.1.1.5 Summary

Across the four cancer types studied, our results did not show any consistent results in favor of the a priori hypothesis stating that exposure to genotoxic TCAs increases the risk of cancer development, as compared with exposure to non-genotoxic TCAs, which does not. Exposure to any of the three groups of TCAs (TCAs as a class, genotoxic TCAs, and non-genotoxic TCAs), at different times prior to the index date, was associated with either an increasing or a decreasing incidence of cancer (table 37). It is worth noting that although increased incidence of cancer was detected in some analyses, most of the instances the RR did not exceed 1.3, which cannot be considered as a major increase in the risk of developing cancer. Nevertheless, most of the confidence intervals calculated around the rate ratios included values which are considered clinically significant, and thus the term "inconclusive" should be applied to these results.

Regarding TCAs, as a class, exposure 2-5 years and 11-15 years prior to the index date, was associated with the incidence of breast cancer (table 37). Similarly, exposure to TCAs in general, 6-10 years before index date, was associated with increasing incidence of ovarian cancer.

As for the genotoxic TCAs, exposure 2-5 years prior to the index date was associated with the incidence of both breast and prostate cancers (table 37). Genotoxic TCAs also increased the incidence of breast cancer and non-Hodgkin's lymphoma when exposure took place 11-15 years prior to the index date. Surprisingly, however, exposure to genotoxic TCAs 6-10 years prior to the index date was associated with a decreasing incidence of prostate cancer.

Exposure to non-genotoxic TCAs, 2-5 years before the index date, was associated with the incidence of breast cancer and non-Hodgkin's lymphoma (table 37). In addition, an increased incidence of ovarian cancer was associated with exposure to non-genotoxic TCAs, 6-10 years before the index date.

6.1.2 SSRI exposure

In most of the analyses, the numbers of exposed cases and controls available for the analyses of the SSRI antidepressants in relation to cancer incidence were too small to rely on the findings. Nevertheless, higher exposure to SSRI drugs, during the periods 2-5 years and 6-10 years prior to the index date, was not associated with any trend of incidence rates of any of the four cancer sites under study.

6.2 Consistency with published results

It is important to note that most of the studies carried out to assess the association between antidepressant drug use and risk of cancer were limited either by small sample size, self-reporting of use, failure to specify dosage, duration, or timing of use, or lack of control of confounding. These limitations, in addition to the short follow-up periods in most of the studies, make it difficult to compare our results to the ones reported in the literature. The much more extensive data used for this study, compared with the data used in other studies, and the considerably different methods of analyses make it more difficult to evaluate whether the results of this study are consistent with those of other studies.

The incidence of cancer (at the four different sites studied) increased with age, which reflects findings in the literature reporting that age is a risk factor for these cancers (figures 8, 10, 12, and 14) (Lenbard, 2001). The yearly incidence rate of each of the cancer sites studied increased slightly from 1980 to 2000 (figures 7, 9, 11, and 13), which suggests either an increase in the incidence of these cancers, or an enhancement in the identification of these cancers, yielding an increase in the number of cases diagnosed.

6.2.1 Female breast cancer

The association between TCA use and the development of breast cancer was assessed in different studies, most of which did not find any positive association (Friedman et al., 1980; Danielson et al., 1982; Friedman et al., 1983; Selby et al., 1989; Friedman et al., 1992; Kelly et al., 1999, and Wang et al., 2001).

In their 15-year follow-up studies, Friedman et al. found a breast cancer risk of 1.07 (95% CI: 0.92 – 1.23) among amitriptyline users (who filled at least one prescription during the follow-up period), whereas the risk was 0.77 (95% CI: 0.40 - 1.34) among the imipramine users (Friedman et al., 1980; Friedman et al., 1983; Selby et al., 1989; and Friedman, 1992). These findings are consistent with the results of our analyses carried out using the ever/never exposure index, for the period 2-15 years prior to index date, where the RR was 1.05 (95% CI: 0.97 – 1.15) (table 2).

In an attempt to avoid reverse causality, we excluded the year prior to cancer diagnosis. The results of the cohort study conducted by Danielson et al. were not comparable with our results since they defined exposure to antidepressants as having an antidepressant dispensed within the six-month period before the breast cancer was diagnosed (Danielson et al., 1982). Similarly, the short follow-up period (2 and a half years) of the study conducted by Wang et al. (Wang et al., 2001) makes it difficult to weigh their results against ours.

Similarly, no association between exposure to antidepressants and risk of breast cancer was found in the study carried out by Kelly et al. (Kelly et al., 1999). The assessment of exposure history through subject interviews was a major limitation, which might explain the discrepancy between our results and theirs.

On the other hand, a positive association between antidepressant drug use and risk of breast cancer was reported by few studies (Wallace et al., 1982; Cotterchio et al., 2000, and Sharpe et al., 2002).

Wallace et al. found a significant positive association between antidepressant drug use and risk of breast cancer (RR = 2.84, p-value < 0.04). However, it is difficult to compare these results to ours, since exposure data were obtained through interviews, and timing of use was not specified (Wallace et al., 1982). Similarly, the results of the case-control study carried out by Cotterchio et al. [OR = 2.5 (95% CI: 1.2 - 5.1)] were based on self-report of antidepressant exposure history, as well as the lack of timing specification, which adds to the difficulty of comparing them with our results (Cotterchio et al., 2000).

Finally, the major finding reported by Sharpe et al. was that higher exposure to genotoxic TCAs was associated with a trend towards an increasing risk of breast cancer 11-15 years later (p-trend = 0.0009), where at the highest exposure level the rate ratio was 2.47 (95% CI: 1.37 - 4.40). No association was found for exposure to non-genotoxic TCAs during the same time period. Table 38 presents a direct comparison between the results reported by the current study and those reported by Sharpe et al. regarding the exposure to high level of genotoxic and non-genotoxic TCAs, 11-15 years before the date of diagnosis with breast cancer (table 38). Even though our results were consistent with what Sharpe et al. found, the effect of exposure to genotoxic TCAs on the development of breast cancer was not as strong. Although the same Saskatchewan health services databases were used in both Sharpe et al.'s study and our study to assess the effects of TCAs on the incidence of breast cancer, some differences could explain the discrepancy in the strength of the association. The first difference was the design of our study, which was a multiple site-specific case-control study using the same set of controls for the analyses of the different cancers. Because of the longer prescription histories in our study, the years 1981 to 2000 as compared with a 15-year period studied by Sharpe et al. (1981 - 1995), our sample size was bigger (7330 cases as compared with 5882 cases) (table 39). Another aspect that differed between the two studies was the inclusion criteria of cases and controls. The age range of subjects ranged between 5 and 82.5 years in our study, whereas only subjects older than 35 years were included in the study that Sharpe et al. conducted. As a consequence, the two sets of data had 72.6% of all cases in common (74.2% of those 35-81 years old were in common) (table 39). Moreover, since the controls were selected randomly from the population of Saskatchewan, we had a completely different set of controls in our study as compared with Sharpe et al.'s study. Lastly, there were few differences in the analyses we carried out to assess the measures of estimates. In their study, Sharpe et al. did not consider any subject's antidepressant exposure in any specified time period if it overlapped with the period of incomplete recording of prescription information by the SPDP (July 1, 1987 and December 31, 1988). Whereas in our study, we assumed that all the subjects were unexposed during this year and a half period, and thus were able to use some valuable information that otherwise would be lost. Finally, in an attempt to replicate the results of Sharpe et al., by using the 72% common cases and applying the same analyses, we got results which were very similar to what was reported by the authors (results not presented). This provided evidence that the discrepancy between Sharpe et al.'s results and our results could be attributed to the differences summarized above.

6.2.2 Prostate cancer

The results of the analyses of the association between antidepressant drug use and risk of prostate cancer could not be compared with any previous studies reported in the literature since, to our knowledge, our study is the first to assess this association.

6.2.3 Ovarian cancer

Four published studies have assessed the association between antidepressant drug use and the risk of ovarian cancer. Two of these studies, carried out by the same group, reported a positive association with ovarian cancer (Harlow et al., 1995; and

Harlow et al., 1998), whereas the other two reported non-significant associations (Coogan et al., 2000; and Dublin et al., 2002).

The first study was conducted by Harlow et al. who found that use of antidepressants 10 or more years prior to date of diagnosis was associated with an increased risk of ovarian cancer [adjusted OR = 9.7 (95% CI: 1.2 - 78.8)] (Harlow et al., 1995). In our study, cumulative dosage exposure to antidepressant drugs 11-20 years prior to the index date was also associated with a relatively elevated non-significant risk of ovarian cancer (RR = 1.16, 95% CI: 0.70 - 1.93) (appendix F.1). The discrepancy of these risk estimates could be due to the very small sample size used by Harlow to calculate the risk (9 cases and 1 control). In their second study, Harlow et al. found that women who reported using any psychotropic medication, for 6 months or longer in the past, had a significantly greater risk of ovarian cancer than nonusers [OR = 1.6 (95% CI: 1.1 - 2.3)] (Harlow et al., 1998). Because the authors did not differentiate between antidepressants use and the use of other psychotropic drugs, it is difficult to compare their results to ours.

In their analyses, Coogan et al. reported that use of TCAs regularly 10 years before the index date was not significantly associated with the risk of ovarian cancer [odds ratio of 1.6 (95% CI: 0.6 - 4.6) when compared with cancer controls and 1.5 (95% CI: 0.5 - 4.10) when compared with non-cancer controls] (Coogan et al., 2000). These results could be compared with the results reported in appendix F.1 where we found that cumulative dosage exposure to TCAs 11-20 years prior to the index date was associated with a RR of 1.16 (95% CI: 0.70 - 1.93). The elevated risk reported by Coogan et al. could be attributed to the recall bias that could have affected the results, because history of medication was obtained through interviews.

The most recent study cited to assess the association between antidepressant drug use and ovarian cancer reported an OR of 0.71 (95% CI: 0.47 – 1.1) for filling two antidepressant prescriptions in any 6-month period prior to the date of diagnosis (Dublin et al., 2002). The analyses of ours that was most comparable to the ones Dublin et al. carried out are presented in appendix F.2 (using ever/never exposure index in those having at least 15 years of history) where we found an non-significant RR of 1.05 for those who were ever exposed during the 2-15 year prior to the index date.

6.2.4 Non-Hodgkin's lymphoma

One published study has assessed the association between antidepressant drug use and the risk of non-Hodgkin's lymphoma (Dalton et al., 2000). The authors found an increased risk of non-Hodgkin's lymphoma among people with five or more TCA prescriptions [Standardized Incidence Ratio = 2.5 (95% CI: 1.4 - 4.2)] when followed for an average of 3.2 years. The analyses carried out by Dalton et al. could be compared with the ones we carried out for the ever/never exposure index (appendix G.4). We have found that ever being exposed to any TCA, in the 2-5 year period, was associated with a significant increase in the incidence of non-Hodgkin's lymphoma (RR = 1.25, 95% CI: 1.06 - 1.47), not as strong as the estimate reported by the authors.

6.2.5 Overall results

Comparing our results with those published in the literature is a difficult task because of the difference in the data structure, as well as the different analyses used. Nevertheless, in general, the results are consistent with most studies found in the literature.

In our study, we found that exposure to any of the three groups of TCAs (TCAs as a class, genotoxic TCAs, and non-genotoxic TCAs), at different time periods prior to diagnosis, was associated with an increased incidence of different cancer sites (table 37). The period before diagnosis during which exposure to antidepressant drugs might have an effect on the development of cancer varied among different sites, as well as different types of TCAs.

The significant trend of an increasing incidence of cancer (breast, prostate and non-Hodgkin's lymphoma) in association with exposure to antidepressants, during the period of 2-5 years before the index date, could have two explanations. The first supports the promoting role contributing to the development of cancer, and the second considers a possible reverse causality. Because exposure occurred close in time to the index date, the possibility of reverse causality bias is more likely:

symptoms caused by the undiagnosed cancer might have resulted in exposure to antidepressants.

The observed differences in the effects of genotoxic and non-genotoxic TCAs on the four cancer sites could have one of two explanations. The observed associations could in fact be reflecting true effects of different types of antidepressants on different cancer sites, which are determined by the pharmacological characteristics of the drugs, as well as the carcinogenesis process of each specific cancer (Angst J, 1992; and Miller L, 1993). This explanation is supported by the fact that some animal studies that assessed the relation between exposure to antidepressants and risk of cancer have found positive associations (Brandes et al., 1992; Miller, 1993; Iishi et al., 1993; Van Schaik et al., 1991; and Van Schaik et al., 1993). Moreover, some well conducted epidemiological studies studying this question have found antidepressants to increase the risk of developing cancer at different sites (Wallace et al., 1982; Harlow et al., 1995; Dalton et al., 2000; and Sharpe et al., 2002). Thus, the inconsistent results, in both animal and human studies, could be considered supportive of the hypothesis stating that exposure to antidepressants does in fact have an effect on cancer development, the specifics of which are still to be understood.

Another possible explanation for the observed differences in the effects of all TCAs combined on the four cancer sites might be the confounding effects of other determinants of cancer associated with antidepressant use. Such a factor might be depression, since it is still believed that depression could be associated with the development of cancer as the result of immunologic and endocrine dysfunction (Linkins et al., 1990). Nevertheless, such an explanation is not fully supported by the results of our study, because we didn't find any association between exposure to SSRIs and risk of cancer development. If confounding by depression were responsible for the observed results on the association between TCAs and risk of cancer, then it would have been expected to find similar effects on the association between SSRIs and cancer.

6.2.6 Cell turnover

The selection of the four cancer sites that we studied was based on different criteria, one of which was the variability in terms of their cell turnover rate (the frequency of cell division). Cells in the prostate and the lymphatic system are long-lived and there is no cell division in postnatal life, whereas those in the breast and the ovaries are short-lived and cell division in postnatal life occurs frequently (Fawcet, 1986).

One of the objectives of our study was to test the hypothesis that the carcinogenic effect of the genotoxic antidepressants varies according to rates of cell turnover. The effects of antidepressant drugs was expected to be more apparent when cell division was high and the turnover was rapid, whereas, the effect was expected to be less obvious when the multiplication was low and turnover was slow (Fawcet, 1986). Accordingly, we expected to see bigger effects of exposure to genotoxic TCAs on each of the breast and ovarian cancer sites (high turnover), as compared with the prostate and non-Hodgkin's lymphoma sites (low turnover). Our study, as summarized in table 37, did not show any difference between sites of high and low cell turnover rates. In other words, we did not find enough evidence to support the hypothesis stating that the carcinogenic effect of genotoxic antidepressants vary according to cell turnover.

6.3 Strengths and limitations of the study

In order to interpret the study results, an overview of the strengths and limitations of this study is presented in the subsections below.

6.3.1 Strengths

6.3.1.1 Study design

The case-control approach adopted to study the association between antidepressant drug use and risk of cancer at different sites was the most efficient design to study the proposed question. Case-control design is suitable for studying the effects of a common exposure on an outcome, which is considered a rare disease.

- Large sample size:

The population-based case-control nature of this study was one of its major strengths. By definition, a geographic population-based study is a study where every case of illness occurring in a geographic area is included in the case series, and a representative sample of the base population is selected as controls (Rothman et al. 1998). In our study, every cancer case (of the four sites under study) diagnosed in the province of Saskatchewan, between the years 1981 and 2000, was potentially eligible for our analyses. Thus, the big sample size available for the analyses was another strength of our project, where the number of cases ranged between 1090 cases (ovarian cancer) and 7767 cases (prostate cancer).

- High precision/power:

For a given type of cancer, the statistical power to detect elevated incidence rates in those exposed to a certain group of drugs, versus those not exposed to any of these drugs, is a function of the numbers of cancer cases, the prevalence of the exposure of interest, and the true rate ratios. For any of the four cancer sites studied, we had a statistical power exceeding 95% to detect a rate ratio of 1.5 at an exposure prevalence of 8%. This is also reflected in the narrow confidence intervals calculated in almost all of the analyses.

- Matching:

Matching in case-control studies is done for two reasons: to prevent confounding and to provide a more efficient stratified analyses (Rothman et al., 1998). Controls were matched to cases on each of the following variables: age and sex. Control for the effect of confounding by these variables was achieved by carrying out matched analyses.

- Incidence density sampling:

Incidence density sampling is a procedure when for every case a number of controls are chosen from among those who have survived, remain under observation, and are free of the disease of interest at the time the corresponding case was diagnosed (MacMahon et al., 1996). When using incidence density sampling, controls are matched to cases on the follow-up time, and thus, time will be incorporated in the design. As a consequence, person-time is inherently accounted for in the analyses and the odds ratio will be an unbiased estimate of the incidence rate ratio without any rare disease assumption (Miettinen, 1985). In our study, incidence density sampling was applied in the selection of cases and controls, which provided the strengths mentioned above.

- <u>No recall bias:</u>

Cases and controls by definition are people who differ with respect to their disease experiences. Recall bias (a type of information bias) is the result of having differences in recall of certain experiences between cases and controls. In our study, if we were to assess previous exposure history to antidepressants from cases and controls through interviews, recall bias might have been a major problem. This is because people who had developed a certain type of cancer would tend to recall exposures more thoroughly as compared with those who were not diagnosed with any cancer. Thus, another major strength of this study was the pre-recorded exposure history of each case and control, which was compiled from a provincial outpatient prescription drug database since 1976. Consequently, the potential of recall bias in terms of exposure to antidepressants was excluded from our study.

- <u>Good control for selection bias:</u>

Selection bias is the error due to systematic differences in characteristics between those who were selected for study and those who were not. Our study included almost all cases diagnosed in Saskatchewan, between the years 1981 and

2000, meeting the study criteria. In addition, the controls represented a random sample of population at risk, and therefore potential for selection bias was minimized.

6.3.1.2 Statistical analyses

- <u>Different exposure definitions:</u>

Another strength of our study was the assessment of the association between antidepressant drug use and the development of cancer using different exposure definitions. Each exposure index was used to cover one or more of the exposure aspects that are thought to be important (cumulative, dosage, duration, and timing).

The simplest definition was whether the subject had ever been exposed to any of the antidepressants under study for different periods (20, 15, 10, or 5 years). This exposure definition was a crude one, because it failed to account for the dosage, duration, and timing of exposure. The second exposure index used was the dosage of the cumulative exposure to the antidepressants being studied for each of the specified periods (20, 15, 10, or 5 years). The cumulative and dosage aspects were accounted for by using this exposure index, whereas the timing and the duration of exposure were not taken into consideration. The third and fourth exposure indices covered the dosage and duration aspects of antidepressants exposure respectively, for different periods before diagnosis, thus taking timing into consideration as well. Nevertheless, these two exposure indices did not account for the cumulative effect of exposure for more than the length of the period before diagnosis itself (4 or 5 years). The unexposed during each period were the referent for that period. This was justified by the fact that ingested antidepressants are excreted and their pharmacologic effects cease when use stops.

Although none of the exposure indices integrated all the important aspects of exposure (cumulative, dosage, duration, and timing), we still carried out the analyses with each of the indices to have the chance to compare the results of each.

The four different methods of calculating exposure gave similar results, implying that they all managed to rank subjects according to an aspect of exposure that was relevant to the diagnosis of cancer.

The effect of using different exposure definitions on the measures of effect was illustrated in a study assessing the association between hormone replacement therapy (HRT) and colorectal cancer risk (Csizmadi et al., 2003). It was found that different definitions of HRT were valid attempts to quantify a complex exposure. The variation of the measures of effect, of different HRT exposure definitions and colorectal cancer risk, was similar to the variation reported in the literature for observational studies investigating the same association (Csizmadi et al., 2003).

- <u>Using continuous and categorical exposures:</u>

Furthermore, another strength of our analyses was the consideration of exposure as categorical variables, as well as continuous ones. The RRs calculated for the association between exposure to different antidepressants and risk of cancer were based on categorizing the exposure into two or three ordinal variables. In addition, p-trends were also calculated to assess the association between the continuous exposure to the antidepressant drugs and risk of cancer.

- <u>Controlling for possible confounding variables:</u>

Considering exposure during different periods to represent separate determinants provided a simple way to represent the exposure history over time with multiple logistic regression, which permitted the study of the effects of the timing of exposure (Miettinen, 1985). As a consequence, multicollinearity could have been a problem in the regression models (which included exposure to the drugs in different periods), since exposure to antidepressants in one period could have been affected by exposure to the same or different antidepressants in other periods. However, the correlation between the exposure to antidepressants in the different periods was found to be low. This could be due to the fact that antidepressants are rarely taken continuously for very long periods of time (Peretti et al., 2000).

Since depression is the indication to use antidepressants (depression in turn might be associated with cancer) an imbalance in the underlying risk profile between the exposed and unexposed groups might generate biased results. One way to avoid confounding by indication is to compare two medications prescribed for the same indication (Strom, 2000). In this case, relative risk, as opposed to absolute risk, would be calculated. Thus, another strength of the study was the control for the effect of confounding by indication, specifically for the hypothesis regarding TCA genotoxicity, where the effects of exposure to genotoxic TCAs, on the risk of cancer, were compared to the effects of exposure to non-genotoxic TCAs.

- Good control of exposure misclassification:

When exposure information for a period was incomplete, due to the subject's coverage initiation date, the subject was assigned to the "other" category of the exposure. This avoided overestimating exposure. Exposure may however be underestimated, biasing the results towards the null.

6.3.2 Limitations

An overview of the limitations of this study is summarized in the subsections below.

6.3.2.1 Study design

The variation in the length of the subjects' exposure records, ranging from 5-24 years, led us to divide exposure history into different time periods. As a consequence, the study was limited by having less statistical power to detect significant associations between exposure to antidepressants in the remote past and the diagnosis of cancer, as compared with recent antidepressant exposure in relation to the diagnosis of cancer.

6.3.2.2 Representation of outcomes

- <u>Outcome misclassification:</u>

The erroneous classification of an individual, a value, or an attribute into a category other than that to which it should be assigned is called misclassification (Last, 1995). Any outcome misclassification, including as a case a subject who did not have a certain cancer type and including as a control a subject who actually did have cancer, is expected to have an effect on the results.

In addition to the 98% of all new cancer cases that are reported to the SCR by physicians and by the submission of all malignant pathology reports, an additional 1-2% of cases are discovered through the biweekly review of death certificates (Parkin, 1997), so registration was likely to have been very nearly complete. Nevertheless, it is possible that a few controls had actually been diagnosed with cancer that went unreported before their index dates. In addition, it is possible that some controls may have received diagnoses of cancer that were reported but not found when the database of the SCR was searched for cancer diagnoses. Such failures of the linkage process would be expected to be rare events and independent of exposure status.

Potential study cases were subjects in the source population who were diagnosed with histologically proven invasive tumors and reported to the SCR. Thus, we cannot exclude the possibility that the diagnostic criteria could have changed somewhat from 1981 to 2000, since a pathologic review was not carried out specifically for this study. In other words, it is possible that this could have led to some misclassification with respect to the invasiveness of the tumors; some tumors classified as "invasive" could have actually been in situ (i.e. non-invasive) or vice versa. Nevertheless, such a misclassification is believed to be non-differential in relation to exposure to antidepressants.

Potential study controls were defined as people in the source population who had not developed any cancer prior to the index dates of the cases to whom they were matched. The validity of such a definition depends on the completeness of registration of cancer cases by the SCR and the validity of the linkage procedures used to link the databases. The linkage process is believed to be valid, since each resident is assigned a unique personal identification number (Strom, 2000).

As long as any of the above mentioned outcome misclassification biases are non-differential with respect to antidepressant exposure, it would bias the RRs towards the null (Brenner et al., 1993). Pathologists do not consider antidepressant exposure when examining tissues and there is no evidence to date that antidepressant use alters the appearance of human tissues so as to make misdiagnosis more or less likely. On the other hand, failing to include few cases with the specified cancer site, because of incomplete registration of cancer, is expected to be a rare occurrence which is independent of exposure to antidepressants. Therefore, any resulting outcome misclassification would likely have no effect on the RRs, since there is no reason to suspect that it would be differential with respect to exposure to antidepressants.

6.3.2.3 Representation of exposure

- <u>Classes instead of individual drugs:</u>

Exposure to antidepressants was characterized as a class of drugs rather than as individual drugs because the numbers of subjects with histories of filling prescriptions for any one drug were relatively small. We made the assumption that all the drugs in each class would have similar effects on the risk of cancer.

- <u>Drug consumed versus drug dispensed:</u>

Exposure to antidepressants was expressed in terms of dispensed antidepressants to outpatients as recorded in the Saskatchewan outpatient prescription drug database during specified periods of time. Although we may have underestimated exposure, because we had no information about some of the TCAs dispensed (subjects while hospitalized or as samples in physicians' offices), these amounts were probably small relative to the amounts used in calculating exposure.

Accurate estimation of the total amounts of antidepressants actually consumed over time could be a very difficult undertaking. Thus, the exposure definition used in this study did not refer to actual consumption of antidepressants, but rather to the dispensed antidepressant prescriptions. As a consequence, overestimation of exposure might have occurred, because it is unlikely that all drugs dispensed were ingested, which could have affected the slope of the dose-risk relationship that we observed to be less than the true slope (MacMahon et al., 1996).

Nevertheless, prescription plans are thought to be reliable sources of drug exposure, as reported in the study carried out by Lau et al. (Lau et al., 1997). The authors assessed the validity of drug exposure based on pharmacy records, taking into account completeness of data and drug compliance. Data on drug prescription were collected from home inventories and community pharmacies in 115 elderly people. With the data on drug exposure in the home inventory taken as the gold standard, the specificity and positive predictive value were found to be generally high (0.93 – 1.00 and 0.67 – 1.00 respectively). The authors concluded that computerized pharmacy records that are collected for administrative and drug surveillance purposes could be a reliable reflection of the true drug exposure (Lau et al., 1997).

Although our exposure definition may be limited by compliance (subjects may have consumed less than the full amounts of antidepressants dispensed), it avoided some issues of exposure misclassification. For example, if a subject filled a prescription for an antidepressant on the last day of one period and consumed the drug during the next period, the timing of exposure defined in terms of dispensed prescriptions would not be misclassified, but it would be if exposure were defined in terms of actual drug consumption.

The main limitation in using dispensed prescriptions over periods of time 4-5 years long was that relatively brief periods of antidepressants use at high dosage levels became indistinguishable from low levels of exposure over prolonged periods. This situation could be remedied by representing exposure over time with more periods of shorter durations, but the number of regression coefficients to be estimated would increase and multicollinearity might develop.

Despite the above limitation, the approach used did capture the timing of the exposure to some extent, especially for the highest level of exposure. Subjects in the highest category of antidepressant exposure must have taken the drugs over prolonged periods, otherwise life-threatening toxicity would have occurred. Thus, the above limitation is believed to be of little consequence to the validity of the analyses.

- <u>Missing drug information:</u>

Another limitation of our study is the fact that information on drug prescription of all subjects (cases and controls) –between July 1, 1987 and December 31, 1988 – was not provided because the capture of outpatient prescription drug information was incomplete during this period.

Before June 1987, residents of Saskatchewan used to pay a portion of the drug fees directly to the pharmacy; whereas in July 1987, the government changed the program to a family-based deductible system in which the consumer paid the total cost of the prescription and submitted claims to the drug plan for partial reimbursement when the family cost exceeded the deductible level. In January 1989, the deductible program continued but the claims processing system was changed, and pharmacies started submitting claims to the drug plan through a point of service computer terminal connected to a central database. Because of this change in systems, between July 1987 and Dec 1988, the drug plan did not capture a complete drug prescription profile for the residents of Saskatchewan since prescription drug data were not compiled on an individual basis.

As a consequence, we considered all the cases and controls to be unexposed during this one and a half year period. In other words, subjects who were in fact exposed to different levels of antidepressants during this period were classified as unexposed. Such an exposure misclassification is thought to be non-differential, since there is no reason to believe that the misclassification was related to the outcome studied (being a case or a control). The effect of non-differential misclassification on a measure of association is thought to bias the measure towards the null value (Brenner et al., 1993), hence to underestimate the true effect.

6.3.2.4 Statistical analyses

- <u>Number of tests performed:</u>

These results could have been affected by the number of tests performed in our analyses. Theoretically, if there were no association between TCA exposure and incidence of cancer, by using the 5% α level we would expect to find 5%, of the number of tests performed, significant associations in the data. Thus, in our study, we would expect some positive associations between exposure to antidepressants and risk of cancer, if in fact there were no association. This is further supported by the results which provided inconsistent pattern in the effect of exposure to antidepressants and risk of cancer. Bonferroni correction (lowering the α level to a value less than 5%) could have been used to deal with limitation. But since the overall relationship between exposure to antidepressants and risk of cancer was not found to be significant at the 5% α level, we did not attempt to apply this correction to our analyses.

- Analyses not covered:

The average effects of exposure to antidepressants during different periods prior to diagnosis were estimated. The RR calculated for exposure during a particular period of time represented the ratio of the incidence of the specific cancer among those exposed to antidepressants during that period to the corresponding incidence among those unexposed during that period, while keeping the pattern of antidepressant exposure during all other periods identical. Nevertheless, we could not determine how the effect of antidepressant exposure during a given period depended on previous or subsequent exposures.

The unit of exposure in two major analyses in this study was the estimated dosage of antidepressants expressed in moles. For different time windows, we assessed the effect of exposure to different levels of antidepressants (low, medium, and high) on the development of the different types of cancer. On the other hand, because of the complexity of the analyses we carried out, we did not attempt to assess whether similar effects exist for the same level of exposure but over a different time periods i.e. longer periods.

6.3.2.5 Control for potential confounding variables

In most of the analyses presented in this thesis, the only variables we controlled for were: age, gender, index date, and the effects of exposure during other periods of time prior to diagnosis. Although we controlled for the effect of exposure to different drugs in the different periods prior to diagnosis, we didn't present these results because the drugs we studied had no effect on the estimated RRs calculated.

Given the number and types of cancer sites addressed in this study, as well as the study design and database structure, we did not have information on the different possibly confounding variables. The effects of not controlling for these variables, on the results of the two different hypotheses tested, are discussed in the following subsections.

- <u>Genotoxic versus non-genotoxic TCAs:</u>

The conclusions drawn on the major hypothesis tested by this study (genotoxicity of TCAs) are believed to be valid unconfounded conclusions. Our primary hypothesis concerned the potential carcinogenic effects of genotoxic TCAs.

Two incidence rate ratios were calculated, one for exposure to genotoxic TCAs (relative to those unexposed to any antidepressant), and the second for exposure to non-genotoxic TCAs (relative to those unexposed to any antidepressant). Comparing these two incidence rate ratios, by calculating a ratio of these ratios, would indicate the relative risk of using genotoxic TCAs relative to non-genotoxic TCAs. Such an association would unlikely be affected by confounding because the choice of a specific group of TCAs was unlikely to be related to any of the risk factors for the cancers considered in this study. The initial choice of TCA prescription is usually based on the pharmacologic characteristics of the antidepressant (onset of action, elimination half-life, therapeutic blood level, side effects, drug interactions, toxicity associated with overdose, and efficacy), patient's characteristics, and cost (Kaplan et al., 1993; and Flint, 1998). Therefore we think that comparing the two estimated incidence rate ratios is a valid unconfounded comparison.

- <u>Antidepressants as classes of drugs:</u>

On the other hand, the conclusions drawn on the effects of TCAs and SSRIs, as classes of drugs, on the risk of cancer could have been affected by confounding bias. The reported results for these analyses could have been biased towards or away from the null, the direction of which being difficult to determine. Nevertheless, an attempt to assess the effects of few major confounders is presented in the following paragraphs.

Family history of cancer: For almost all tumors, the incidence of same-site cancer is increased in close relatives of persons with cancer (Schottenfeld et al., 1996). Two to threefold increased risk of breast cancer has been observed in first-degree relatives of breast cancer cases, and fivefold increased risk has been found for women with multiple first-degree relatives with breast cancer (Colditz et al., 1993; Brekelmans, 2003). As for ovarian cancer, of all the risk factors, the most significant one appears to be that of family history (7% to 10% of ovarian cancers are due to inherited susceptibility genes) (Frank et al., 1998). Available epidemiologic data support a familial tendency towards prostate cancer occurrence. It has been reported that men with one first-degree relative with prostate cancer had a twofold increase in risk, whereas a positive family history for a second-degree relative was associated with a 70% increase in risk (Steinberg et al., 1990). Finally, the risk of non-Hodgkin's lymphoma has been found to be associated with a threefold increase when a history of lymphoma in first-degree relatives was present (Zhu et al., 1998).

A family history of cancer might be considered to have a potential confounding effect on the association between the exposure to antidepressants and risk of cancer, if it is associated with antidepressant drug use. Although depression and cancer might be weakly associated (Shekelle et al., 1981; Penninx et al., 1998), there is no evidence for an association between family history of cancer and risk of depression. Thus, it is unlikely that family history of cancer could have confounded our results.

Diet: The nutrient content of diet, which has been reported to have the highest correlation with the risk of cancer, is fat intake. The most important sites for which associations have been suggested are cancers of the breast and the prostate (Schottenfeld et al., 1996; Key et al., 2002)). Much of the support for these relationships is based on the international correlations between per capita fat intake and rates of these malignancies. However, epidemiological studies within populations show little or inconsistent associations (Byrne et al., 2002). Taken together, the available evidence for a relation between dietary fat and cancer is weak (Zock, 2001; Smith-Warner et al., 2001).

As for the association between nutrient intake and occurrence of depression, there is no evidence supporting such a relationship. A study investigated the nutrient intake of depressed and non-depressed subjects, revealed that both groups consume similar amounts of dietary fats (Christensen et al., 1996). The lack of such an association would lead to a balanced distribution of subjects exposed to high and low dietary fats among the different exposure groups under study (antidepressant drugs). Thus, no bias in the reported results could be attributable to the difference in the dietary fat intake of the subjects in our study.

Alcohol consumption: Many studies have shown positive associations between alcohol use and the risk of breast cancer, with dose-response relationships (Rosenberg et al., 1993; Bowlin et al., 1997). In 1994, Longnecker et al. published a meta-analysis in which estimates of the RR as a linear function of daily alcohol consumption were calculated for case-control and cohort studies (Longnecker et al., 1994). The risk of breast cancer was associated with the consumption of one, two, or three drinks per day, compared with non-drinkers, where the OR were as follows: 1.1 (95% CI: 1.07 – 1.15), 1.2 (95% CI: 1.5 – 1.34, and 1.4 (95% CI: 1.23 – 1.55).

Cross-sectional studies using community samples have consistently shown that alcohol use is associated with an elevated risk of depressive symptoms (Wang et al., 2002). On the other hand, longitudinal studies provide inconsistent results regarding the association between alcohol consumption and depression (Wang et al., 2001; Hasin et al., 2002). These inconsistencies could be explained by the use of different exposure indices (frequency of drinking, average daily alcohol consumption, etc.) and different definitions of depression, in the different epidemiological studies. Nevertheless, it is widely accepted that excessive alcohol consumption is associated with major depression.

Based on the above associations, we would expect that the results of the breast cancer analyses be biased by the potentially confounding effect of alcohol consumption. The effect of alcohol consumption might have partially accounted for the observed effects between exposure to antidepressant drugs and the risk of breast cancer. This bias could have been introduced because of the difference in the distribution of alcohol consumption in the different antidepressants exposure groups. In other words, subjects who were exposed to antidepressant drugs could have had higher alcohol consumption levels, as compared to those who were not exposed to antidepressant drugs.

Physical activity: There is increasing consistency across studies that physical activity reduces the risk of breast cancer. In 2001, it was reported that 23 out of 35 studies have demonstrated a breast cancer risk reduction among those women who were most active in their occupational and/or recreational activities, as compared with inactive women (Friedenreich et al., 2001). It has been suggested that sustained activity throughout life, and particularly activity done later in life, may have the most benefit in reducing breast cancer risk (Friedenreich et al., 2001; Dorn et al., 2002). The association between physical activity and risk of ovarian cancer is not yet established. The authors of one of the studies that studied this association reported that increasing duration of moderate activity in pre- and postmenopausal women decreased the risk of ovarian cancer (Zhang et al., 2003). Up to our knowledge, no study has ever reported a relationship between physical activity and non-Hodgkin's lymphoma or prostate cancer.

It is also well accepted that physical activity has protective effects on depression (Dunn et al., 2001; Strawbridge et al., 2002). In 2001, Dunn et al. carried out a literature review to examine the scientific evidence for a dos-response relation of physical activity with depressive and anxiety disorders (Dunn et al., 2001). In their search, the authors reported that observational studies demonstrate that greater amounts of occupational and leisure time physical activity are generally associated with reduced symptoms of depression, which was consistent across different cultures. Nevertheless, they concluded that there is little evidence for dose-response effect, which was due to a lack of studies rather than a lack of evidence (Dunn et al., 2001).

Taking this into consideration, we would expect a difference in the level of physical activity between cases and controls, as well as between exposed and non-exposed. Controls and subjects who were not depressed, and thus not exposed to antidepressants, would tend to have had a higher physical activity (as compared to cases and subjects who were exposed to antidepressant drugs). As a result, the conclusions drawn from the analyses pertaining to the effect of exposure to antidepressant drugs on the risk of breast and ovarian cancer could have been biased by the confounding effect of physical activity.

Early menarche and late menopause: Breast cancer risk is increased by early menarche and by late menopause (Pike et al., 1993). These relationships indicate that the high serum concentrations of estradiol and/or progesterone in premenopausal women cause a greater increase in breast cancer risk per year than the much lower concentrations of estradiol and prprogesterone in postmenopausal women. Neither estradiol nor progesterone is genotoxic but it is possible that the high serum concentrations of these hormones in premenopausal women increase breast cancer risk by increasing the mitotic rate of the breast epithelial cells (Pike et al., 1993). In general, an approximately 20% decrease in breast cancer risk results from each year that menarche is delayed. It has also been estimated that women who experience menopause before age 45 have only one-half the breast cancer risk of those whose menopause occurs after age 55 (Schottenfeld et al., 1996).

As for the association between age at menarche and age at menopause and risk of ovarian cancer, no consistent findings have emerged from the studies that assessed these associations (Schottenfeld et al., 1996).

Psychiatric disorders often begin at adolescence, the reason why it has been thought that menarche marks a transition in the risk of depression and anxiety in girls. It has been reported that early menarche (prior to 11.6 years) was associated with elevated rates of depression (Stice et al., 2001). In a study that was carried out by Patton el al., the authors found that levels of depression and anxiety increased with secondary school years and menarchal status was found to be the strongest predictor for such an increase (Patton et al., 1996).

The menopause has been described as a deficiency disease associated with a wide variety of physical and psychological symptoms including hot flushes, night sweats, dyspareunia, urinary frequency, sleep disturbance, depression and anxiety (Neugarten et al., 1965; Studd et al., 1990; Sagoz et al., 2001). There are suggestive data that estrogen deficiency may increase the susceptibility for depression (Birkhauser, 2002; Maartens et al., 2002). It was estimated that the transition from pre to perimenopause and peri to postmenopause was significantly related to a high increase in a depression score (OR = 1.8, 96% CI: 1.1 – 3.3 and OR = 1.8, 95% CI: 1.5 – 2.7 respectively) (Maartens et al., 2002).

Thus, the results of the breast cancer analyses could have been biased by the potentially confounding effect of the subjects' menarche and menopause status. In other words, the average ages at which subjects experienced menarche and menopause would differ between cases and controls, and between those exposed to antidepressants and those who were not. Breast cancer cases and subjects exposed to antidepressants would be expected to have had a lower average age at menarche and a higher average age at menopause.

Region: Another factor that could have had an impact on the validity of the results of the four cancers is the region in which the subjects resided. The availability and the utilization of screening and diagnostic services in rural areas could have affected the incidence rates of cancers identified by the Saskatchewan Cancer Agency. Nevertheless, studies carried out in the US have shown little difference in the cancer incidence and mortality rates of rural and urban populations (Montroe et al., 1992; Howe et al., 1992; Higginbotham et al., 2001).

In addition, both pharmacotherapy and psychotherapy treatment regimens for depression, which require frequent provider contact, could differ according to the place of residence of an individual (urban vs. rural). In a study carried out in the US, it was found that travel barriers might prevent rural patients from making a sufficient number of visits to receive effective antidepressant treatment (Fortney et al., 1999).

Based on the above discussed associations, we would expect a higher proportion of urbanized subjects in the group exposed to antidepressants (relative to those unexposed to antidepressants) and in the case group (relative to the control group). As a result, the odds ratios and the confidence intervals reported for the association between exposure to antidepressants and risk of cancer (at any of the 4 anatomic sites) could have been biased by the confounding effect of geographical area of residence.

6.4 Conclusion and future research

TCAs were categorized into two groups, based on their genotoxicity in Drosophila, as well as in the results of a human epidemiological study. The non-genotoxic TCAs were amitriptyline, maprotiline, nortriptyline, and protriptyline, whereas the genotoxic ones included amoxapine, clomipramine, desipramine, doxepin, imipramine, and trimipramine (Van Schaik et al., 1991; and Van Schaik et al., 1993). Based on the epidemiological study carried out by Sharpe et al. (Sharpe et al., 2002), which found an increased risk of breast cancer associated with the use of genotoxic antidepressants but not with the non-genotoxic ones, we tested the hypothesis that exposure to genotoxic TCAs increases the risk of developing cancer at different sites relative to exposure to non-genotoxic ones.

Although some associations (between TCA exposure and cancer risk) were found to support this hypothesis, others did not support it, or even contradicted it. In general, our study did not find enough evidence for an increased risk of cancer development in association with TCAs and SSRIs drug use. Moreover, we did not find strong evidence to support the hypothesis which states that the genotoxic TCAs are responsible for the carcinogenicity of TCAs.

Because of the complexity of this association, as well as the contradictory results found in this study and in the literature, further research is required to shed more light on the effects of antidepressants on the incidence of cancer. Thus, associations between different antidepressants and different cancer sites should be further explored.

Chapter 7: References

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Figure 1: Multistage process of carcinogenesis

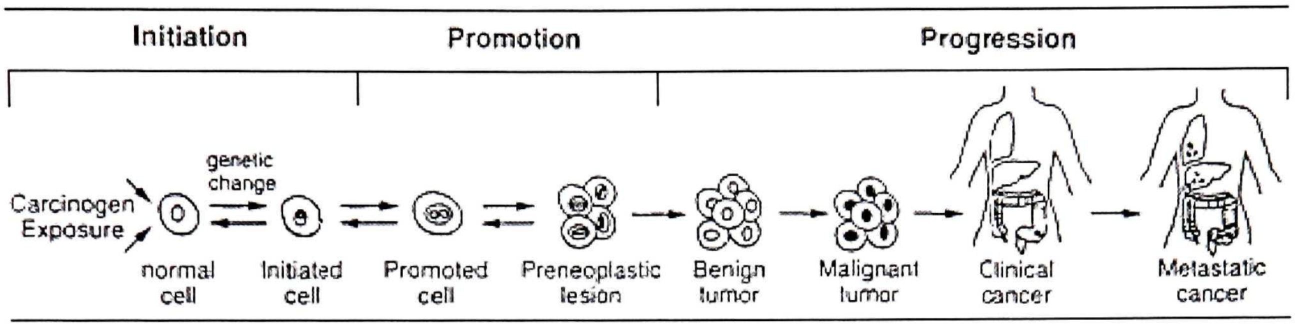


Figure 2: Schematic version of experiments performed on mouse skin which allowed the distinction between initiation and promotion

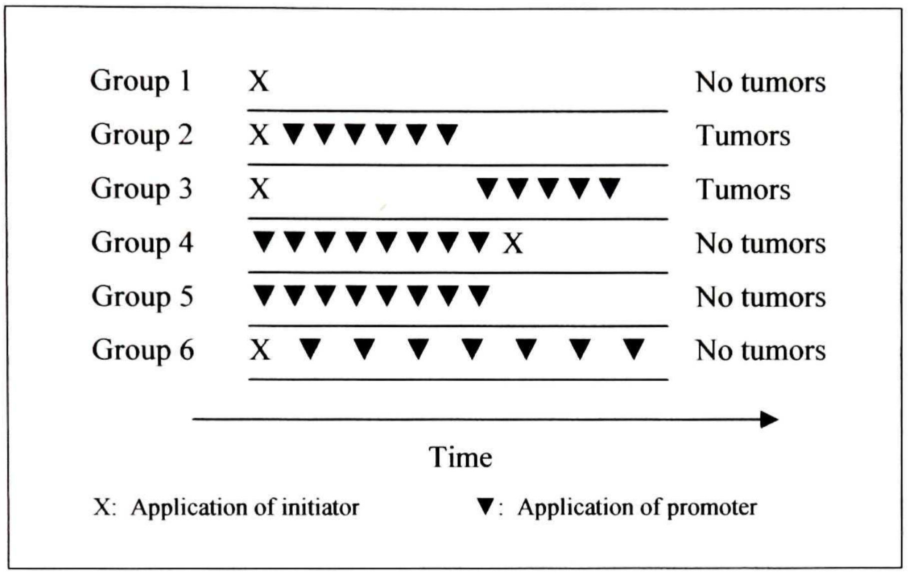
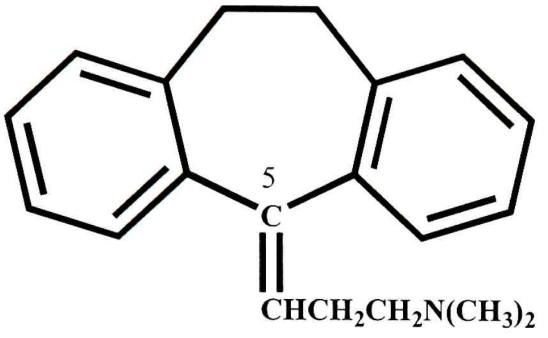
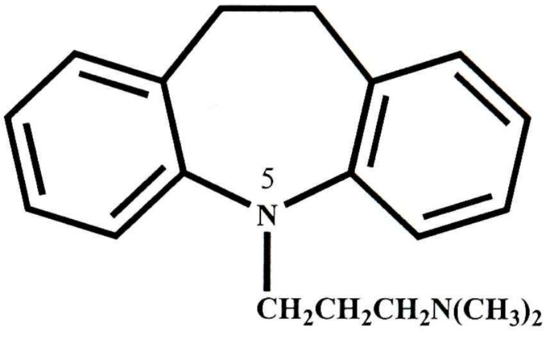


Figure 3: Structural formulas of TCAs amitriptyline and imipramine



Amitriptyline



Imipramine

Figure 4: The dose-response relationships for the TCAs amitriptyline, desipramine, and imipramine in an experiment carried out in Drosophila melanogaster to assess genotoxicity of TCAs (Van Schaik et al., 1991; and Van Schaik et al., 1993)

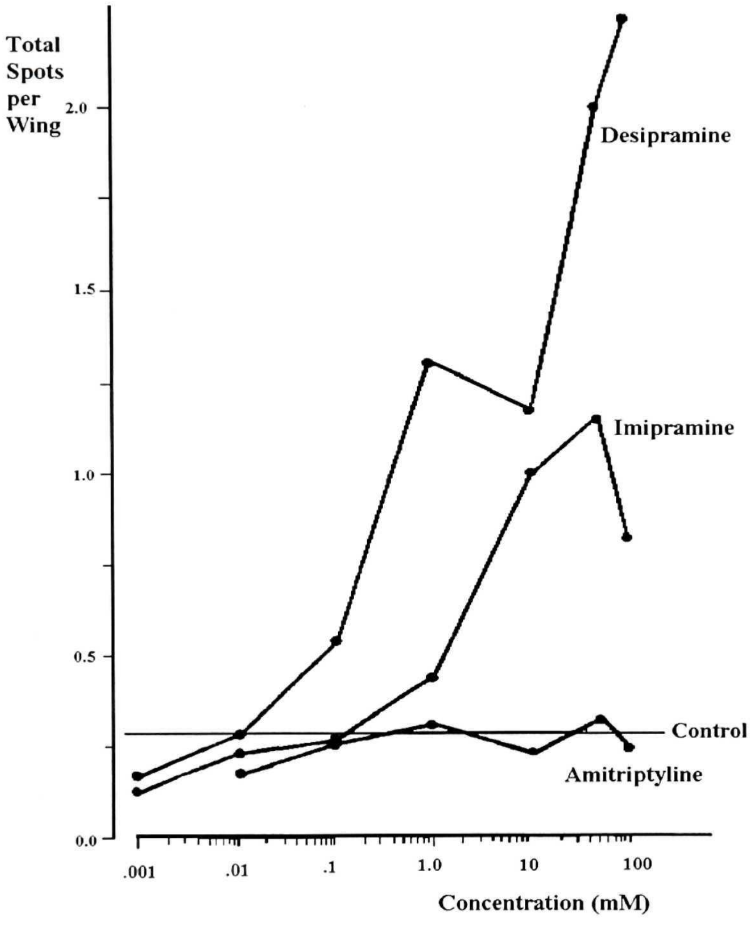


Figure 5: Illustration of how controls were selected for female cancers according to the two other matching variables (age and time of diagnosis)

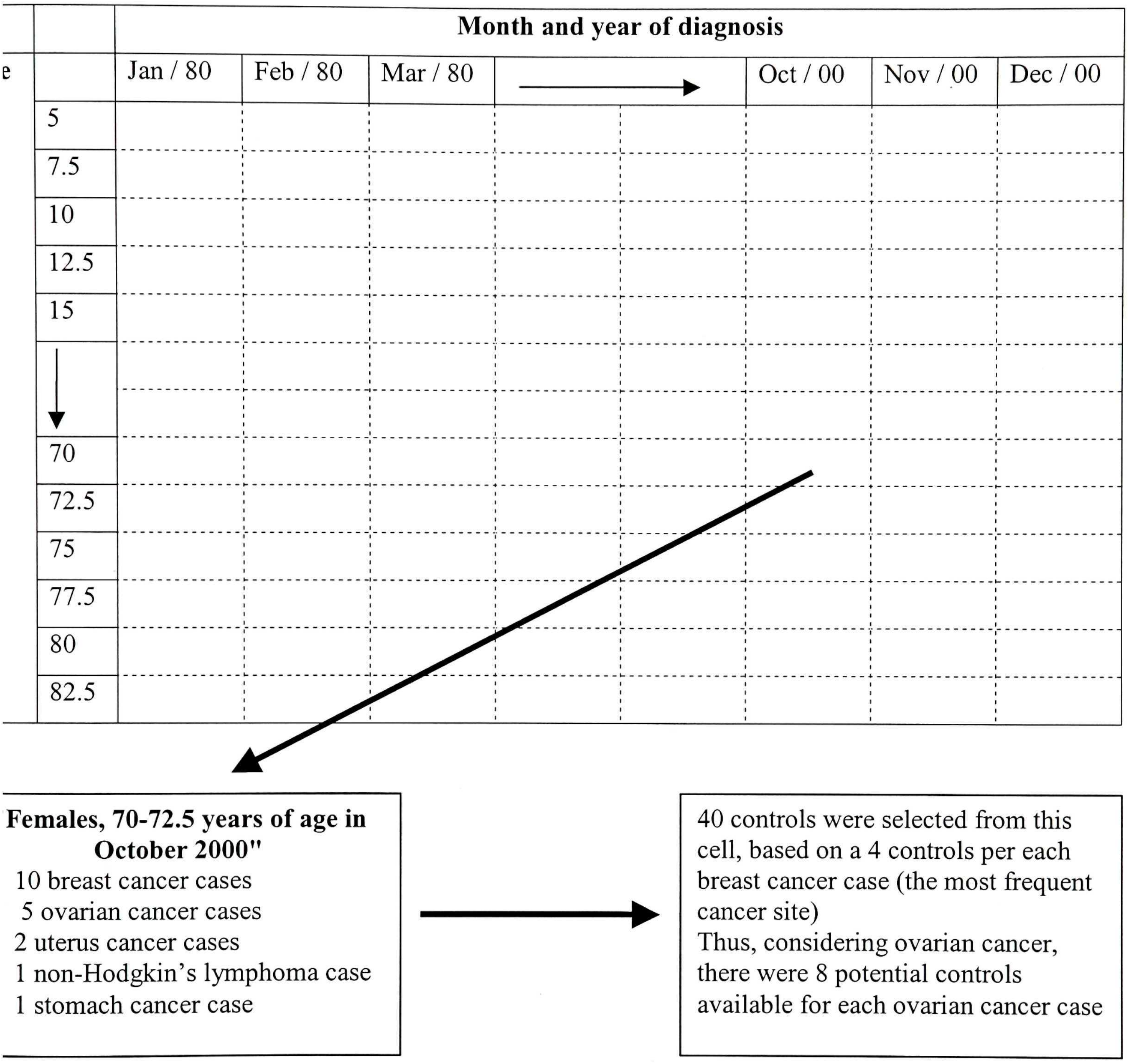
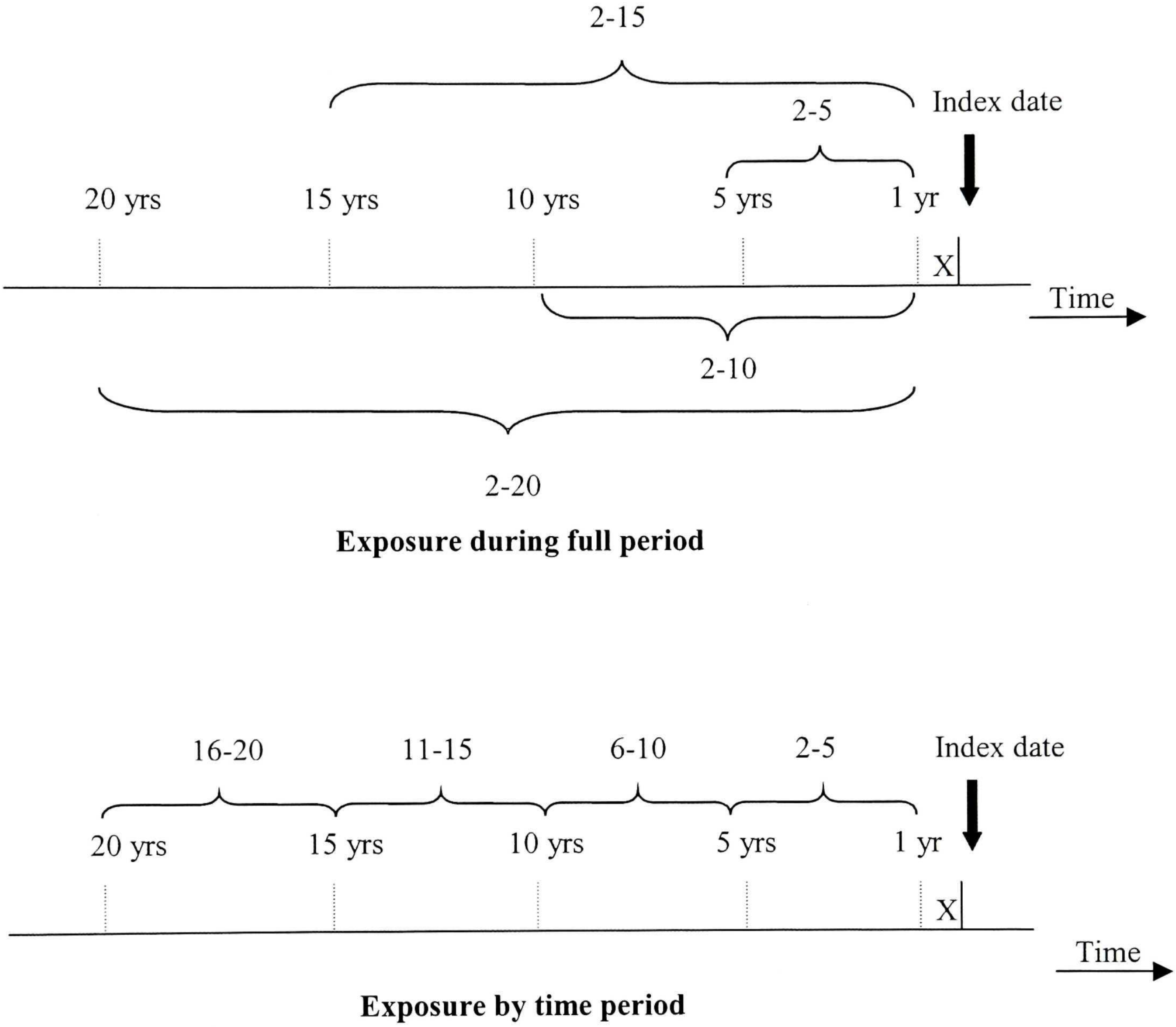


Figure 6: Illustration of how drug history (before the index date) was categorized for the two groups of exposure definitions (during full period and by time period)



X:	Exposure during the year prior to the date of diagnosis was excluded from the analyses
Index date:	Date of diagnosis

Figure 7: Yearly incidence of breast cancer cases in Saskatchewan among people aged between 5 and 82.5 years

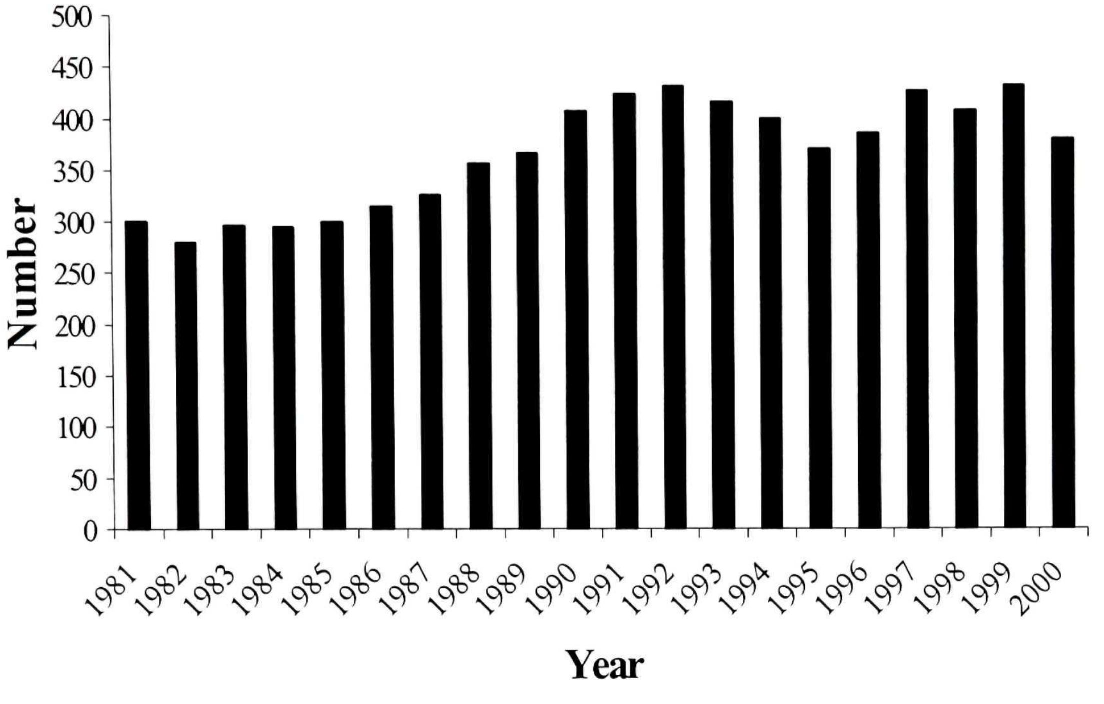


Figure 8: Age distribution of breast cancer cases in Saskatchewan between the year 1981 and 2000

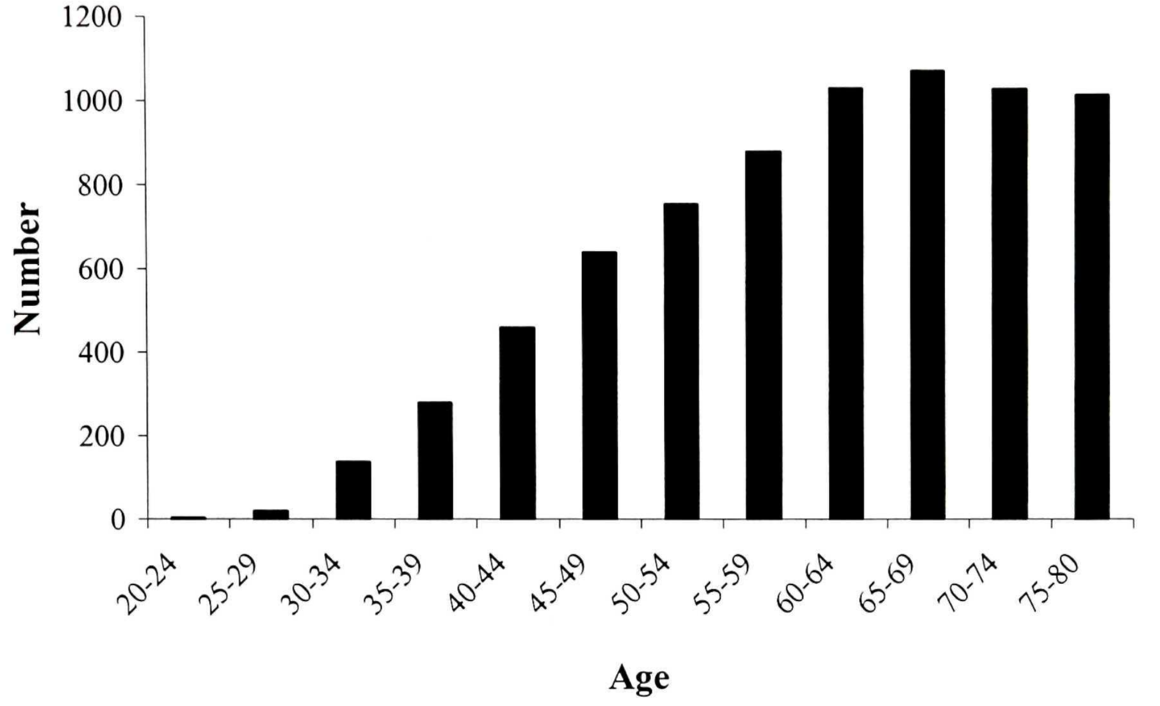


Figure 9: Yearly incidence of prostate cancer cases in Saskatchewan among people aged between 5 and 82.5 years

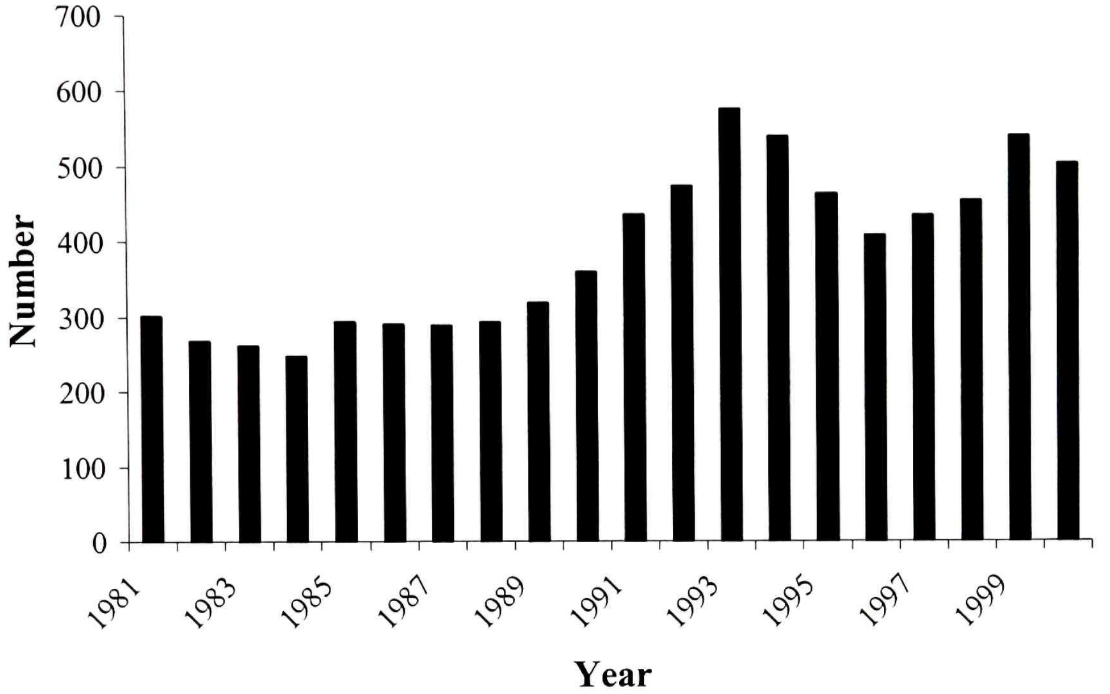


Figure 10: Age distribution of prostate cancer cases in Saskatchewan between the year 1981 and 2000

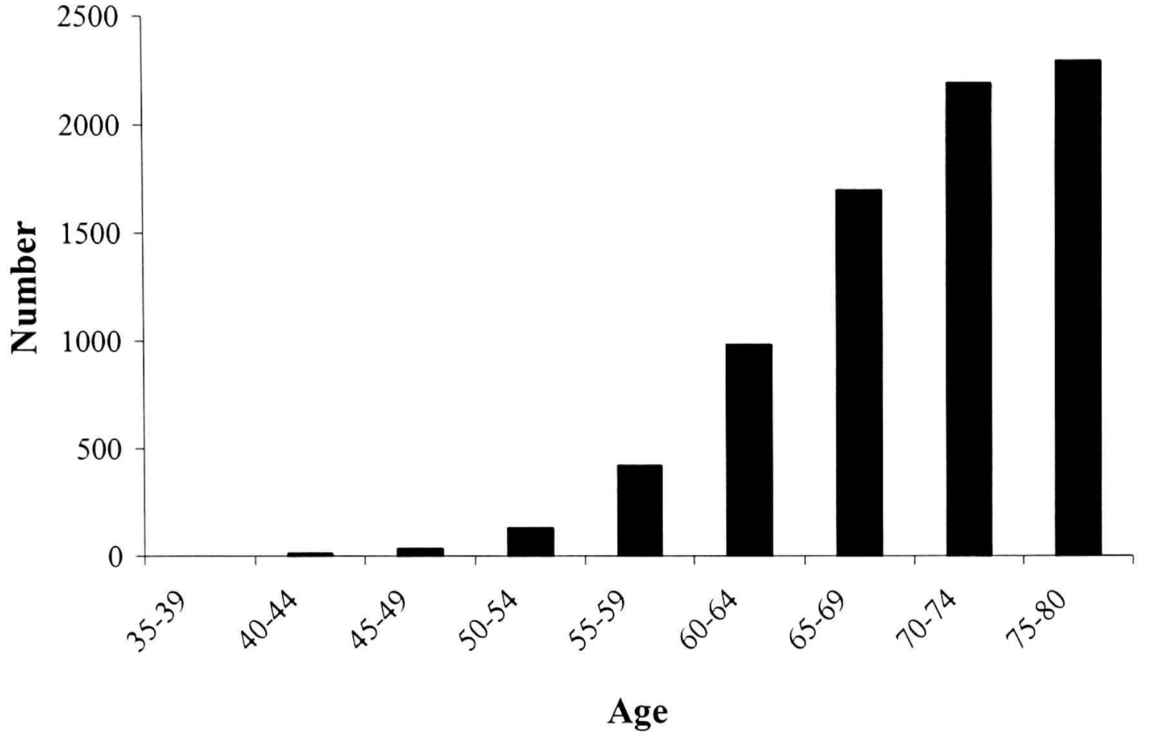


Figure 11: Yearly incidence of ovarian cancer cases in Saskatchewan among people aged between 5 and 82.5 years

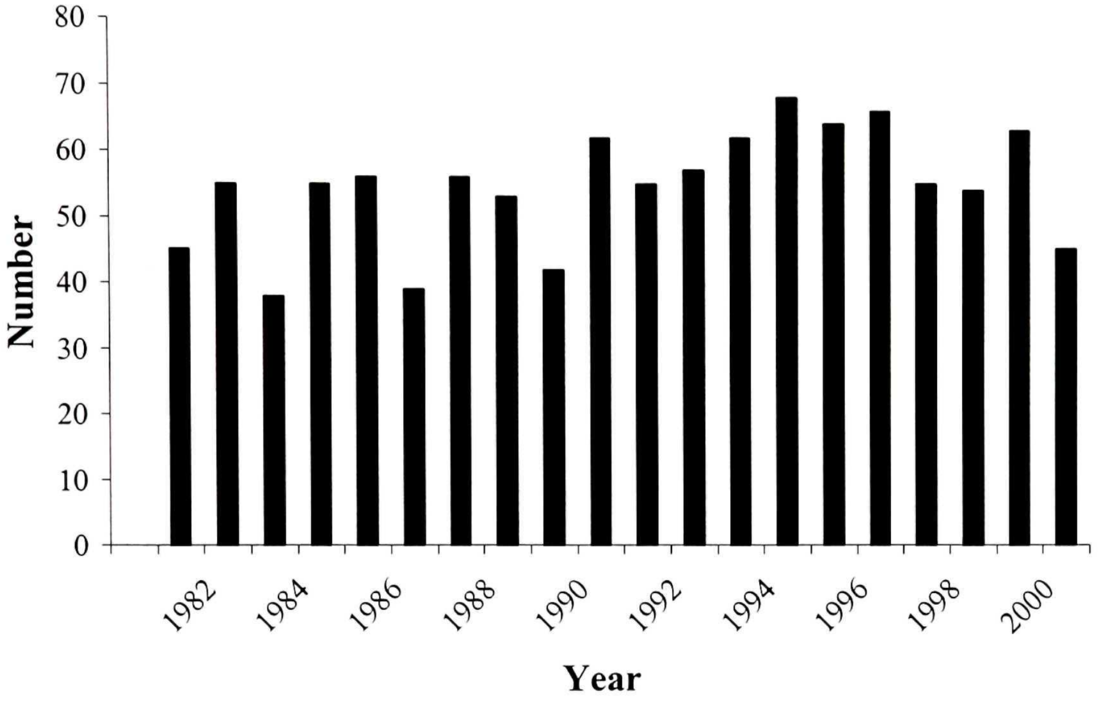


Figure 12: Age distribution of ovarian cancer cases in Saskatchewan between the year 1981 and 2000

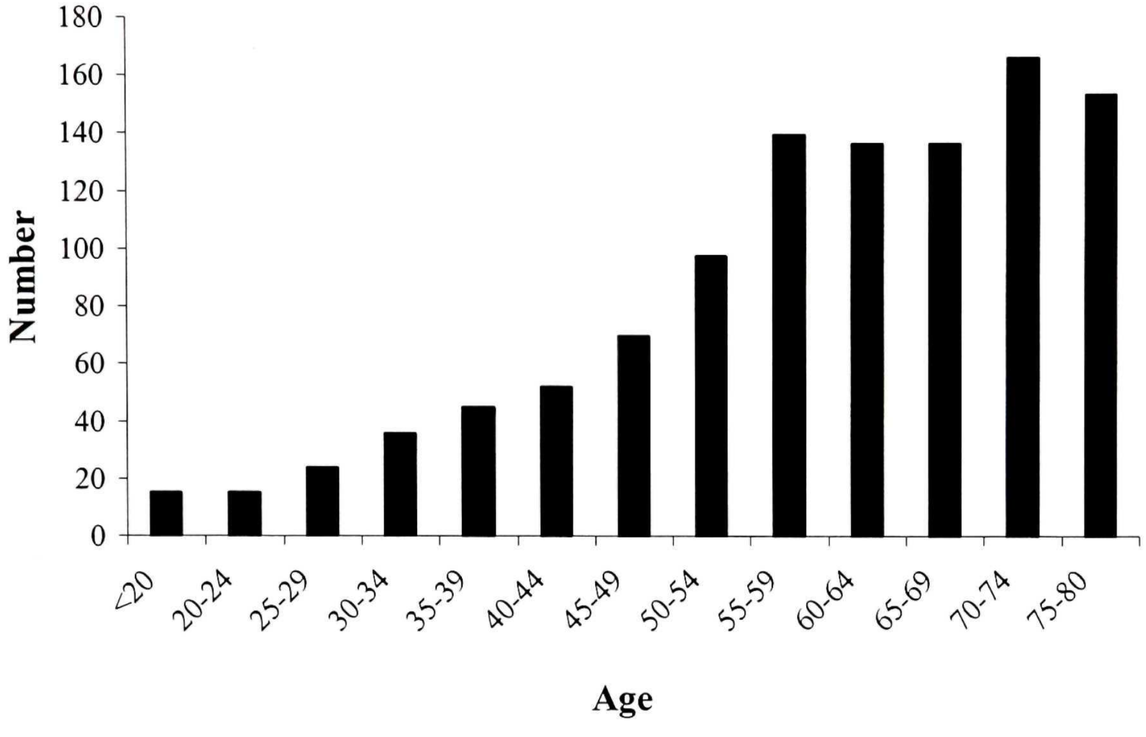


Figure 13: Yearly incidence of non-Hodgkin's lymphoma cases in Saskatchewan among people aged between 5 and 82.5 years

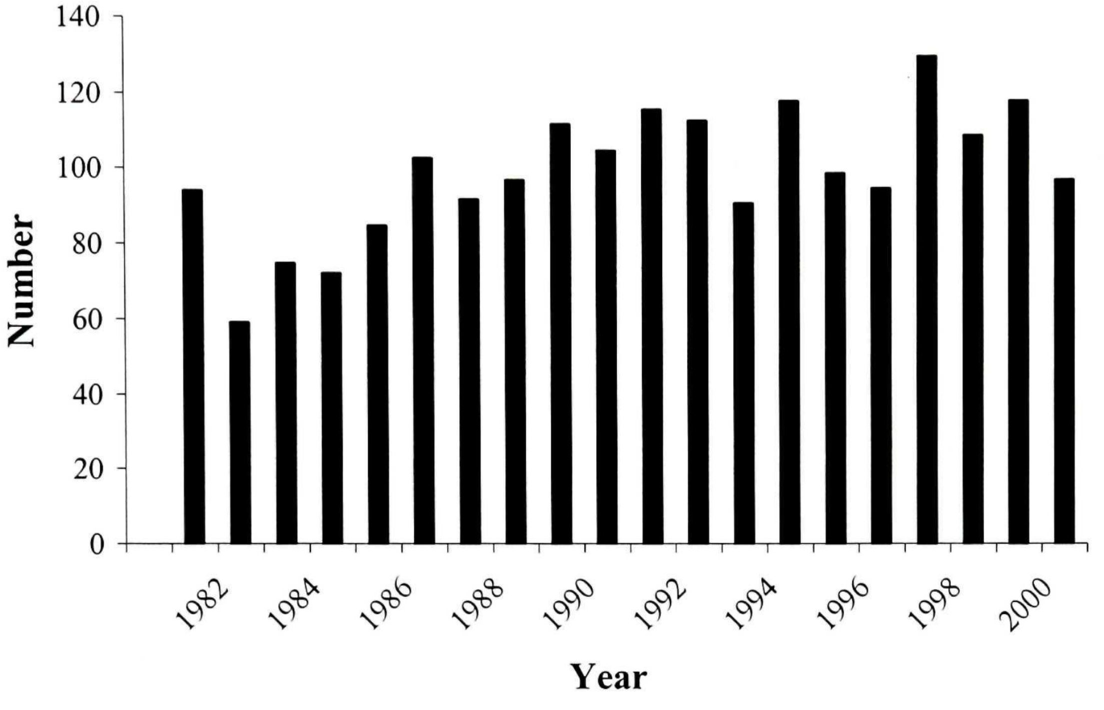


Figure 14: Age distribution of non-Hodgkin's Lymphoma cases in Saskatchewan between the year 1981 and 2000

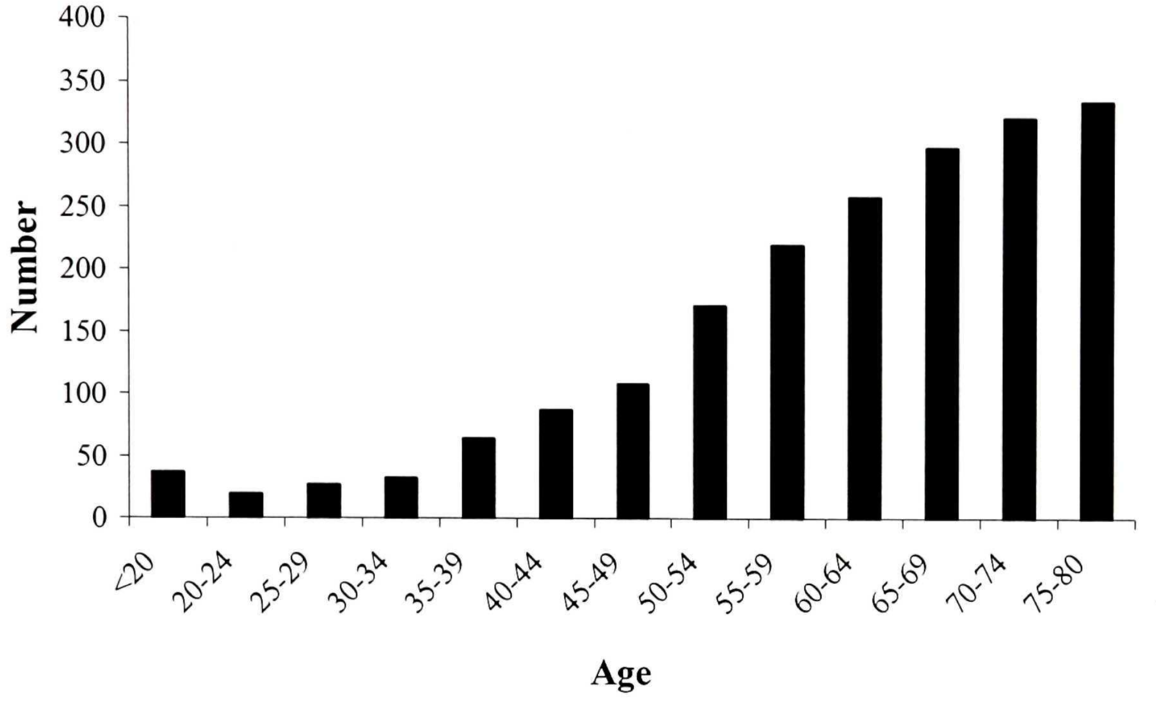


Table 1: Incidence of breast cancer, for those having at least 20 years of history, as a function of two exposure indices of TCA drugs: ever/never and cumulative dosage exposure

TCA exposure				Cases N=1876	Controls N=7362	RR	95% CI
r/Never exposed							
nbined	2-20 years		Unexposed	1343	5227	1.00	Referent
			Any	533	2135	0.97	0.86-1.08
tegorized	2-20 years		Unexposed	1343	5227	1.00	Referent
			Genotoxic	167	638	1.04	0.86-1.26
			Non-Genotoxic	228	830	1.06	0.90-1.26
			Both	138	667	0.78	0.63-0.95
mulative dosage exposure							
mbined	2-20 years		Unexposed	1343	5227	1.00	Referent
			Low	239	977	0.94	0.80-1.10
			High	294	1158	099	0.86-1.14
			P-trend				*0.58*
	6-20 years		Unexposed	1433	5537	1.00	Referent
			Low	203	833	0.93	0.79-1.11
			High	240	992	0.93	0.80-1.09
			P-trend				*0.71*
	11-20 years		Unexposed	1541	5993	1.00	Referent
			Low	156	640	0.94	0.78-1.14
			High	179	729	0.96	0.80-1.14
			P-trend				*0.77*
	16-20 years		Unexposed	1654	6428	1.00	Referent
			Low	117	454	0.98	0.79-1.21
			High	105	480	0.86	0.69-1.08
			P-trend				*0.99*
tegorized	2-20 years	Genotoxic	Unexposed	1343	5227	1.00	Referent
			Low	87	352	0.95	0.74-1.22
			High	80	286	1.20	0.91-1.57
			P-trend				*0.30*
		Non-Genotoxic	Unexposed	1343	5227	1.00	Referent
			Low	135	513	1.03	0.84-1.27
			High	93	317	1.11	0.86-1.43
			P-trend				*0.25*
	6-20 years	Genotoxic	Unexposed	1433	5537	1.00	Referent
			Low	91	350	1.02	0.79-1.30
			High	78	287	1.10	0.84-1.45
			P-trend				*0.19*
		Non-Genotoxic	Unexposed	1433	5537	1.00	Referent
			Low	101	399	0.96	0.76-1.21
			High	74	248	1.12	0.84-1.48
			P-trend				*0.41*
	11-20 years	Genotoxic	Unexposed	1541	5993	1.00	Referent
			Low	83	294	1.08	0.83-1.39
			High	61	245	1.02	0.76-1.38
			P-trend				*0.89*
		Non-Genotoxic	Unexposed	1541	5993	1.00	Referent
			Low	69	289	0.94	0.71-1.24
			High	56	170	1.21	0.88-1.67
			P-trend				*0.56*

16-20 years	**Genotoxic**	**Unexposed**	1654	6428	1.00	Referent
		Low	55	222	0.92	0.67-1.25
		High	44	185	0.96	0.69-1.35
		P-trend				*0.80*
	Non-Genotoxic	**Unexposed**	1654	6428	1.00	Referent
		Low	57	205	1.08	0.80-1.47
		High	28	140	0.78	0.52-1.19
		P-trend				*0.68*

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
All combined: both types of TCAs (genotoxic or non-genotoxic)
Genotoxic: exposure to genotoxic TCAs only
Non-genotoxic: exposure to non-genotoxic TCAs only
Both: exposure to both types of TCAs (genotoxic and non-genotoxic)

Table 2: Incidence of breast cancer, for those having at least 15 years of history, as a function of two exposure indices of TCA drugs: ever/never and cumulative dosage exposure

TCA exposure				Cases N=3883	Controls N=15389	RR	95% CI
er/Never exposed							
l mbined	2-15 years		Unexposed	2920	11722	1.00	Referent
			Any	963	3667	1.05	0.97-1.15
ıtegorized	2-15 years		Unexposed	2920	11722	1.00	Referent
			Genotoxic	320	1203	1.06	0.92-1.21
			Non-Genotoxic	399	1463	1.08	0.96-1.22
			Both	244	1001	1.01	0.87-1.18
ımulative dosage exposure							
l mbined	2-15 years		Unexposed	2920	11722	1.00	Referent
			Low	418	1678	0.98	0.87-1.10
			High	545	1989	1.11	1.00-1.24
			P-trend				*0.10*
	6-15 years		Unexposed	3143	12432	1.00	Referent
			Low	329	1357	0.95	0.84-1.08
			High	411	1600	1.02	0.91-1.15
			P-trend				*0.06*
	11-15 years		Unexposed	3409	13495	1.00	Referent
			Low	201	886	0.91	0.77-1.07
			High	273	1008	1.08	0.94-1.25
			P-trend				*0.03*
ategorized	2-15 years	Genotoxic	Unexposed	2920	11722	1.00	Referent
			Low	153	661	0.91	0.76-1.10
			High	167	542	1.20	1.04-1.51
			P-trend				*0.18*
		Non-Genotoxic	Unexposed	2920	11722	1.00	Referent
			Low	237	868	1.05	0.90-1.23
			High	162	595	1.11	0.92-1.34
			P-trend				*0.81*
	6-15 years	Genotoxic	Unexposed	3143	12432	1.00	Referent
			Low	142	614	0.93	0.77-1.13
			High	144	516	1.10	0.91-1.34
			P-trend				*0.06*
		Non-Genotoxic	Unexposed	3143	12432	1.00	Referent
			Low	166	648	0.99	0.82-1.18
			High	113	448	1.03	0.82-1.27
			P-trend				*0.62*
	11-15 years	Genotoxic	Unexposed	3409	13495	1.00	Referent
			Low	102	442	0.92	0.74-1.15
			High	106	385	1.14	0.91-1.42
			P-trend				*0.01*
		Non-Genotoxic	Unexposed	3409	13495	1.00	Referent
			Low	88	394	0.90	0.71-1.14
			High	80	298	1.04	0.81-1.35
			P-trend				*0.18*

Table 3: Incidence of breast cancer, for those having at least 10 years of history, as a function of two exposure indices of TCA drugs: ever/never and cumulative dosage exposure

TCA exposure				Cases N=5689	Controls N=22775	RR	95% CI
er/Never exposed							
l mbined	2-10 years		**Unexposed**	4554	18545	1.00	Referent
			Any	1135	4230	1.09	1.01-1.17
ıtegorized	2-10 years		**Unexposed**	4554	18545	1.00	Referent
			Genotoxic	406	1489	1.12	1.00-1.26
			Non-Genotoxic	493	1818	1.09	0.98-1.22
			Both	236	923	1.05	0.90-1.22
ımulative dosage exposure							
l mbined	2-10 years		**Unexposed**	4554	18545	1.00	Referent
			Low	503	1929	1.04	0.94-1.16
			High	632	2301	1.13	1.02-1.24
			P-trend				*0.07*
	6-10 years		**Unexposed**	4925	19817	1.00	Referent
			Low	328	1335	0.98	0.86-1.11
			High	436	1623	1.07	0.96-1.20
			P-trend				*0.09*
ategorized	2-10 years	Genotoxic	**Unexposed**	4554	18545	1.00	Referent
			Low	190	755	1.03	0.87-1.22
			High	216	734	1.23	1.04-1.44
			P-trend				*0.04*
		Non-Genotoxic	**Unexposed**	4554	18545	1.00	Referent
			Low	277	1029	1.07	0.93-1.23
			High	216	789	1.12	0.96-1.32
			P-trend				*0.88*
	6-10 years	Genotoxic	**Unexposed**	4925	19817	1.00	Referent
			Low	142	591	0.95	0.79-1.15
			High	163	628	1.04	0.87-1.24
			P-trend				*0.05*
		Non-Genotoxic	**Unexposed**	4925	19817	1.00	Referent
			Low	167	668	0.99	0.83-1.18
			High	156	562	1.12	0.93-1.35
			P-trend				*0.78*

Table 4: Incidence of breast cancer, for those having at least 5 years of history, as a function of two exposure indices of TCA drugs: ever/never and cumulative dosage exposure

TCA exposure			Cases N=7330	Controls N=29320	RR	95% CI
er/Never exposed						
l mbined	2-5 years	Unexposed	6353	25858	1.00	Referent
		Any	977	3462	1.15	1.07-1.24
itegorized	2-5 years	Unexposed	6353	25858	1.00	Referent
		Genotoxic	386	1313	1.20	1.06-1.35
		Non-Genotoxic	468	1651	1.15	1.03-1.28
		Both	123	498	1.05	0.86-1.29
imulative dosage exposure						
l mbined	2-5 years	Unexposed	6353	25858	1.00	Referent
		Low	418	1532	1.10	0.98-1.23
		High	559	1930	1.19	1.08-1.31
		P-trend				*0.06*
ategorized	2-5 years Genotoxic	Unexposed	6353	25858	1.00	Referent
		Low	158	587	1.08	0.90-1.30
		High	228	726	1.29	1.10-1.50
		P-trend				*0.02*
	2-5 years Non-Genotoxic	Unexposed	6353	25858	1.00	Referent
		Low	240	874	1.10	0.95-1.28
		High	228	777	1.19	1.02-1.38
		P-trend				*0.22*

Table 5: Incidence of breast cancer as a function of average daily dose of TCA exposure by time period before diagnosis

	TCA exposure						
riod before ignosis	Average daily dose	Cases N=7330	Controls N=29320	Crude		Adjusted*	
				RR	95% CI	RR	95% CI
5 years	**Unexposed**	6353	25858	1.00	Referent	1.00	Referent
	Low	414	1519	1.11	0.99-1.24	1.12	1.00-1.26
	Medium	263	902	1.19	1.03-1.37	1.20	1.04-1.39
	High	300	1041	1.18	1.03-1.34	1.19	1.01-1.40
	P-trend				*0.06*		*0.21*
	Other	-	-				
10 years	**Unexposed**	4925	19819	1.00	Referent	1.00	Referent
	Low	359	1480	0.98	0.87-1.10	0.96	0.85-1.08
	Medium	193	718	1.08	0.92-1.27	1.01	0.85-1.20
	High	212	760	1.12	0.96-1.31	0.98	0.79-1.21
	P-trend				*0.08*		*0.66*
	Other	1641	6545				
-15 years	**Unexposed**	3409	13495	1.00	Referent	1.00	Referent
	Low	224	975	0.91	0.78-1.06	0.90	0.78-1.05
	Medium	124	475	1.04	0.85-1.27	1.02	0.83-1.26
	High	126	444	1.13	0.92-1.38	1.10	0.85-1.42
	P-trend				*0.04*		*0.05*
	Other	3447	13931				
-20 years	**Unexposed**	1654	6428	1.00	Referent	1.00	Referent
	Low	129	497	1.01	0.83-1.24	1.00	0.81-1.22
	Medium	45	240	0.73	0.53-1.01	0.70	0.51-0.98
	High	48	197	0.95	0.69-1.31	0.82	0.58-1.17
	P-trend				*0.95*		*0.53*
	Other	5454	21958				

P-trend was based on the continuous data rather than the categorical data

RR: rate (incidence) ratio

*: Adjustment for the exposure in the other periods was carried out for each period

Other: subjects with incomplete information during the specified period

Table 6: Incidence of <u>breast</u> cancer as a function of <u>average daily dose</u> of genotoxic and non-genotoxic <u>TCA</u> exposure by time period before diagnosis

od re nosis	Average daily dose	Non-Genotoxic TCAs				Genotoxic TCAs			
		Cases N=7330	Controls N=29320	Adjusted RR*	Adjusted 95% CI*	Cases N=7330	Controls N=29320	Adjusted RR*	Adjusted 95% CI*
	Unexposed	6739	27171	1.00	Referent	6821	27509	1.00	Referent
	Low	297	1079	1.11	0.97-1.27	207	784	1.06	0.91-1.24
ears	**Medium**	146	540	1.06	0.87-1.28	142	495	1.16	0.95-1.41
	High	148	530	1.08	0.87-1.35	160	532	1.19	0.96-1.47
	P-trend				*0.85*				*0.26*
	Other	-	-			-	-		
	Unexposed	5230	21036	1.00	Referent	5248	21047	1.00	Referent
	Low	249	995	1.00	0.86-1.16	210	876	0.94	0.80-1.10
	Medium	110	383	1.12	0.89-1.41	111	441	0.93	0.75-1.16
s	**High**	100	361	1.08	0.81-1.43	120	411	0.97	0.74-1.26
	P-trend				*0.55*				*0.41*
	Other	1641	6545			1641	6545		
	Unexposed	3617	14322	1.00	Referent	3577	14187	1.00	Referent
	Low	144	616	0.91	0.75-1.10	148	654	0.91	0.75-1.09
5	**Medium**	70	244	1.07	0.81-1.43	81	309	1.04	0.80-1.35
s	**High**	52	207	0.91	0.63-1.30	77	239	1.27	0.92-1.74
	P-trend				*0.13*				*0.002*
	Other	3447	13931			3447	13931		
	Unexposed	1753	6835	1.00	Referent	1739	6773	1.00	Referent
	Low	75	319	0.93	0.72-1.21	75	312	0.93	0.72-1.21
0	**Medium**	27	128	0.85	0.55-1.31	31	162	0.73	0.49-1.09
s	**High**	21	80	0.98	0.59-1.65	31	115	0.90	0.58-1.39
	P-trend				*0.45*				*0.85*
	Other	5454	21958			5454	21958		

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period
Non-genotoxic TCAs: regardless of any exposure to genotoxic TCAs
Genotoxic TCAs: regardless of any exposure to non-genotoxic TCAs

Table 7: Incidence of <u>breast</u> cancer as a function of <u>average daily dose</u> of <u>exclusive</u> genotoxic and non-genotoxic <u>TCA</u> exposure by time period before diagnosis

eriod before diagnosis		Average daily dose	Cases N=7330	Controls N=29320	Crude		Adjusted*	
					RR	95% CI	RR	95% CI
5 years		Unexposed	6353	25858	1.00	Referent	1.00	Referent
	Exclusive non-genotoxic TCA exposure	Low	239	863	1.13	0.98-1.31	1.14	0.98-1.32
		Medium	112	382	1.20	0.97-1.48	1.20	0.96-1.49
		High	117	406	1.18	0.96-1.45	1.21	0.95-1.53
		P-trend				*0.18*		*0.21*
	Exclusive genotoxic TCA exposure	Low	156	586	1.09	0.91-1.30	1.10	0.92-1.31
		Medium	107	335	1.30	1.05-1.62	1.34	1.07-1.68
		High	123	392	1.28	1.04-1.57	1.32	1.04-1.67
		P-trend				*0.02*		*0.03*
		Both	123	498	1.01	0.82-1.23	1.03	0.83-1.27
		Other	-	-				
10 ears		Unexposed	4925	19817	1.00	Referent	1.00	Referent
	Exclusive non-genotoxic TCA exposure	Low	182	728	1.01	0.85-1.19	0.99	0.84-1.17
		Medium	72	244	1.19	0.91-1.55	1.12	0.85-1.47
		High	69	258	1.08	0.82-1.41	0.99	0.71-1.38
		P-trend				*0.97*		*0.54*
	Exclusive genotoxic TCA exposure	Low	153	655	0.94	0.79-1.12	0.92	0.76-1.10
		Medium	73	283	1.04	0.80-1.35	0.96	0.73-1.25
		High	79	281	1.13	0.88-1.46	0.95	0.70-1.29
		P-trend				*0.04*		*0.23*
		Both	136	509	1.08	0.89-1.30	0.99	0.80-1.23
		Other	1641	6545				
-15 ears		Unexposed	3409	13495	1.00	Referent	1.00	Referent
	Exclusive non-genotoxic TCA exposure	Low	98	428	0.91	0.73-1.13	0.89	0.71-1.12
		Medium	39	136	1.14	0.79-1.63	1.12	0.78-1.63
		High	31	128	0.96	0.65-1.43	0.95	0.61-1.48
		P-trend				*0.30*		*0.23*
	Exclusive genotoxic TCA exposure	Low	112	479	0.93	0.75-1.14	0.92	0.75-1.14
		Medium	53	204	1.03	0.76-1.40	1.01	0.74-1.39
		High	43	144	1.19	0.84-1.67	1.17	0.79-1.74
		P-trend				*0.02*		*0.03*
		Both	98	375	1.04	0.83-1.30	1.02	0.80-1.30
		Other	3447	13931				
-20 ears		Unexposed	1654	6428	1.00	Referent	1.00	Referent
	Exclusive non-genotoxic TCA exposure	Low	60	223	1.05	0.78-1.40	1.04	0.78-1.39
		Medium	14	73	0.75	0.42-1.34	0.71	0.40-1.28
		High	11	49	0.87	0.45-1.68	0.81	0.41-1.59
		P-trend				*0.65*		*0.54*
	Exclusive genotoxic TCA exposure	Low	62	241	1.00	0.75-1.33	0.99	0.74-1.31
		Medium	21	92	0.89	0.55-1.44	0.86	0.53-1.38
		High	16	74	0.85	0.49-1.45	0.74	0.42-1.30
		P-trend				*0.78*		*0.49*
		Both	38	182	0.81	0.57-1.16	0.74	0.51-1.07
		Other	5454	21958				

*: Adjustment for the exposure in the other periods was carried out for each period
Unexposed: no exposure to either type of TCAs (genotoxic and non-genotoxic)
Both: exposure to both types of TCAs (genotoxic and non-genotoxic)

Table 8: Incidence of breast cancer as a function of duration of TCA exposure by time period before diagnosis

riod before gnosis	TCA exposure Duration	Cases N=7330	Controls N=29320	Crude RR	Crude 95% CI	Adjusted* RR	Adjusted* 95% CI
5 years	**Unexposed**	6354	25862	1.00	Referent	1.00	Referent
	Short	319	1245	1.04	0.92-1.19	1.06	0.93-1.20
	Medium	335	1141	1.20	1.06-1.36	1.22	1.07-1.39
	Long	322	1072	1.23	1.08-1.39	1.32	1.12-1.54
	P-trend				*0.0007*		*0.0004*
	Other	-	-				
10 years	**Unexposed**	4930	19830	1.00	Referent	1.00	Referent
	Short	373	1525	0.98	0.88-1.11	0.96	0.85-1.08
	Medium	214	750	1.15	0.98-1.34	1.04	0.88-1.23
	Long	176	680	1.04	0.88-1.23	0.83	0.66-1.04
	P-trend				*0.27*		*0.21*
	Other	1637	6535				
-15 years	**Unexposed**	3420	13540	1.00	Referent	1.00	Referent
	Short	240	1035	0.92	0.79-1.06	0.91	0.79-1.06
	Medium	123	464	1.05	0.86-1.29	1.04	0.84-1.28
	Long	110	398	1.10	0.89-1.36	1.08	0.82-1.43
	P-trend				*0.36*		*0.53*
	Other	3437	13883				
-20 years	**Unexposed**	1672	6502	1.00	Referent	1.00	Referent
	Short	138	545	0.99	0.81-1.20	0.97	0.80-1.19
	Medium	44	241	0.72	0.52-0.99	0.69	0.49-0.96
	Long	45	162	1.08	0.78-1.52	0.97	0.67-1.41
	P-trend				*0.57*		*0.25*
	Other	5431	21870				

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period

Table 9: Incidence of <u>breast</u> cancer as a function of <u>duration</u> of genotoxic and non-genotoxic <u>TCA</u> exposure by time period before diagnosis

d e iosis	Duration	Non-Genotoxic TCAs				Genotoxic TCAs			
		Cases N=7330	Controls N=29320	Adjusted RR*	Adjusted 95% CI*	Cases N=7330	Controls N=29320	Adjusted RR*	Adjusted 95% CI*
ears	**Unexposed**	6739	27173	1.00	Referent	6822	27511	1.00	Referent
	Short	220	899	0.98	0.84-1.14	177	691	1.02	0.86-1.21
	Medium	215	698	1.21	1.03-1.43	180	624	1.16	0.97-1.38
	Long	156	550	1.18	0.95-1.46	151	494	1.30	1.04-1.63
	P-trend				*0.03*				*0.01*
	Other	-	-			-	-		
s	**Unexposed**	5234	21046	1.00	Referent	5252	21064	1.00	Referent
	Short	263	1017	1.02	0.89-1.18	236	964	0.94	0.81-1.10
	Medium	114	407	1.05	0.84-1.32	121	421	1.01	0.81-1.26
	Long	82	315	0.93	0.68-1.26	84	336	0.75	0.54-1.02
	P-trend				*0.99*				*0.07*
	Other	1637	6535			1637	6535		
5 s	**Unexposed**	3632	14371	1.00	Referent	3585	14234	1.00	Referent
	Short	146	647	0.87	0.72-1.06	165	735	0.90	0.75-1.08
	Medium	69	231	1.11	0.84-1.49	83	275	1.23	0.94-1.60
	Long	46	188	0.93	0.63-1.38	60	193	1.34	0.94-1.92
	P-trend				*0.70*				*0.10*
	Other	3437	13883			3437	13883		
0 s	**Unexposed**	1772	6917	1.00	Referent	1760	6851	1.00	Referent
	Short	81	353	0.91	0.71-1.17	86	356	0.92	0.72-1.18
	Medium	30	110	1.11	0.72-1.69	28	158	0.65	0.42-0.98
	Long	16	70	0.88	0.49-1.59	25	85	0.95	0.58-1.55
	P-trend				*0.68*				*0.20*
	Other	5431	21870			5431	21870		

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period
Non-genotoxic TCAs: regardless of any exposure to genotoxic TCAs
Genotoxic TCAs: regardless of any exposure to non-genotoxic TCAs

Table 10: Incidence of breast cancer as a function of duration of exclusive genotoxic and non-genotoxic TCA exposure by time period before diagnosis

iod before diagnosis		Duration	Cases N=7330	Controls N=29320	Crude RR	Crude 95% CI	Adjusted* RR	Adjusted* 95% CI
years		**Unexposed**	6354	25862	1.00	Referent	1.00	Referent
	Exclusive non-genotoxic TCA exposure	**Short**	180	715	1.03	0.87-1.21	1.03	0.87-1.22
		Medium	154	487	1.29	1.07-1.55	1.30	1.08-1.56
		Long	134	447	1.23	1.01-1.49	1.27	1.01-1.60
		P-trend				*0.008*		*0.008*
	Exclusive genotoxic TCA exposure	**Short**	135	517	1.06	0.88-1.29	1.07	0.89-1.30
		Medium	124	405	1.25	1.02-1.53	1.29	1.05-1.59
		Long	126	389	1.32	1.08-1.62	1.44	1.14-1.83
		P-trend				*0.003*		*0.001*
		Both	123	498	1.01	0.82-1.23	1.03	0.84-1.27
		Other	-	-				
0 ars		**Unexposed**	4930	19830	1.00	Referent	1.00	Referent
	Exclusive non-genotoxic TCA exposure	**Short**	181	731	1.00	0.84-1.17	0.98	0.83-1.16
		Medium	74	256	1.16	0.90-1.51	1.08	0.83-1.42
		Long	67	247	1.09	0.83-1.43	0.99	0.71-1.38
		P-trend				*0.27*		*0.75*
	Exclusive genotoxic TCA exposure	**Short**	167	707	0.95	0.80-1.13	0.92	0.77-1.09
		Medium	77	266	1.17	0.90-1.51	1.05	0.80-1.37
		Long	60	243	0.99	0.75-1.32	0.76	0.54-1.09
		P-trend				*0.75*		*0.19*
		Both	134	505	1.09	0.90-1.32	0.99	0.80-1.22
		Other	1637	6535				
-15 ars		**Unexposed**	3420	13540	1.00	Referent	1.00	Referent
	Exclusive non-genotoxic TCA exposure	**Short**	102	444	0.91	0.73-1.13	0.90	0.72-1.12
		Medium	33	120	1.09	0.74-1.61	1.04	0.71-1.56
		Long	30	130	0.91	0.61-1.36	0.82	0.51-1.30
		P-trend				*0.60*		*0.31*
	Exclusive genotoxic TCA exposure	**Short**	124	528	0.93	0.76-1.14	0.93	0.76-1.13
		Medium	51	171	1.19	0.86-1.63	1.17	0.85-1.63
		Long	37	132	1.12	0.77-1.61	1.14	0.74-1.75
		P-trend				*0.46*		*0.48*
		Both	96	372	1.02	0.81-1.28	1.00	0.78-1.28
		Other	3437	13883				
-20 ars		**Unexposed**	1672	6502	1.00	Referent	1.00	Referent
	Exclusive non-genotoxic TCA exposure	**Short**	63	245	1.00	0.76-1.33	1.00	0.75-1.32
		Medium	14	61	0.90	0.51-1.62	0.90	0.50-1.62
		Long	11	43	1.00	0.51-1.94	1.01	0.50-2.04
		P-trend				*0.79*		*0.81*
	Exclusive genotoxic TCA exposure	**Short**	70	262	1.04	0.79-1.36	1.03	0.78-1.35
		Medium	15	101	0.58	0.34-1.00	0.56	0.32-0.96
		Long	15	52	1.13	0.64-2.01	0.90	0.54-1.81
		P-trend				*0.52*		*0.99*
		Both	39	184	0.83	0.58-1.17	0.78	0.54-1.12
		Other	5431	21870				

*: Adjustment for the exposure in the other periods was carried out for each period
Unexposed: no exposure to either type of TCAs (genotoxic and non-genotoxic)
Both: exposure to both types of TCAs (genotoxic and non-genotoxic)

Table 11: Incidence of breast cancer, for those having at least 10 years of history, as a function of two exposure indices of SSRI drugs: ever/never and cumulative dosage exposure

SSRI exposure			Cases N=4682	Controls N=18728	RR	95% CI
:r/Never exposed						
	2-10 years	Unexposed	4468	17937	1.00	Referent
		Any	214	791	1.09	0.93-1.27
mulative dosage exposure						
	2-10 years	Unexposed	4468	17937	1.00	Referent
		Low	121	431	1.14	0.93-1.40
		High	93	360	1.02	0.81-1.29
		P-trend				*0.15*
	6-10 years	Unexposed	4619	18462	1.00	Referent
		Low	33	171	0.77	0.53-1.13
		High	30	95	1.27	0.84-1.92
		P-trend				*0.94*

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
Unexposed: no exposure to any SSRI
Any: exposure to any SSRI

Table 12: Incidence of breast cancer, for those having at least 5 years of history, as a function of two exposure indices of SSRI drugs: ever/never and cumulative dosage exposure

SSRI exposure			Cases N=4682	Controls N=18728	RR	95% CI
er/Never exposed						
	2-5 years	Unexposed	4497	18066	1.00	Referent
		Any	185	662	1.13	0.95-1.33
mulative dosage exposure						
	2-5 years	Unexposed	4497	18066	1.00	Referent
		Low	106	350	1.23	0.99-1.54
		High	79	312	1.01	0.78-1.29
		P-trend				*0.10*

Table 13: Incidence of breast cancer as a function of average daily dose of SSRI exposure by time period before diagnosis

	SSRI exposure			Crude		Adjusted*	
riod before gnosis	Average daily dose	Cases N=4682	Controls N=18728	RR	95% CI	RR	95% CI
5 years	**Unexposed**	4497	18066	1.00	Referent	1.00	Referent
	Low	106	346	1.23	0.99-1.54	1.26	1.01-1.57
	Medium	50	222	0.91	0.67-1.24	0.91	0.67-1.26
	High	29	94	1.24	0.82-1.89	1.24	0.78-1.98
	P-trend				*0.10*		*0.13*
	Other	-	-				
10 years	**Unexposed**	4619	18462	1.00	Referent	1.00	Referent
	Low	38	185	0.82	0.58-1.17	0.78	0.55-1.12
	Medium	22	70	1.26	0.78-2.04	1.17	0.70-1.98
	High	3	11	1.09	0.30-3.89	0.95	0.25-3.59
	P-trend				*0.94*		*0.77*
	Other	-	-				

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period

Table 14: Incidence of <u>breast</u> cancer as a function of <u>duration</u> of <u>SSRI</u> exposure by time period before diagnosis

	SSRI exposure						
iod before gnosis	**Duration**	**Cases N=4682**	**Controls N=18728**	**Crude**		**Adjusted***	
				RR	**95% CI**	**RR**	**95% CI**
years	**Unexposed**	4497	18067	1.00	Referent	1.00	Referent
	Short	69	231	1.20	0.92-1.58	1.22	0.93-1.60
	Medium	76	293	1.05	0.81-1.35	1.06	0.82-1.38
	Long	40	137	1.18	0.83-1.69	1.22	0.83-1.82
	P-trend				*0.14*		*0.10*
	Other	-	-				
10 years	**Unexposed**	4619	18460	1.00	Referent	1.00	Referent
	Short	32	156	0.82	0.56-1.20	0.78	0.53-1.15
	Medium	26	93	1.11	0.72-1.73	1.01	0.64-1.61
	Long	5	19	1.05	0.39-2.81	0.90	0.32-2.52
	P-trend				*0.50*		*0.80*
	Other	-	-				

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period

Table 15: Incidence of prostate cancer as a function of average daily dose of genotoxic and non-genotoxic TCA exposure by time period before diagnosis

riod fore agnosis	Average daily dose	Non-Genotoxic TCAs				Genotoxic TCAs			
		Cases N=7767	Controls N=31068	Adjusted RR*	Adjusted 95% CI*	Cases N=7767	Controls N=31068	Adjusted RR*	Adjusted 95% CI*
5 years	**Unexposed**	7454	30070	1.00	Referent	7489	30173	1.00	Referent
	Low	177	545	1.25	1.05-1.49	134	424	1.19	0.98-1.46
	Medium	83	248	1.27	0.98-1.64	77	227	1.33	1.02-1.74
	High	53	205	1.04	0.74-1.48	67	244	1.23	0.90-1.67
	P-trend				*0.68*				*0.50*
	Other	-	-			-	-		
10 ars	**Unexposed**	6058	24272	1.00	Referent	6054	24261	1.00	Referent
	Low	150	511	1.07	0.89-1.30	148	426	1.28	1.06-1.56
	Medium	60	195	1.09	0.81-1.49	63	244	0.89	0.66-1.20
	High	40	165	0.88	0.58-1.36	43	212	0.66	0.44-0.98
	P-trend				*0.70*				*0.06*
	Other	1459	5925			1459	5925		
-15 ars	**Unexposed**	4512	18030	1.00	Referent	4495	17960	1.00	Referent
	Low	111	352	1.19	0.95-1.48	121	377	1.19	0.97-1.48
	Medium	40	165	0.88	0.61-1.27	44	192	0.85	0.60-1.19
	High	30	108	1.10	0.68-1.77	33	126	1.08	0.69-1.69
	P-trend				*0.71*				*0.81*
	Other	3074	12413			3074	12413		
-20 ars	**Unexposed**	2146	8508	1.00	Referent	2133	8456	1.00	Referent
	Low	49	176	1.01	0.72-1.40	55	198	1.02	0.75-1.40
	Medium	30	67	1.65	1.04-2.61	28	73	1.39	0.88-2.12
	High	9	48	0.74	0.34-1.59	18	72	0.96	0.55-1.69
	P-trend				*0.31*				*0.39*
	Other	5533	22269			5533	22269		

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period
Non-genotoxic TCAs: regardless of any exposure to genotoxic TCAs
Genotoxic TCAs: regardless of any exposure to non-genotoxic TCAs

Table 16: Incidence of prostate cancer as a function of average daily dose of exclusive genotoxic and non-genotoxic TCA exposure by time period before diagnosis

Period before diagnosis		Average daily dose	Cases N=7767	Controls N=31068	Crude RR	Crude 95% CI	Adjusted* RR	Adjusted* 95% CI
2-5 years		**Unexposed**	7230	29361	1.00	Referent	1.00	Referent
	Exclusive non-genotoxic TCA exposure	**Low**	156	459	1.39	1.15-1.67	1.34	1.12-1.62
		Medium	62	187	1.35	1.01-1.80	1.33	0.99-1.79
		High	41	166	1.00	0.71-1.41	1.02	0.69-1.50
		P-trend				*0.76*		*0.72*
	Exclusive genotoxic TCA exposure	**Low**	109	347	1.28	1.03-1.58	1.25	1.00-1.55
		Medium	57	171	1.36	1.00-1.83	1.39	1.02-1.89
		High	58	191	1.24	0.92-1.66	1.47	1.06-2.03
		P-trend				*0.35*		*0.08*
		Both	54	186	1.18	0.87-1.60	1.21	0.88-1.65
		Other	-	-				
6-10 years		**Unexposed**	5868	23618	1.00	Referent	1.00	Referent
	Exclusive non-genotoxic TCA exposure	**Low**	116	391	1.19	0.97-1.47	1.11	0.90-1.38
		Medium	41	135	1.22	0.86-1.74	1.11	0.77-1.59
		High	29	117	1.00	0.66-1.50	0.93	0.57-1.51
		P-trend				*0.69*		*0.99*
	Exclusive genotoxic TCA exposure	**Low**	120	330	1.46	1.19-1.80	1.36	1.10-1.68
		Medium	44	161	1.10	0.79-1.54	0.97	0.68-1.37
		High	26	163	0.64	0.42-0.97	0.48	0.30-0.77
		P-trend				*0.12*		*0.01*
		Both	64	228	1.13	0.85-1.49	0.95	0.71-1.28
		Other	1459	5925				
11-15 years		**Unexposed**	4362	17490	1.00	Referent	1.00	Referent
	Exclusive non-genotoxic TCA exposure	**Low**	88	281	1.25	0.99-1.60	1.19	0.93-1.52
		Medium	27	111	0.98	0.64-1.49	0.90	0.59-1.39
		High	18	78	0.93	0.56-1.55	0.83	0.46-1.51
		P-trend				*0.54*		*0.33*
	Exclusive genotoxic TCA exposure	**Low**	99	312	1.27	1.01-1.60	1.21	0.96-1.52
		Medium	29	142	0.82	0.55-1.22	0.78	0.52-1.17
		High	22	86	1.03	0.64-1.65	1.16	0.68-1.98
		P-trend				*0.28*		*0.42*
		Both	48	155	1.24	0.90-1.72	1.15	0.81-1.62
		Other	3074	12413				
16-20 years		**Unexposed**	2078	8262	1.00	Referent	1.00	Referent
	Exclusive non-genotoxic TCA exposure	**Low**	32	122	1.04	0.70-1.55	0.99	0.66-1.48
		Medium	15	43	1.37	0.76-2.47	1.36	0.75-2.47
		High	8	29	1.09	0.50-2.37	1.28	0.54-2.99
		P-trend				*0.56*		*0.75*
	Exclusive genotoxic TCA exposure	**Low**	40	155	1.03	0.72-1.45	0.99	0.69-1.40
		Medium	18	44	1.64	0.94-2.84	1.59	0.91-2.77
		High	10	47	0.85	0.43-1.68	0.86	0.42-1.78
		P-trend				*0.17*		*0.16*
		Both	33	97	1.35	0.91-2.01	1.29	0.85-1.96
		Other	5533	22269				

*: Adjustment for the exposure in the other periods was carried out for each period
Unexposed: no exposure to either type of TCAs (genotoxic and non-genotoxic)
Both: exposure to both types of TCAs (genotoxic and non-genotoxic)

Table 17: Incidence of prostate cancer as a function of duration of genotoxic and non-genotoxic TCA exposure by time period before diagnosis

riod fore agnosis	Duration	Non-Genotoxic TCAs				Genotoxic TCAs			
		Cases N=7767	Controls N=31068	Adjusted RR*	Adjusted 95% CI*	Cases N=7767	Controls N=31068	Adjuste d RR*	Adjusted 95% CI*
5 years	**Unexposed**	7454	30073	1.00	Referent	7489	30174	1.00	Referent
	Short	144	454	1.24	1.02-1.50	123	389	1.21	0.98-1.48
	Medium	117	343	1.31	1.05-1.63	94	285	1.24	0.97-1.59
	Long	52	198	1.01	0.70-1.44	61	220	1.19	0.86-1.65
	P-trend				*0.64*				*0.16*
	Other	-	-			-	-		
10 ears	**Unexposed**	6061	24288	1.00	Referent	6058	24274	1.00	Referent
	Short	158	534	1.09	0.91-1.32	152	492	1.14	0.94-1.38
	Medium	54	208	0.90	0.65-1.23	63	218	1.02	0.76-1.37
	Long	37	123	1.12	0.71-1.78	37	169	0.75	0.49-1.16
	P-trend				*0.79*				*0.22*
	Other	1457	5915			1457	5915		
1-15 ears	**Unexposed**	4531	18105	1.00	Referent	4516	18036	1.00	Referent
	Short	122	409	1.12	0.90-1.38	131	434	1.12	0.91-1.37
	Medium	39	140	1.00	0.69-1.46	47	174	0.97	0.69-1.37
	Long	21	80	0.88	0.50-1.56	19	90	0.73	0.41-1.31
	P-trend				*0.86*				*0.43*
	Other	3054	12334			3054	12334		
6-20 ears	**Unexposed**	2163	8577	1.00	Referent	2145	8522	1.00	Referent
	Short	58	192	1.06	0.78-1.46	68	222	1.14	0.86-1.52
	Medium	22	60	1.36	0.81-2.27	25	76	1.23	0.76-1.99
	Long	8	36	0.90	0.39-2.07	13	45	1.30	0.65-2.59
	P-trend				*0.45*				*0.73*
	Other	5516	22203			5516	22203		

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period
Non-genotoxic TCAs: regardless of any exposure to genotoxic TCAs
Genotoxic TCAs: regardless of any exposure to non-genotoxic TCAs

Table 18: Incidence of prostate cancer as a function of duration of exclusive genotoxic and non-genotoxic TCA exposure by time period before diagnosis

Period before diagnosis		Duration	Cases N=7767	Controls N=31068	Crude		Adjusted*	
					RR	95% CI	RR	95% CI
2-5 years		Unexposed	7230	29365	1.00	Referent	1.00	Referent
	Exclusive non-genotoxic TCA exposure	Short	127	377	1.38	1.21-1.69	1.35	1.10-1.66
		Medium	92	258	1.45	1.14-1.84	1.43	1.12-1.83
		Long	40	174	0.93	0.66-1.31	0.87	0.59-1.29
		P-trend				*0.47*		*0.79*
	Exclusive genotoxic TCA exposure	Short	100	326	1.24	0.99-1.56	1.22	0.98-1.54
		Medium	69	203	1.38	1.05-1.82	1.37	1.03-1.81
		Long	55	179	1.25	0.92-1.69	1.42	1.01-2.00
		P-trend				*0.05*		*0.01*
		Both	54	186	1.18	0.87-1.60	1.19	0.87-1.63
		Other	-	-				
6-10 years		Unexposed	5872	23635	1.00	Referent	1.00	Referent
	Exclusive non-genotoxic TCA exposure	Short	122	401	1.22	1.00-1.50	1.16	0.94-1.42
		Medium	36	147	0.99	0.68-1.42	0.88	0.60-1.28
		Long	28	91	1.24	0.81-1.90	1.27	0.76-2.13
		P-trend				*0.40*		*0.70*
	Exclusive genotoxic TCA exposure	Short	123	366	1.35	1.10-1.66	1.25	1.01-1.54
		Medium	37	150	1.00	0.69-1.43	0.90	0.62-1.30
		Long	29	137	0.85	0.57-1.27	0.70	0.44-1.12
		P-trend				*0.49*		*0.09*
		Both	63	226	1.12	0.85-1.49	0.98	0.73-1.32
		Other	1457	5915				
11-15 years		Unexposed	4382	17565	1.00	Referent	1.00	Referent
	Exclusive non-genotoxic TCA exposure	Short	94	320	1.18	0.93-1.49	1.12	0.88-1.41
		Medium	26	88	1.19	0.76-1.85	1.09	0.69-1.71
		Long	14	63	0.89	0.50-1.59	0.72	0.37-1.40
		P-trend				*0.70*		*0.74*
	Exclusive genotoxic TCA exposure	Short	107	353	1.21	0.98-1.51	1.14	0.92-1.43
		Medium	30	119	1.01	0.68-1.51	0.93	0.62-1.42
		Long	12	68	0.71	0.38-1.32	0.67	0.34-1.33
		P-trend				*0.52*		*0.39*
		Both	48	158	1.22	0.88-1.69	1.07	0.76-1.51
		Other	3054	12334				
16-20 years		Unexposed	2090	8330	1.00	Referent	1.00	Referent
	Exclusive non-genotoxic TCA exposure	Short	38	128	1.19	0.82-1.71	1.10	0.76-1.60
		Medium	9	39	0.91	0.44-1.88	0.88	0.42-1.84
		Long	8	25	1.27	0.57-2.82	1.42	0.60-3.39
		P-trend				*0.42*		*0.31*
	Exclusive genotoxic TCA exposure	Short	52	172	1.20	0.88-1.64	1.16	0.85-1.60
		Medium	14	42	1.34	0.73-2.46	1.31	0.71-2.43
		Long	7	33	0.85	0.38-1.92	0.97	0.40-2.33
		P-trend				*0.76*		*0.95*
		Both	33	96	1.37	0.92-2.04	1.36	0.90-2.06
		Other	5516	22203				

*: Adjustment for the exposure in the other periods was carried out for each period
Unexposed: no exposure to either type of TCAs (genotoxic and non-genotoxic)
Both: exposure to both types of TCAs (genotoxic and non-genotoxic)

Table 19: Incidence of prostate cancer as a function of average daily dose of SSRI exposure by time period before diagnosis

Period before diagnosis	SSRI exposure: Average daily dose	Cases N=5346	Controls N=21384	Crude RR	Crude 95% CI	Adjusted* RR	Adjusted* 95% CI
2-5 years	**Unexposed**	5255	21019	1.00	Referent	1.00	Referent
	Low	50	219	0.91	0.67-1.25	0.91	0.67-1.25
	Medium	32	100	1.28	0.86-1.91	1.28	0.86-1.92
	High	9	46	0.78	0.38-1.60	0.76	0.36-1.59
	P-trend				*0.25*		*0.20*
	Other	-	-				
6-10 years	**Unexposed**	5313	21252	1.00	Referent	1.00	Referent
	Low	24	97	0.99	0.63-1.55	0.99	0.62-1.56
	Medium	8	32	1.00	0.46-1.55	1.04	0.47-2.29
	High	1	3	1.33	0.14-12.8	1.67	0.16-17.2
	P-trend				*0.70*		*0.56*
	Other	-	-				

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period

Table 20: Incidence of prostate cancer as a function of duration of SSRI exposure by time period before diagnosis

Period before diagnosis	SSRI exposure: Duration	Cases N=5346	Controls N=21384	Crude RR	Crude 95% CI	Adjusted* RR	Adjusted* 95% CI
2-5 years	**Unexposed**	5255	21018	1.00	Referent	1.00	Referent
	Short	37	148	1.00	0.70-1.44	1.00	0.69-1.44
	Medium	45	161	1.12	0.80-1.56	1.10	0.78-1.54
	Long	9	57	0.63	0.31-1.28	0.59	0.29-1.21
	P-trend				*0.63*		*0.48*
	Other	-	-				
6-10 years	**Unexposed**	5313	21252	1.00	Referent	1.00	Referent
	Short	19	95	0.80	0.49-1.31	0.81	0.49-1.34
	Medium	13	32	1.62	0.85-3.09	1.76	0.90-3.43
	Long	1	5	0.82	0.10-7.01	0.95	0.11-8.30
	P-trend				*0.42*		*0.26*
	Other	-	-				

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period

Table 21: Incidence of ovarian cancer as a function of average daily dose of genotoxic and non-genotoxic TCA exposure by time period before diagnosis

eriod efore iagnosis	Average daily dose	Non-Genotoxic TCAs				Genotoxic TCAs			
		Cases N=1090	Controls N=4360	Adjusted RR*	Adjusted 95% CI*	Cases N=1090	Controls N=4360	Adjusted RR*	Adjusted 95% CI*
-5 years	**Unexposed**	1004	4019	1.00	Referent	1015	4095	1.00	Referent
	Low	37	165	0.90	0.62-1.31	30	126	1.08	0.71-1.63
	Medium	24	93	0.90	0.55-1.47	25	66	1.66	1.02-2.72
	High	25	83	0.79	0.44-1.42	20	73	1.48	0.84-2.72
	P-trend				*0.90*				*0.55*
	Other	-	-			-	-		
-10 ears	**Unexposed**	748	3011	1.00	Referent	756	3040	1.00	Referent
	Low	27	152	0.71	0.46-1.10	33	122	1.03	0.69-1.56
	Medium	14	59	1.05	0.56-1.97	18	63	0.95	0.53-1.71
	High	24	46	3.72	1.79-7.75	6	43	0.42	0.16-1.10
	P-trend				*0.0001*				*0.18*
	Other	277	1092			277	1092		
1-15 ears	**Unexposed**	522	2053	1.00	Referent	506	2052	1.00	Referent
	Low	16	95	0.59	0.34-1.04	30	85	1.51	0.96-2.38
	Medium	7	35	0.53	0.21-1.32	13	45	1.33	0.69-2.55
	High	8	33	0.37	0.13-1.06	4	34	0.70	0.22-2.23
	P-trend				*0.82*				*0.30*
	Other	537	2144			537	2144		
6-20 ears	**Unexposed**	224	937	1.00	Referent	221	927	1.00	Referent
	Low	12	41	1.22	0.61-0.02	11	40	1.18	0.59-2.37
	Medium	1	20	0.19	0.02-1.58	8	27	1.32	0.54-3.24
	High	4	10	1.97	0.52-7.51	1	14	0.37	0.04-3.07
	P-trend				*0.75*				*0.97*
	Other	849	3352			849	3352		

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period
Non-genotoxic TCAs: regardless of any exposure to genotoxic TCAs
Genotoxic TCAs: regardless of any exposure to non-genotoxic TCAs

Table 22: Incidence of ovarian cancer as a function of average daily dose of exclusive genotoxic and non-genotoxic TCA exposure by time period before diagnosis

Period before diagnosis		Average daily dose	Cases N=1090	Controls N=4360	Crude RR	Crude 95% CI	Adjusted* RR	Adjusted* 95% C
2-5 years		**Unexposed**	954	3836	1.00	Referent	1.00	Referen
	Exclusive non-genotoxic TCA exposure	**Low**	29	129	0.91	0.60-1.36	0.92	0.61-1.3
		Medium	12	61	0.79	0.42-1.48	0.76	0.40-1.4
		High	20	69	1.17	0.70-1.93	0.89	0.47-1.6
		P-trend				*0.19*		*0.73*
	Exclusive genotoxic TCA exposure	**Low**	24	88	1.10	0.70-1.73	1.18	0.74-1.8
		Medium	14	47	1.20	0.66-2.19	1.24	0.67-2.3
		High	12	48	1.01	0.53-1.89	1.13	0.56-2.2
		P-trend				*0.79*		*0.62*
		Both	25	82	1.23	0.78-1.94	1.31	0.81-2.1
		Other	-	-				
6-10 years		**Unexposed**	706	2852	1.00	Referent	1.00	Referen
	Exclusive non-genotoxic TCA exposure	**Low**	24	118	0.82	0.52-1.28	0.82	0.52-1.3
		Medium	10	39	1.03	0.51-2.08	1.13	0.54-2.3
		High	16	31	2.10	1.14-3.85	3.01	1.34-6.7
		P-trend				*0.002*		*0.0005*
	Exclusive genotoxic TCA exposure	**Low**	25	90	1.12	0.71-1.75	1.05	0.66-1.6
		Medium	12	44	1.11	0.58-2.11	1.11	0.56-2.1
		High	5	25	0.81	0.31-2.12	0.86	0.29-2.5
		P-trend				*0.82*		*0.97*
		Both	15	69	0.89	0.50-1.56	0.84	0.45-1.5
		Other	277	1092				
11-15 years		**Unexposed**	483	1944	1.00	Referent	1.00	Referen
	Exclusive non-genotoxic TCA exposure	**Low**	13	69	0.76	0.41-1.39	0.72	0.39-1.3
		Medium	5	16	1.29	0.46-3.57	1.43	0.48-4.2
		High	5	23	0.87	0.33-2.31	0.44	0.13-1.4
		P-trend				*0.45*		*0.96*
	Exclusive genotoxic TCA exposure	**Low**	24	58	1.65	1.02-2.68	1.67	1.00-2.7
		Medium	11	29	1.50	0.75-3.01	1.58	0.77-3.2
		High	4	22	0.73	0.25-2.15	0.78	0.23-2.6
		P-trend				*0.41*		*0.23*
		Both	8	55	0.58	0.27-1.24	0.44	0.19-1.0
		Other	537	2144				
16-20 years		**Unexposed**	210	880	1.00	Referent	1.00	Referen
	Exclusive non-genotoxic TCA exposure	**Low**	8	30	1.10	0.50-2.44	1.10	0.49-2.4
		Medium	-	10	-	-	-	-
		High	3	7	1.74	0.45-6.77	2.17	0.48-9.8
		P-trend				*0.67*		*0.72*
	Exclusive genotoxic TCA exposure	**Low**	8	35	0.96	0.44-2.10	0.91	0.41-2.0
		Medium	5	10	2.06	0.70-6.06	1.97	0.65-6.0
		High	1	12	0.35	0.05-2.71	0.33	0.04-2.6
		P-trend				*0.91*		*0.88*
		Both	6	24	1.06	0.43-2.65	1.12	0.43-2.9
		Other	849	3352				

*: Adjustment for the exposure in the other periods was carried out for each period
Unexposed: no exposure to either type of TCAs (genotoxic and non-genotoxic)
Both: exposure to both types of TCAs (genotoxic and non-genotoxic)

Table 23: Incidence of ovarian cancer as a function of duration of genotoxic and non-genotoxic TCA exposure by time period before diagnosis

eriod efore iagnosis	Duration	Non-Genotoxic TCAs Cases N=1090	Non-Genotoxic TCAs Controls N=4360	Non-Genotoxic TCAs Adjusted RR*	Non-Genotoxic TCAs Adjusted 95% CI*	Genotoxic TCAs Cases N=1090	Genotoxic TCAs Controls N=4360	Genotoxic TCAs Adjusted RR*	Genotoxic TCAs Adjusted 95% CI*
-5 years	**Unexposed**	1005	4020	1.00	Referent	1015	4096	1.00	Referent
	Short	30	135	0.88	0.58-1.32	27	115	1.05	0.68-1.62
	Medium	31	125	0.94	0.61-1.44	26	83	1.47	0.92-2.36
	Long	24	80	0.81	0.45-1.45	22	66	1.67	0.95-2.95
	P-trend				*0.34*				*0.14*
	Other	-	-			-	-		
-10 ears	**Unexposed**	748	3012	1.00	Referent	756	3039	1.00	Referent
	Short	29	154	0.76	0.50-1.16	38	130	1.15	0.78-1.70
	Medium	17	62	1.30	0.72-2.35	12	62	0.65	0.33-1.27
	Long	19	40	3.00	0.77-2.20	7	37	0.58	0.22-1.54
	P-trend				*0.01*				*0.16*
	Other	277	1092			277	1092		
1-15 ears	**Unexposed**	522	2056	1.00	Referent	507	2056	1.00	Referent
	Short	19	99	0.67	0.40-1.13	30	100	1.34	0.85-2.09
	Medium	4	42	0.23	0.08-0.70	14	43	1.55	0.79-3.04
	Long	9	24	0.76	0.27-2.13	3	22	0.66	0.17-2.54
	P-trend				*0.24*				*0.98*
	Other	536	2139			536	2139		
6-20 ears	**Unexposed**	226	944	1.00	Referent	223	932	1.00	Referent
	Short	11	47	1.09	0.54-2.20	13	48	1.10	0.57-2.09
	Medium	3	15	0.93	0.24-3.59	5	28	0.72	0.25-2.02
	Long	3	9	0.99	0.21-4.64	2	7	1.04	0.19-5.62
	P-trend				*0.52*				*0.84*
	Other	847	3345			847	3345		

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period
Non-genotoxic TCAs: regardless of any exposure to genotoxic TCAs
Genotoxic TCAs: regardless of any exposure to non-genotoxic TCAs

Table 24: Incidence of <u>ovarian</u> cancer as a function of <u>duration</u> of <u>exclusive</u> genotoxic and non-genotoxic <u>TCA</u> exposure by time period before diagnosis

Period before diagnosis		Duration	Cases N=1090	Controls N=4360	Crude		Adjusted*	
					RR	95% CI	RR	95% CI
2-5 years		**Unexposed**	954	3838	1.00	Referent	1.00	Referen
	Exclusive non-genotoxic TCA exposure	**Short**	23	107	0.87	0.55-1.36	0.86	0.54-1.3
		Medium	20	86	0.94	0.57-1.54	0.99	0.60-1.6
		Long	18	65	1.11	0.66-1.89	0.87	0.45-1.6
		P-trend				*0.94*		*0.48*
	Exclusive genotoxic TCA exposure	**Short**	20	80	1.01	0.61-1.65	1.09	0.66-1.7
		Medium	17	55	1.25	0.72-2.15	1.36	0.77-2.3
		Long	14	47	1.20	0.66-2.17	1.40	0.70-2.8
		P-trend				*0.62*		*0.38*
		Both	24	82	1.18	0.74-1.87	1.27	0.78-2.0
		Other	-	-				
6-10 years		**Unexposed**	706	2852	1.00	Referent	1.00	Referent
	Exclusive non-genotoxic TCA exposure	**Short**	26	117	0.90	0.58-1.39	0.92	0.59-1.4
		Medium	10	40	1.00	0.50-2.01	1.07	0.52-2.2
		Long	14	30	1.88	0.99-3.58	2.47	1.04-5.8
		P-trend				*0.07*		*0.04*
	Exclusive genotoxic TCA exposure	**Short**	30	92	1.32	0.87-2.02	1.27	0.82-1.9
		Medium	7	44	0.65	0.29-1.44	0.56	0.24-1.3
		Long	5	24	0.86	0.33-2.25	0.69	0.21-2.2
		P-trend				*0.64*		*0.40*
		Both	15	69	0.89	0.51-1.57	0.84	0.45-1.5
		Other	277	1092				
11-15 years		**Unexposed**	484	1946	1.00	Referent	1.00	Referent
	Exclusive non-genotoxic TCA exposure	**Short**	14	67	0.84	0.47-1.52	0.83	0.46-1.5
		Medium	3	23	0.53	0.16-1.77	0.49	0.14-1.6
		Long	6	20	1.20	0.48-3.03	0.71	0.22-2.3
		P-trend				*0.96*		*0.34*
	Exclusive genotoxic TCA exposure	**Short**	23	67	1.37	0.84-2.22	1.36	0.83-2.2
		Medium	12	25	1.90	0.95-3.82	1.82	0.87-3.8
		Long	3	18	0.68	0.20-2.32	0.74	0.18-2.9
		P-trend				*0.75*		*0.69*
		Both	9	55	0.66	0.32-1.35	0.57	0.26-1.2
		Other	536	2139				
16-20 years		**Unexposed**	212	885	1.00	Referent	1.00	Referent
	Exclusive non-genotoxic TCA exposure	**Short**	8	33	1.01	0.45-2.25	1.02	0.46-2.2
		Medium	1	8	0.51	0.06-4.10	0.58	0.07-1.8
		Long	2	6	1.41	0.28-6.98	1.39	0.22-8.6
		P-trend				*0.43*		*0.41*
	Exclusive genotoxic TCA exposure	**Short**	9	37	1.01	0.48-2.11	0.95	0.45-2.0
		Medium	3	15	0.84	0.24-2.91	0.77	0.21-2.8
		Long	2	7	1.19	0.25-5.76	1.06	0.19-5.8
		P-trend				*0.96*		*0.95*
		Both	6	24	1.04	0.42-2.60	1.08	0.41-2.8
		Other	847	3345				

*: Adjustment for the exposure in the other periods was carried out for each period
Unexposed: no exposure to either type of TCAs (genotoxic and non-genotoxic)
Both: exposure to both types of TCAs (genotoxic and non-genotoxic)

Table 25: Incidence of ovarian cancer as a function of average daily dose of SSRI exposure by time period before diagnosis

	SSRI exposure						
Period before diagnosis	**Average daily dose**	**Cases N=672**	**Controls N=2688**	**Crude**		**Adjusted***	
				RR	**95% CI**	**RR**	**95% CI**
2-5 years	**Unexposed**	652	2597	1.00	Referent	1.00	Referent
	Low	10	46	0.87	0.44-1.72	0.85	0.43-1.7
	Medium	7	28	1.00	0.42-2.35	0.91	0.37-2.2
	High	3	17	0.69	0.20-2.42	0.19	0.02-1.5
	P-trend				*0.70*		*0.49*
	Other	-	-				
6-10 years	**Unexposed**	663	2660	1.00	Referent	1.00	Referent
	Low	5	21	0.98	0.37-2.63	1.18	0.43-3.2
	Medium	2	6	1.33	0.27-6.61	2.26	0.39-13.
	High	2	1	7.99	0.72-88.2	42.4	1.71-105
	P-trend				*0.14*		*0.04*
	Other	-	-				

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period

Table 26: Incidence of <u>ovarian</u> cancer as a function of <u>duration</u> of <u>SSRI</u> exposure by time period before diagnosis

Period before diagnosis	SSRI exposure Duration	Cases N=672	Controls N=2688	Crude RR	Crude 95% CI	Adjusted* RR	Adjusted* 95% CI
2-5 years	**Unexposed**	652	2597	1.00	Referent	1.00	Referent
	Short	7	27	1.03	0.45-2.39	1.04	0.45-2.41
	Medium	8	43	0.74	0.34-1.58	0.64	0.29-1.41
	Long	5	21	0.94	0.35-2.51	0.51	0.14-1.84
	P-trend				*0.81*		*0.23*
	Other	-	-				
6-10 years	**Unexposed**	663	2660	1.00	Referent	1.00	Referent
	Short	3	18	0.67	0.20-2.31	0.74	0.21-2.58
	Medium	4	7	2.29	0.67-7.81	3.44	0.86-13.7
	Long	2	3	2.62	0.44-15.7	4.73	0.60-37.6
	P-trend				*0.36*		*0.24*
	Other	-	-				

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period

Table 27: Incidence of non-Hodgkin's lymphoma as a function of average daily dose of genotoxic and non-genotoxic TCA exposure by time period before diagnosis

eriod efore iagnosis	Average daily dose	Non-Genotoxic TCAs				Genotoxic TCAs			
		Cases N=1980	Controls N=7920	Adjusted RR*	Adjusted 95% CI*	Cases N=1980	Controls N=7920	Adjusted RR*	Adjusted 95% CI*
-5 years	**Unexposed**	1849	7498	1.00	Referent	1867	7530	1.00	Referent
	Low	66	206	1.32	0.99-1.76	55	176	1.23	0.90-1.68
	Medium	34	121	1.14	0.76-1.71	29	100	1.10	0.72-1.70
	High	31	95	1.28	0.98-2.53	29	114	0.88	0.52-1.47
	P-trend				*0.28*				*0.91*
	Other	-	-						
-10 ears	**Unexposed**	1455	5842	1.00	Referent	1453	5837	1.00	Referent
	Low	50	218	0.90	0.65-1.25	44	186	0.91	0.64-1.28
	Medium	22	73	1.12	0.67-1.88	19	100	0.74	0.43-1.20
	High	14	67	0.84	0.43-1.67	25	77	1.08	0.59-1.97
	P-trend				*0.57*				*0.48*
	Other	439	1720			439	1720		
1-15 ears	**Unexposed**	981	3846	1.00	Referent	955	3824	1.00	Referent
	Low	28	117	0.88	0.57-1.35	39	131	1.33	0.91-1.95
	Medium	17	51	1.13	0.61-2.09	19	68	1.19	0.69-2.04
	High	4	40	0.29	0.09-0.93	17	31	3.01	1.42-6.36
	P-trend				*0.12*				*0.01*
	Other	950	3866			950	3866		
6-20 ears	**Unexposed**	480	1869	1.00	Referent	478	1849	1.00	Referent
	Low	15	67	0.91	0.50-1.64	12	59	0.71	0.37-1.37
	Medium	4	26	0.63	0.21-1.93	5	34	0.43	0.15-1.20
	High	3	8	2.97	0.62-14.2	7	28	0.64	0.24-1.69
	P-trend				*0.20*				*0.74*
	Other	1478	5950			1478	5950		

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period
Non-genotoxic TCAs: regardless of any exposure to genotoxic TCAs
Genotoxic TCAs: regardless of any exposure to non-genotoxic TCAs

Table 28: Incidence of non-Hodgkin's lymphoma as a function of average daily dose of exclusive genotoxic and non-genotoxic TCA exposure by time period before diagnosis

Period before diagnosis		Average daily dose	Cases N=1980	Controls N=7920	Crude RR	Crude 95% CI	Adjusted* RR	Adjusted* 95% C
2-5 years		Unexposed	1765	7214	1.00	Referent	1.00	Referen
	Exclusive non-genotoxic TCA exposure	Low	52	158	1.35	0.98-1.86	1.41	1.02-1.9
		Medium	23	79	1.19	0.74-1.90	1.25	0.77-2.0
		High	27	79	1.41	0.91-2.19	1.71	1.04-2.8
		P-trend				*0.45*		*0.14*
	Exclusive genotoxic TCA exposure	Low	38	130	1.20	0.83-1.72	1.21	0.84-1.7
		Medium	23	70	1.34	0.84-2.15	1.39	0.85-2.2
		High	23	84	1.12	0.71-1.78	1.09	0.63-1.9
		P-trend				*0.44*		*0.67*
		Both	29	106	1.13	0.74-1.70	1.15	0.74-1.7
		Other	-	-				
6-10 years		Unexposed	1390	5590	1.00	Referent	1.00	Referen
	Exclusive non-genotoxic TCA exposure	Low	36	151	0.96	0.66-1.39	0.90	0.61-1.3
		Medium	19	47	1.61	0.95-2.75	1.36	0.77-2.3
		High	8	49	0.66	0.31-1.39	0.63	0.27-1.4
		P-trend				*0.76*		*0.80*
	Exclusive genotoxic TCA exposure	Low	32	131	0.98	0.67-1.45	0.93	0.63-1.3
		Medium	15	69	0.87	0.50-1.53	0.78	0.43-1.3
		High	18	52	1.39	0.81-2.37	0.95	0.47-1.9
		P-trend				*0.09*		*0.60*
		Both	23	111	0.83	0.53-1.31	0.73	0.45-1.1
		Other	439	1720				
11-15 years		Unexposed	928	3677	1.00	Referent	1.00	Referen
	Exclusive non-genotoxic TCA exposure	Low	20	90	0.88	0.54-1.44	0.86	0.53-1.4
		Medium	6	30	0.82	0.34-1.97	0.80	0.32-2.0
		High	1	27	0.15	0.02-1.10	0.17	0.02-1.3
		P-trend				*0.20*		*0.37*
	Exclusive genotoxic TCA exposure	Low	28	100	1.11	0.72-1.69	1.19	0.77-1.8
		Medium	13	48	1.07	0.58-1.97	1.13	0.60-2.1
		High	12	21	2.25	1.11-4.58	2.76	1.15-6.6
		P-trend				*0.03*		*0.06*
		Both	22	61	1.44	0.88-2.36	1.56	0.90-2.6
		Other	950	3866				
16-20 years		Unexposed	465	1786	1.00	Referent	1.00	Referen
	Exclusive non-genotoxic TCA exposure	Low	10	46	0.84	0.42-1.67	0.87	0.43-1.7
		Medium	1	12	0.32	0.04-2.43	0.35	0.04-2.7
		High	2	5	1.52	0.29-7.83	1.80	0.30-10.
		P-trend				*0.74*		*0.98*
	Exclusive genotoxic TCA exposure	Low	7	43	0.61	0.27-1.38	0.56	0.25-1.2
		Medium	3	18	0.64	0.19-2.18	0.50	0.14-1.7
		High	5	22	0.87	0.33-2.31	0.52	0.18-1.5
		P-trend				*0.69*		*0.22*
		Both	9	38	0.92	0.43-1.93	0.68	0.30-1.5
		Other	1478	5950				

*: Adjustment for the exposure in the other periods was carried out for each period
Unexposed: no exposure to either type of TCAs (genotoxic and non-genotoxic)
Both: exposure to both types of TCAs (genotoxic and non-genotoxic)

Table 29: Incidence of non-Hodgkin's lymphoma as a function of duration of genotoxic and non-genotoxic TCA exposure by time period before diagnosis

Period before diagnosis	Duration	Non-Genotoxic TCAs				Genotoxic TCAs			
		Cases N=1980	Controls N=7920	Adjusted RR*	Adjusted 95% CI*	Cases N=1980	Controls N=7920	Adjusted RR*	Adjusted 95% CI*
2-5 years	**Unexposed**	1849	7502	1.00	Referent	1867	7531	1.00	Referent
	Short	54	170	1.32	0.96-1.81	44	160	1.06	0.75-1.50
	Medium	40	154	1.05	0.73-1.53	42	131	1.26	0.87-1.82
	Long	37	94	1.95	1.23-3.10	27	98	0.94	0.55-1.63
	P-trend				*0.01*				*0.93*
	Other	-	-			-	-		
6-10 years	**Unexposed**	1454	5840	1.00	Referent	1454	5843	1.00	Referent
	Short	56	234	0.96	0.70-1.31	46	202	0.85	0.60-1.20
	Medium	17	70	0.90	0.51-1.62	19	106	0.68	0.40-1.15
	Long	14	57	0.89	0.44-1.81	22	50	1.27	0.64-2.49
	P-trend				*0.91*				*0.69*
	Other	439	1719			439	1719		
11-15 years	**Unexposed**	984	3860	1.00	Referent	957	3837	1.00	Referent
	Short	31	121	0.94	0.62-1.41	44	159	1.23	0.86-1.76
	Medium	15	53	0.93	0.49-1.78	18	50	1.65	0.91-3.00
	Long	3	33	0.19	0.04-0.84	14	21	3.77	1.61-8.85
	P-trend				*0.03*				*0.003*
	Other	947	3853			947	3853		
16-20 years	**Unexposed**	486	1890	1.00	Referent	484	1870	1.00	Referent
	Short	16	75	0.87	0.49-1.55	14	68	0.71	0.38-1.33
	Medium	3	20	0.67	0.19-2.34	5	37	0.38	0.14-1.04
	Long	3	8	0.63	0.64-20.0	5	18	0.40	0.12-1.34
	P-trend				*0.81*				*0.06*
	Other	1472	5927			1472	5927		

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period
Non-genotoxic TCAs: regardless of any exposure to genotoxic TCAs
Genotoxic TCAs: regardless of any exposure to non-genotoxic TCAs

Table 30: Incidence of non-Hodgkin's lymphoma as a function of duration of exclusive genotoxic and non-genotoxic TCA exposure by time period before diagnosis

Period before diagnosis		Duration	Cases N=1980	Controls N=7920	Crude RR	Crude 95% CI	Adjusted* RR	Adjusted* 95% C
2-5 years		Unexposed	1765	7218	1.00	Referent	1.00	Referer
	Exclusive non-genotoxic TCA exposure	Short	42	130	1.33	0.94-1.89	1.36	0.96-1.9
		Medium	27	105	1.06	0.69-1.62	1.10	0.71-1.7
		Long	33	78	1.74	1.15-2.62	2.28	1.40-3.7
		P-trend				*0.02*		*0.002*
	Exclusive genotoxic TCA exposure	Short	30	117	1.05	0.70-1.57	1.06	0.71-1.5
		Medium	31	92	1.38	0.92-2.08	1.41	0.93-2.1
		Long	23	75	1.25	0.78-2.00	1.11	0.62-1.9
		P-trend				*0.29*		*0.76*
		Both	29	105	1.14	0.75-1.73	1.21	0.78-1.8
		Other	-	-				
6-10 years		Unexposed	1390	5593	1.00	Referent	1.00	Referer
	Exclusive non-genotoxic TCA exposure	Short	41	162	1.02	0.72-1.44	0.95	0.66-1.3
		Medium	13	44	1.19	0.64-2.23	0.95	0.49-1.8
		Long	10	44	0.92	0.46-1.83	0.73	0.32-1.6
		P-trend				*0.93*		*0.55*
	Exclusive genotoxic TCA exposure	Short	33	146	0.91	0.62-1.34	0.84	0.56-1.2
		Medium	14	64	0.88	0.49-1.57	0.77	0.42-1.4
		Long	17	37	1.83	1.03-3.26	1.20	0.56-2.5
		P-trend				*0.19*		*0.70*
		Both	23	111	0.83	0.53-1.31	0.73	0.45-1.1
		Other	439	1719				
11-15 years		Unexposed	930	3690	1.00	Referent	1.00	Referer
	Exclusive non-genotoxic TCA exposure	Short	20	93	0.86	0.53-1.39	0.85	0.52-1.4
		Medium	6	32	0.77	0.32-1.84	0.72	0.28-1.8
		Long	1	22	0.18	0.03-1.35	0.14	0.02-1.1
		P-trend				*0.07*		*0.06*
	Exclusive genotoxic TCA exposure	Short	32	122	1.03	0.69-1.53	1.09	0.73-1.6
		Medium	12	34	1.40	0.72-2.70	1.51	0.75-3.0
		Long	10	14	2.82	1.25-6.36	3.72	1.36-10
		P-trend				*0.02*		*0.02*
		Both	22	60	1.47	0.89-2.41	1.61	0.93-2.8
		Other	947	3853				
16-20 years		Unexposed	471	1806	1.00	Referent	1.00	Referer
	Exclusive non-genotoxic TCA exposure	Short	10	48	0.80	0.40-1.59	0.83	0.41-1.6
		Medium	1	12	0.32	0.04-2.47	0.34	0.04-2.6
		Long	2	4	1.88	0.34-10.3	2.26	0.33-15
		P-trend				*0.58*		*0.69*
	Exclusive genotoxic TCA exposure	Short	9	48	0.71	0.35-1.47	0.65	0.31-1.3
		Medium	3	22	0.53	0.16-1.77	0.36	0.10-1.2
		Long	3	14	0.82	0.24-2.85	0.30	0.07-1.2
		P-trend				*0.42*		*0.05*
		Both	9	39	0.89	0.42-1.88	0.67	0.30-1.4
		Other	1472	5927				

*: Adjustment for the exposure in the other periods was carried out for each period
Unexposed: no exposure to either type of TCAs (genotoxic and non-genotoxic)
Both: exposure to both types of TCAs (genotoxic and non-genotoxic)

Table 31: Incidence of non-Hodgkin's lymphoma as a function of average daily dose of SSRI exposure by time period before diagnosis

Period before diagnosis	SSRI exposure: Average daily dose	Cases N = 1243	Controls N = 4972	Crude RR	Crude 95% CI	Adjusted* RR	Adjusted* 95% CI
2-5 years	**Unexposed**	1214	4833	1.00	Referent	1.00	Referent
	Low	16	73	0.87	0.51-1.50	0.88	0.51-1.5
	Medium	9	46	0.78	0.38-1.59	0.82	0.40-1.7
	High	4	20	0.79	0.27-2.32	0.90	0.30-2.7
	P-trend				*0.60*		*0.93*
	Other	-	-				
6-10 years	**Unexposed**	1233	4918	1.00	Referent	1.00	Referent
	Low	7	38	0.73	0.32-1.65	0.77	0.34-1.7
	Medium	3	13	0.93	0.26-3.24	1.00	0.27-3.6
	High	-	3	-	-	-	-
	P-trend				*0.33*		*0.39*
	Other	-	-				

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period

Table 32: Incidence of non-Hodgkin's lymphoma as a function of duration of SSRI exposure by time period before diagnosis

	SSRI exposure						
Period before diagnosis	Duration	Cases N=1243	Controls N=4972	Crude		Adjusted*	
				RR	95% CI	RR	95% CI
2-5 years	**Unexposed**	1214	4833	1.00	Referent	1.00	Referent
	Short	10	51	0.78	0.39-1.54	0.80	0.40-1.58
	Medium	13	62	0.83	0.46-1.53	0.87	0.48-1.60
	Long	6	26	0.91	0.38-2.22	1.07	0.39-3.00
	P-trend				*0.53*		*0.71*
	Other	-	-				
6-10 years	**Unexposed**	1233	4918	1.00	Referent	1.00	Referent
	Short	7	33	0.84	0.37-1.92	0.87	0.38-1.99
	Medium	2	17	0.47	0.11-2.03	0.48	0.10-2.20
	Long	1	4	1.00	0.11-8.95	0.92	0.08-10.3
	P-trend				*0.45*		*0.49*
	Other	-	-				

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period

Table 33: Summary table of the incidence for each of the four cancer sites under study as a function of average daily dose of TCA exposure, by time period before diagnosis

		Time period before diagnosis			
Cancer site	**Average daily dose**	**2-5 years**	**6-10 years**	**11-15 years**	**16-20 years**
Breast	**Low**	1.12*	0.96	0.90	1.00
	Medium	1.20*	1.01	1.02	0.70
	High	1.19*	0.98	1.10	0.82
	P-trend	*0.21*	*0.66*	*0.05**	*0.53*
Prostate	**Low**	1.31*	1.19*	1.18*	0.99
	Medium	1.33*	1.05	0.91	1.52*
	High	1.20	0.76	1.04	0.99
	P-trend	*0.82*	*0.08*	*0.58*	*0.26*
Ovarian	**Low**	0.95	0.93	1.13	1.13
	Medium	0.96	0.97	1.02	1.09
	High	1.23	1.53	0.53	0.88
	P-trend	*0.63*	*0.01**	*0.79*	*0.79*
Non-Hodgkin's	**Low**	1.33*	0.93	1.03	0.73
	Medium	1.26	0.87	1.10	0.58
	High	1.37	0.74	1.57	0.69
	P-trend	*0.25*	*0.54*	*0.09*	*0.85*

Numbers in the body of the table correspond to RR
RR: rate (incidence) ratio
P-trend was based on the continuous data rather than the categorical data
The referent group included those who were unexposed to any TCA
*: Significant at the 0.05 level

Table 34: Summary table of the incidence for each of the four cancer sites under study as a function of duration of TCA exposure, by time period before diagnosis

		Time period before diagnosis			
Cancer site	**Duration**	**2-5 years**	**6-10 years**	**11-15 years**	**16-20 years**
Breast	**Short**	1.06	0.96	0.91	0.97
	Medium	1.22*	1.04	1.04	0.69
	Long	1.32*	0.83	1.08	0.97
	P-trend	*0.0004**	*0.21*	*0.53*	*0.25*
Prostate	**Short**	1.29*	1.14	1.11	1.11
	Medium	1.35*	1.02	1.05	1.25
	Long	1.12	0.93	0.74	1.34
	P-trend	*0.13*	*0.27*	*0.55*	*0.28*
Ovarian	**Short**	0.93	1.05	1.10	1.11
	Medium	0.97	0.76	0.78	0.66
	Long	1.38	1.27	0.77	1.39
	P-trend	*0.55*	*0.59*	*0.34*	*0.52*
Non-Hodgkin's	**Short**	1.23	0.91	1.03	0.75
	Medium	1.31*	0.70	1.19	0.48
	Long	1.44*	0.96	1.34	0.76
	P-trend	*0.06*	*0.47*	*0.44*	*0.19*

Numbers in the body of the table correspond to RR
RR: rate (incidence) ratio
P-trend was based on the continuous data rather than the categorical data
The referent group included those who were unexposed to any TCA
*: Significant at the 0.05 level

Table 35: Summary table of the incidence for each of the four cancer sites under study as a function of average daily dose of exclusive genotoxic and non-genotoxic TCA exposure, by time period before diagnosis

			Time period before diagnosis			
Cancer site	**TCA group**	**Average daily dose**	**2-5 years**	**6-10 years**	**11-15 years**	**16-20 years**
Breast	**Genotoxic**	**Low**	1.10	0.92	0.92	0.99
		Medium	1.34*	0.96	1.01	0.86
		High	1.32*	0.95	1.17	0.74
		P-trend	*0.03**	*0.23*	*0.03**	*0.49*
	Non-genotoxic	**Low**	1.14	0.99	0.89	1.04
		Medium	1.20	1.12	1.12	0.71
		High	1.21	0.99	0.95	0.81
		P-trend	*0.21*	*0.54*	*0.23*	*0.54*
Prostate	**Genotoxic**	**Low**	1.25*	1.36*	1.21	0.99
		Medium	1.39*	0.97	0.78	1.59
		High	1.47*	0.48	1.16	0.86
		P-trend	*0.08*	*0.01**	*0.42*	*0.16*
	Non-genotoxic	**Low**	1.34*	1.11	1.19	0.99
		Medium	1.33	1.11	0.90	1.36
		High	1.02	0.93	0.83	1.28
		P-trend	*0.72*	*0.99*	*0.33*	*0.75*
Ovarian	**Genotoxic**	**Low**	1.18	1.05	1.67*	0.91
		Medium	1.24	1.11	1.58	1.97
		High	1.13	0.86	0.78	0.33
		P-trend	*0.62*	*0.97*	*0.23*	*0.88*
	Non-genotoxic	**Low**	0.92	0.82	0.72	1.10
		Medium	0.76	1.13	1.43	-
		High	0.89	3.01*	0.44	2.17
		P-trend	*0.73*	*0.0005**	*0.96*	*0.72*
Non-Hodgkin's	**Genotoxic**	**Low**	1.21	0.93	1.19	0.56
		Medium	1.39	0.78	1.13	0.50
		High	1.09	0.95	2.76*	0.52
		P-trend	*0.67*	*0.60*	*0.06*	*0.22*
	Non-genotoxic	**Low**	1.41*	0.90	0.86	0.87
		Medium	1.25	1.36	0.80	0.35
		High	1.71	0.63	0.17	1.80
		P-trend	*0.14*	*0.80*	*0.37*	*0.98*

Numbers in the body of the table correspond to RR
RR: rate (incidence) ratio
P-trend was based on the continuous data rather than the categorical data
The referent group included those who were unexposed to any TCA
*: Significant at the 0.05 level

Table 36: Summary table of the incidence for each of the four cancer sites under study as a function of duration of exclusive genotoxic and non-genotoxic TCA exposure, by time period before diagnosis

			Time period before diagnosis			
Cancer site	**TCA group**	**Duration**	**2-5 years**	**6-10 years**	**11-15 years**	**16-20 years**
Breast	**Genotoxic**	**Short**	1.07	0.92	0.93	1.03
		Medium	1.29*	1.05	1.17	0.56
		Long	1.44*	0.76	1.14	0.90
		P-trend	*0.001**	*0.19*	*0.48*	*0.99*
	Non-genotoxic	**Short**	1.03	0.98	0.90	1.00
		Medium	1.30*	1.08	1.04	0.90
		Long	1.27*	0.99	0.82	1.01
		P-trend	*0.008**	*0.75*	*0.31*	*0.81*
Prostate	**Genotoxic**	**Short**	1.22	1.25*	1.14	1.16
		Medium	1.37*	0.90	0.93	1.31
		Long	1.42*	0.70	0.67	0.97
		P-trend	*0.01**	*0.09*	*0.39*	*0.95*
	Non-genotoxic	**Short**	1.35*	1.16	1.12	1.10
		Medium	1.43*	0.88	1.09	0.88
		Long	0.87	1.27	0.72	1.42
		P-trend	*0.79*	*0.70*	*0.74*	*0.31*
Ovarian	**Genotoxic**	**Short**	1.09	1.27	1.36	0.95
		Medium	1.36	0.56	1.82	0.77
		Long	1.40	0.69	0.74	1.06
		P-trend	*0.38*	*0.40*	*0.69*	*0.95*
	Non-genotoxic	**Short**	0.86	0.92	0.83	1.02
		Medium	0.99	1.07	0.49	0.58
		Long	0.87	2.47*	0.71	1.39
		P-trend	*0.48*	*0.04**	*0.34*	*0.41*
Non-Hodgkin's	**Genotoxic**	**Short**	1.06	0.84	1.09	0.65
		Medium	1.41	0.77	1.51	0.36
		Long	1.11	1.20	3.72*	0.30
		P-trend	*0.76*	*0.70*	*0.02*	*0.05**
	Non-genotoxic	**Short**	1.36	0.95	0.85	0.83
		Medium	1.10	0.95	0.72	0.34
		Long	2.28*	0.73	0.14	2.26
		P-trend	*0.002**	*0.55*	*0.06**	*0.69*

Numbers in the body of the table correspond to RR
RR: rate (incidence) ratio
P-trend was based on the continuous data rather than the categorical data
The referent group included those who were unexposed to any TCA
*: Significant at the 0.05 level

Table 37: Summary of the general effects of genotoxic and non-genotoxic TCAs on the four types of cancer, for the four periods prior to the index date

Cancer site	Time period before diagnosis			
	2-5 years	**6-10 years**	**11-15 years**	**16-20 years**
Breast Cancer	- TCAs - Genotoxic - Non-Genotoxic		- TCAs - Genotoxic	
Prostate Cancer	- Genotoxic	- Genotoxic (Protective)		
Ovarian Cancer		- TCAs - Non-Genotoxic		
N-Hodgkin's Lymphoma	- Non-Genotoxic		- Genotoxic	

TCAs: Tricyclic antidepressants as a class
Genotoxic: Genotoxic TCAs
Non-Genotoxic: Non-Genotoxic TCAs

Table 38: Comparison of the results reported by the current study and those reported by Sharpe et al.'s study for exposure to high levels of genotoxic and non-genotoxic TCAs 11-15 years before diagnosis with breast cancer

	TCAs		**RR (95% CI) p-trend**
Sharpe et al's study	**High exposure**	Genotoxic	2.47 (1.37 – 4.40) 0.0009
		Non-genotoxic	0.99 (0.49 – 1.99) 0.58
	High *exclusive* exposure	Genotoxic	1.92 (0.93 – 3.95) N/A
		Non-genotoxic	0.84 (0.36 – 1.93) N/A
Current study	**High exposure**	Genotoxic	1.27 (0.92 – 1.74) 0.002
		Non-genotoxic	0.91 (0.63 – 1.30) 0.13
	High *exclusive* exposure	Genotoxic	1.17 (0.79 – 1.74) 0.03
		Non-genotoxic	0.95 (0.61 – 1.48) 0.13

High exposure: the reference groups used for the analyses of the genotoxic and non-genotoxic TCAs were different

High exclusive exposure: the reference groups used for the analyses of the genotoxic and non-genotoxic TCAs were the same

Table 39: Overlap of data used by Sharpe et al.'s study and the current study

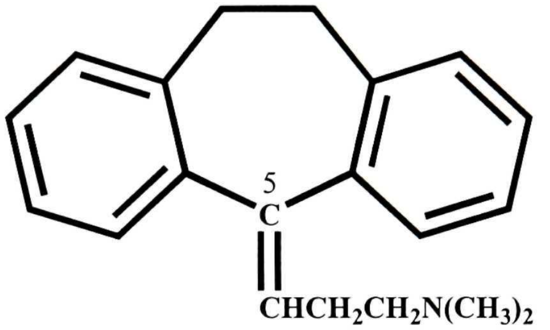
	Age group	Number of cases
Sharpe et al's study	Younger than 35	None
	Between 35 and 81	5324
	Older than 82	558
	Total	**5882**
Current study	Younger than 35	159
	Between 35 and 81	7171
	Older than 82	None
		7330

Appendix A.1: Tricyclic antidepressant drugs

Amitriptyline:

Chemical name: 3-(10,11-Dihydro-5H-dibenzo[a,d]cycloheptene -5-ylidene)-N,N-dimethyl-1-propanamine

Chemical structure:



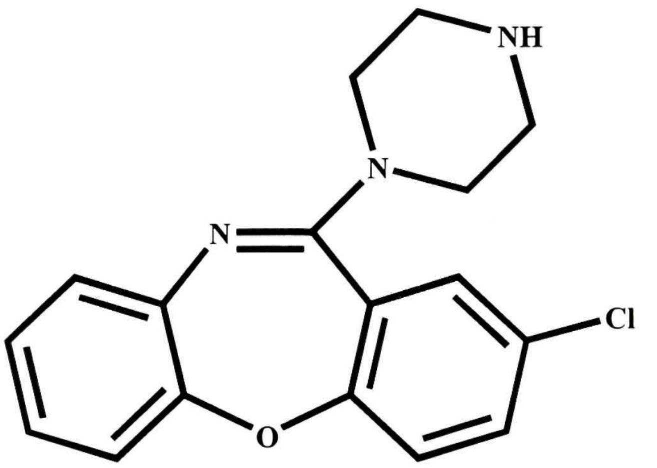
Empirical formula: $C_{20}H_{23}N$·

Molecular weight: 277.39

Amoxapine:

Chemical name: 2-Chloro-11-(1-piperazinyl)dibenz-[b,f][1,4] oxazepine

Chemical structure:



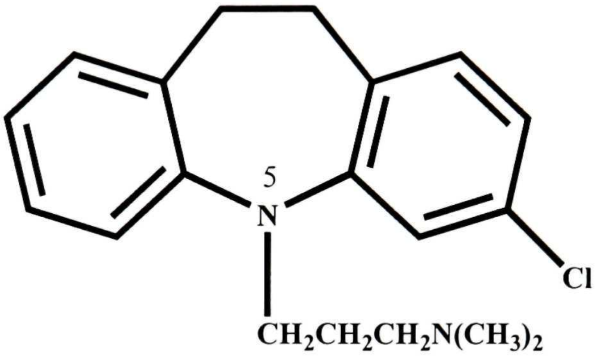
Empirical formula: $C_{17}H_{16}ClN_3O$

Molecular weight: 313.79

Clomipramine:

Chemical name: 3-Chloro-10,11-dihydro-N,N-dimethyl-5H-dibenz[b,f]azepine-5-propanamine

Chemical strucure:



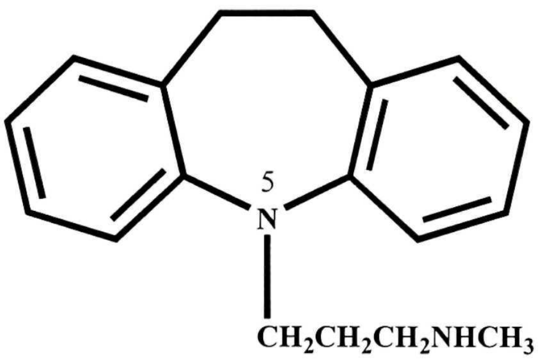
Empirical formula: $C_{19}H_{23}ClN_2$

Molecular weight: 314.87

Desipramine:

Chemical name: 10,11-Dihydro-N-methyl-5H-dibenz[b,f]azepine-5propanamine

Chemical structure:



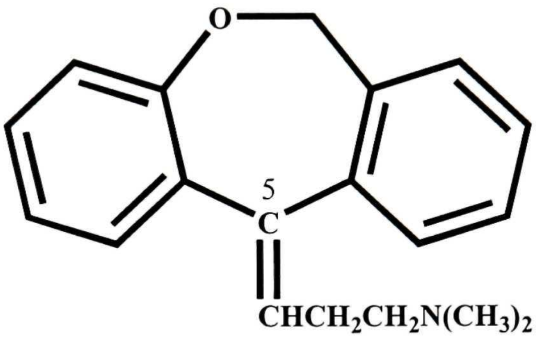
Empirical formula: $C_{18}H_{22}N_2$

Molecular weight: 266.37

Doxepin:

Chemical name: 3-Dibenz[b,e]oxepin-11(6H)-ylidene-N,-N-dimethyl-1-propanamine

Chemical structure:



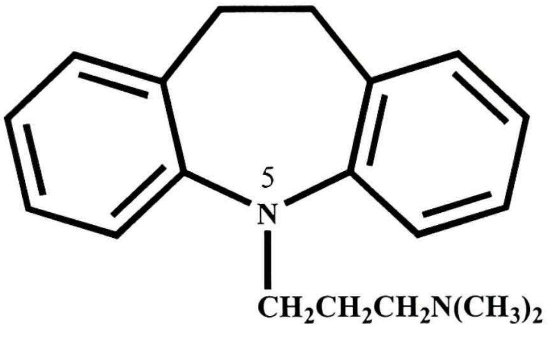
Empirical formula: $C_{19}H_{21}NO$

Molecular weight: 279.37

Imipramine:

Chemical name: 10,11-Dihydro-N,N-dimethyl-5H-dibenz[b,f]azepine-5-propanamine

Chemical structure:



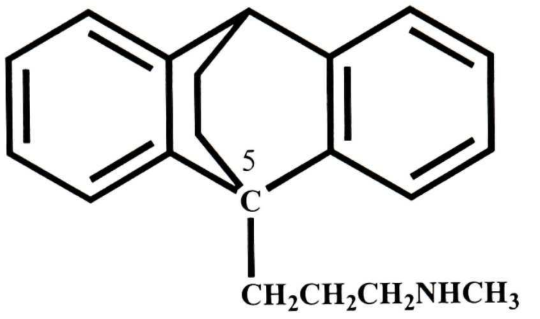
Empirical formula: $C_{19}H_{24}N_2$

Molecular weight: 280.40

Maprotiline:

Chemical name: N-Methyl-9,10-ethanoanthracene-9(10H)-propanamine

Chemical structure:



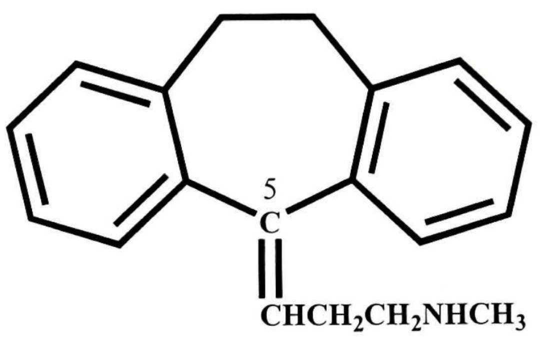
Empirical formula: $C_{20}H_{23}N$

Molecular weight: 277.41

Nortriptyline:

Chemical name: 3-(10,11-Dihydro-5H-dibenzo[a,d] cyclohepten-5-ylidene)-N-methyl-1-propanamine

Chemical structure:



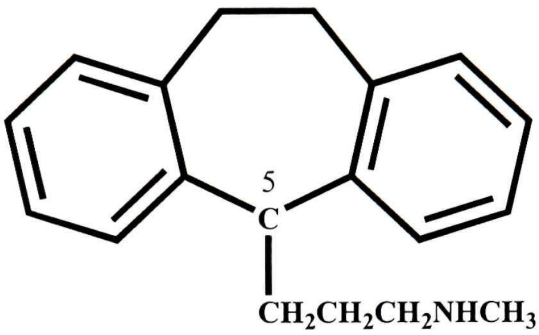
Empirical formula: $C_{19}H_{21}N$

Molecular weight: 263.37

Protriptyline:

Chemical name: N-Methyl-5H-dibenzo[a,d]cycloheptene-5-propanamine

Chemical structure:



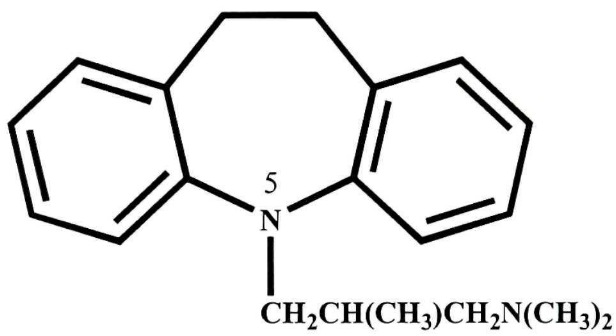
Empirical formula: $C_{19}H_{21}N$

Molecular weight: 263.37

Trimipramine:

Chemical name: 10,11-Dihydro-N,N,β-trimethyl-5H-dibenz[b,f]azepine-5-propanamine

Chemical structure:



Empirical formula: $C_{20}H_{26}N_2$

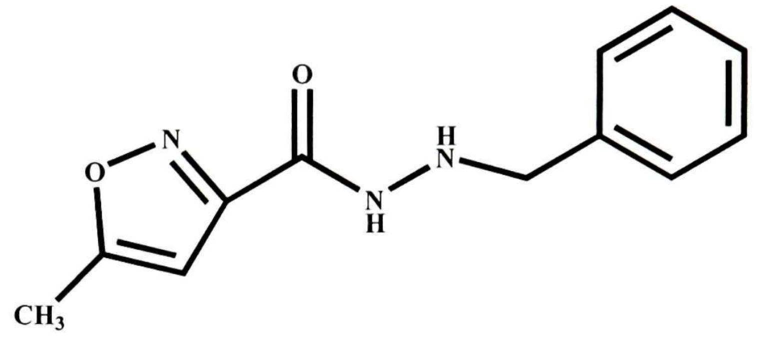
Molecular weight: 294.42

Appendix A.2: Monoamine oxidase inhibitor drugs

Isocarboxazid:

Chemical name: 5-Methyl-3-isoxazole-carboxylic acid 2-benzyl hydrazide

Chemical structure:



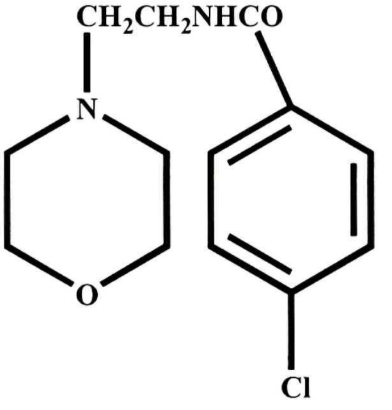
Empirical formula: $C_{12}H_{13}N_3O_2$

Molecular weight: 231.25

Moclobemide:

Chemical name: 4-Chloro-N-[2-(4-morpholinyl)-ethyl]benzamide

Chemical structure:



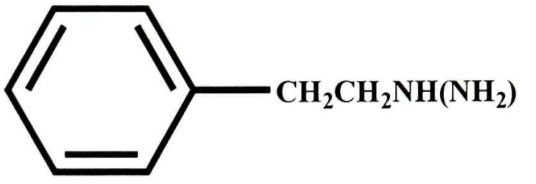
Empirical formula: $C_{13}H_{17}ClN_2O_2$

Molecular weight: 268.74

Phenelzine:

Chemical name: (2-Phenethyl)hydrazine

Chemical structure:



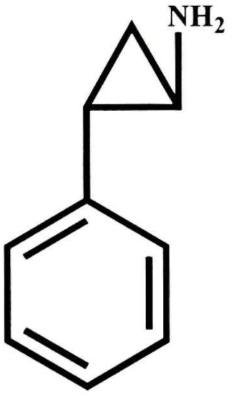
Empirical formula: $C_8H_{12}N_2$

Molecular weight: 136.19

Tranylcypromine:

Chemical name: Trans-(±)-2-Phenylcyclopropanamine

Chemical structure:



Empirical formula: $C_9H_{11}N$

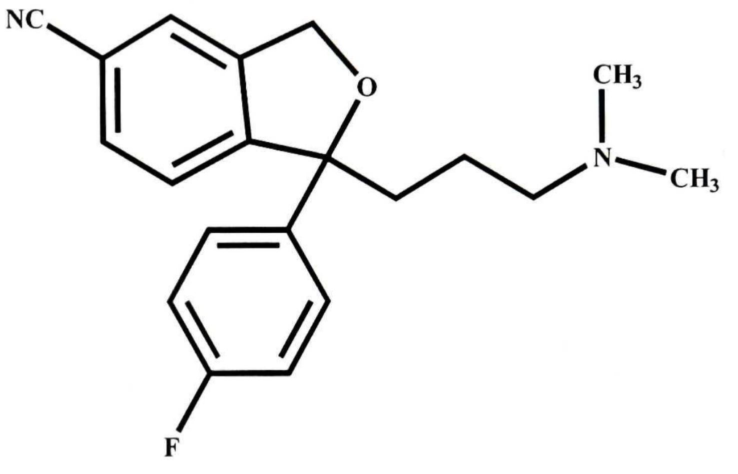
Molecular weight: 133.19

Appendix A.3: Selective serotonin reuptake inhibitor drugs

Citalopram:

Chemical name: 1-[3-(Dimethylamino)-propyl]-1-(4-fluorophenyl)-1,3-dizohydro-5-isobenzo-furancarbonitrile

Chemical structure:



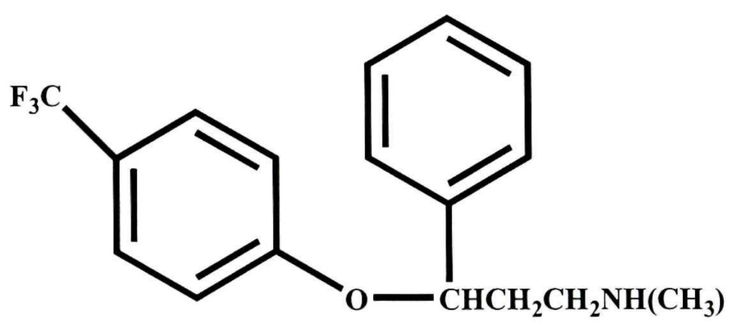
Empirical formula: $C_{20}H_{21}FN_2O$

Molecular weight: 324.39

Fluoxetine:

Chemical name: (±)-N-Methyl-γ-[4-(trifluoromethyl)phenoxy] benzenepropanamine

Chemical structure:



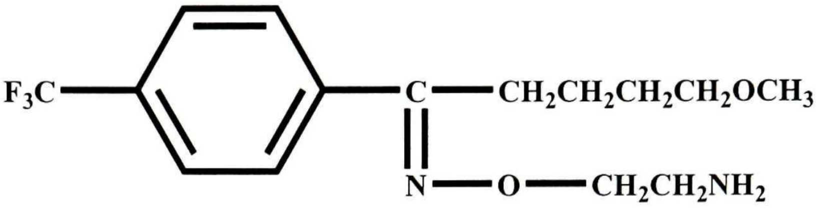
Empirical formula: $C_{17}H_{18}F_3NO$

Molecular weight: 309.33

Fluvoxamine:

Chemical name: 5-Methoxy-1-[4-(trifluoromethyl)-phenyl]-1-pentanone O-(2-aminoethyl)oxime

Chemical structure:



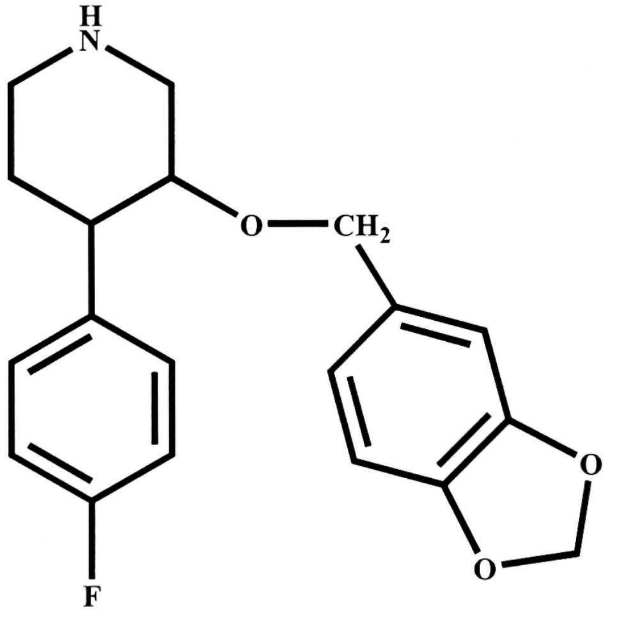
Empirical formula: $C_{15}H_{21}F_3N_2O_2$

Molecular weight: 318.35

Paroxetine:

Chemical name: Trans-(−)-3-[(1,3-Benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine

Chemical structure:



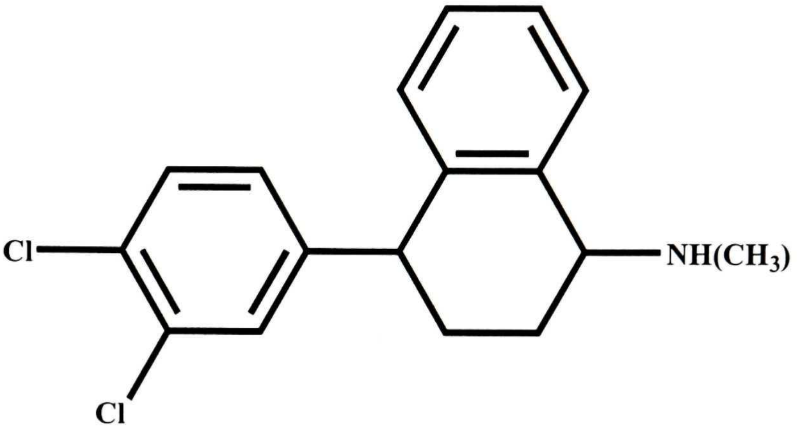
Empirical formula: $C_{19}H_{20}FNO_3$

Molecular weight: 329.37

Sertraline:

Chemical name: (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-nanphthalenamine

Chemical structure:



Empirical formula: $C_{17}H_{17}Cl_2N$

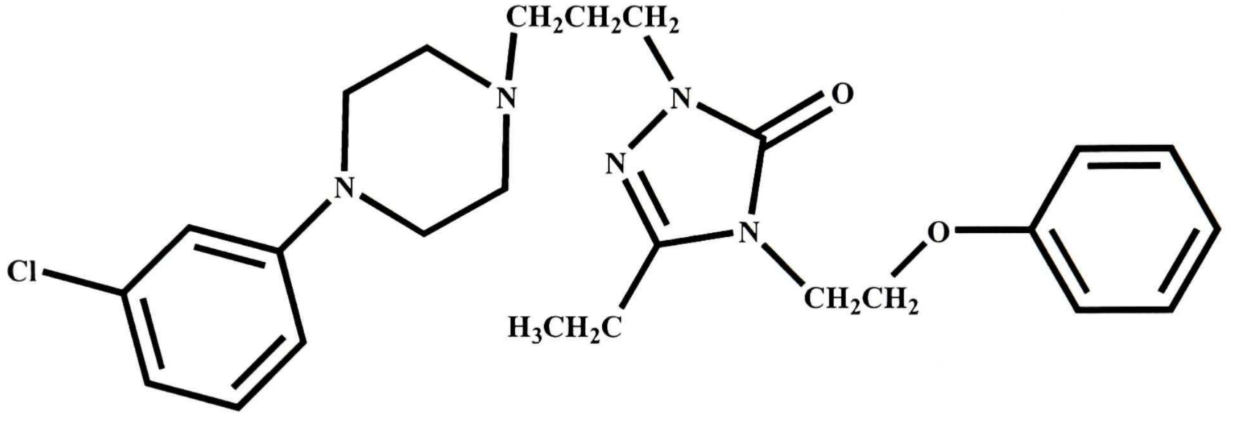
Molecular weight: 306.23

Appendix A.4: Atypical antidepressant drugs

Nefazodone:

Chemical name: 2-(3-(4-(3-chlorophenyl)-1-piperazinyl)propyl)-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one

Chemical structure:



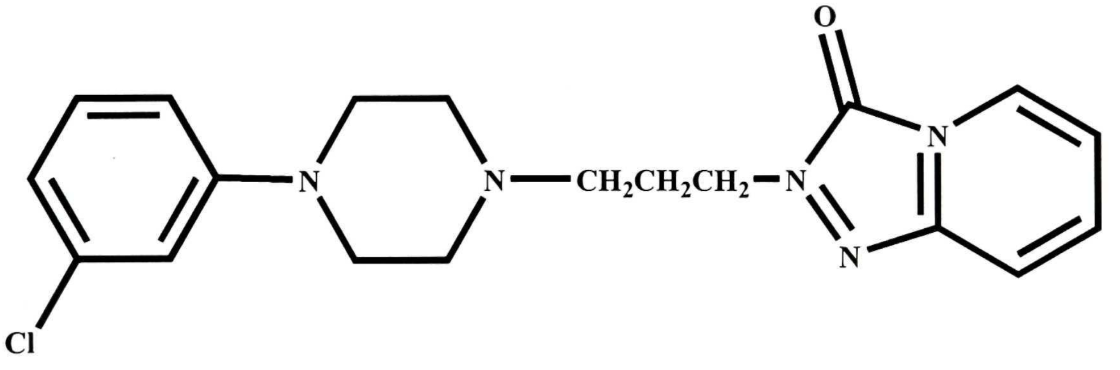
Empirical formula: $C_{25}H_{32}ClN_5O_2$

Molecular weight: 470.01

Trazodone:

Chemical name: 2-[3-[4-(3- Chlorophenyl)-1-piperazinyl]propyl]-1,2,4-triazolo[4,3-a]pyridine-3(2H)-one

Chemical structure:



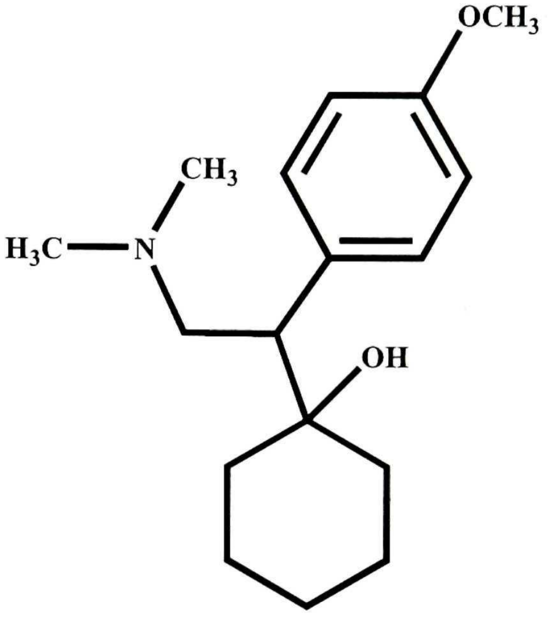
Empirical formula: $C_{19}H_{22}ClN_5O$

Molecular weight: 371.88

Venlafaxine:

Chemical name: (±)-1-[a[(dimethylamino)methyl]p-methoxybenzyl] cyclohexanol

Chemical structure:



Empirical formula: $C_{17}H_{27}NO_2$

Molecular weight: 277.40

Appendix B: Summary of the epidemiological studies assessing the association between antidepressant drug use and risk of cancer

Author	Drugs	Cancer site	Study design and sample size	Results
Friedman et al. 1980, 1983, and 1992 Selby et al. 1989	-215 drugs -TCAs: amitriptyline and imipramine	56 cancer sites	-Systematic screening, cohort study -143,574 subjects	-No significant association between TCAs and any cancer -Amitriptyline: SMR=1.07, 95% CI: 0.92–1.23 -Imipramine: SMR=0.77, 95% CI: 0.40–0.34
Danielson et al., 1982	-Nonestrogenic drugs -TCAs	Breast cancer	-Retrospective cohort -283,000 subjects	RR=0.5, 90% CI: 0.3–0.8
Wallace et al., 1982	-Psychotropic drugs -Antidepressants in general	Breast cancer	-Case-control -151 cases and matched hospital controls	RR=1.62, p-value > 0.2
Harlow et al., 1995	Antidepressants in general	Ovarian cancer	-Population-based case-control -450 cases and 454 matched controls	Women who initiated treatment before age 50: OR=3.5, 95% CI: 1.3-9.2
Harlow et al., 1998	Antidepressants in general	Ovarian cancer	-Population-based case-control -563 cases and 523 controls	-Use > 2years: OR=2.9, 95% CI: 1.3-6.6
Kelly et al., 1999	-TCAs -SSRIs	Breast cancer	-Hospital-based case-control -5814 cases -5095 cancer controls -5814 non-cancer controls	No significant association between any antidepressant and breast cancer
Dalton et al., 2000	-TCAs -MAOIs -SSRIs	All possible cancer sites	-Population-based cohort study -Average of 3.2 years follow-up -30,807 users	-Increased risk of non-Hodgkin's lymphoma (≥5 prescriptions) -SIR=2.5, 95% CI: 1.4-4.2

Coogan et al., 2000	TCAs and SSRIs	Ovarian cancer	-Case-control study -748 cases -1496 cancer controls -1496 non-cancer control	No significant association between any antidepressant and ovarian cancer
Cotterchio et al., 2000	-TCAs -SSRIs	Breast cancer	-Population-based case-control -701 cases -702 controls	No significant association between any antidepressant and breast cancer
Wang et al., 2001	Antidepressants in general	Breast cancer	-Retrospective cohort -38,273 antidepressant users -32.949 non-users	No significant association between any antidepressant and risk of breast cancer, HR =1.04, 95% CI: 0.87-1.25
Dublin et al., 2002	TCAs	Ovarian cancer	-Population-based case-control -314 cases -790 matched controls	No significant association between any antidepressant and risk of ovarian cancer OR =0.64, 95% CI: 0.36-1.1
Sharpe et al., 2002	TCAs	Breast cancer	-Population-based case-control -5,882 cases -23,517 population controls	-Heavy exposure to any TCA increased risk of breast cancer, 11-15 years later, RR=2.02, 95% CI: 1.34-3.04 -Heavy exposure to genotoxic TCAs increased risk of breast cancer 11-15 years later, RR=2.47, 95% CI: 1.37-4.40 as compared to non-genotoxic TCAs, RR=0.99, 95% CI: 0.49-1.99

Appendix C: Cut off points used for categorizing the 3 exposure indices, for the two classes of antidepressants (TCAs and SSRIs), for the four cancer sites

Exposure Index	Breast	Prostate	Ovarian	Non-Hodgkin's lymphoma
TCAs				
Cumulative dosage (moles)				
Low	0-0.015	0-0.015	0-0.025	0-0.02
High	0.015+	0.015+	0.025+	0.02+
Average daily dose (moles)				
Low	0-0.00001	0-0.00001	0-0.00001	0-0.00001
Medium	0.00001-0.00005	0.00001-0.00005	0.00001-0.00005	0.00001-0.00005
High	0.00005+	0.00005+	0.00005+	0.00005+
Duration (percentage)				
Short	0-10	0-10	0-10	0-10
Medium	10-40	10-40	10-40	10-40
Long	40+	40+	40+	40+
SSRIs				
Cumulative dosage (moles)				
Low	0-0.015	0-0.015	0-0.025	0-0.02
High	0.015+	0.015+	0.025+	0.02+
Average daily dose (moles)				
Low	0-0.00001	0-0.00001	0-0.00001	0-0.00001
Medium	0.00001-0.00005	0.00001-0.00005	0.00001-0.00005	0.00001-0.00005
High	0.00005+	0.00005+	0.00005+	0.00005+
Duration (percentage)				
Short	0-10	0-10	0-10	0-10
Medium	10-40	10-40	10-40	10-40
Long	40+	40+	40+	40+

Appendix D.1: Incidence of breast cancer as a function of average daily dose of genotoxic and non-genotoxic TCA exposure by time period before diagnosis for those aged 50 years or younger

eriod efore agnosis	Average daily dose	Non-Genotoxic TCAs				Genotoxic TCAs			
		Cases N=1539	Controls N=6147	Adjusted RR*	Adjusted 95% CI*	Cases N=1539	Controls N=6147	Adjusted RR*	Adjusted 95% CI*
5 years	**Unexposed**	1415	5729	1.00	Referent	1457	5805	1.00	Referent
	Low	83	211	1.63	1.25-2.14	41	167	0.95	0.67-1.36
	Medium	30	123	0.98	0.64-1.50	23	104	0.86	0.54-1.39
	High	11	84	0.53	0.27-1.04	18	71	1.01	0.55-1.83
	P-trend				*0.43*				*0.34*
	Other	-	-			-	-		
-10 ears	**Unexposed**	1069	4357	1.00	Referent	1094	4380	1.00	Referent
	Low	64	193	1.37	1.02-1.86	31	156	0.76	0.50-1.14
	Medium	16	69	0.96	0.54-1.72	17	73	0.89	0.50-1.56
	High	8	41	1.08	0.47-2.51	15	51	1.16	0.58-2.31
	P-trend				*0.29*				*0.95*
	Other	382	1487			382	1487		
1-15 ears	**Unexposed**	734	2913	1.00	Referent	733	2889	1.00	Referent
	Low	21	102	0.79	0.48-1.31	19	114	0.63	0.38-1.04
	Medium	12	32	1.59	0.77-3.29	12	38	1.12	0.56-2.27
	High	3	14	1.22	0.32-4.69	6	20	1.02	0.37-2.83
	P-trend				*0.57*				*0.53*
	Other	769	3086			769	3086		
6-20 ears	**Unexposed**	377	1453	1.00	Referent	366	1457	1.00	Referent
	Low	10	53	0.68	0.34-1.37	16	42	1.67	0.91-3.07
	Medium	3	12	0.74	0.19-2.94	7	19	1.63	0.63-4.22
	High	-	6	-	-	1	6	0.74	0.09-6.40
	P-trend				*0.32*				*0.64*
	Other	1149	4623			1149	4623		

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period
Non-genotoxic TCAs: regardless of any exposure to genotoxic TCAs
Genotoxic TCAs: regardless of any exposure to non-genotoxic TCAs

Appendix D.2: Incidence of breast cancer as a function of average daily dose of genotoxic and non-genotoxic TCA exposure by time period before diagnosis for those aged between 50 and 65 years of age

eriod efore agnosis	Average daily dose	Non-Genotoxic TCAs				Genotoxic TCAs			
		Cases N=2670	Controls N=10682	Adjusted RR*	Adjusted 95% CI*	Cases N=2670	Controls N=10682	Adjusted RR*	Adjusted 95% CI*
5 years	**Unexposed**	2442	9876	1.00	Referent	2467	10054	1.00	Referent
	Low	103	411	1.02	0.81-1.28	77	266	1.21	0.93-1.57
	Medium	61	203	1.17	0.87-1.59	57	169	1.40	1.02-1.92
	High	64	192	1.38	0.99-1.94	69	193	1.48	1.06-2.08
	P-trend				*0.42*				*0.44*
	Other	-	-			-	-		
-10 ears	**Unexposed**	1854	7451	1.00	Referent	1851	7443	1.00	Referent
	Low	88	366	0.95	0.74-1.21	80	331	0.94	0.73-1.21
	Medium	46	147	1.16	0.81-1.65	40	167	0.83	0.57-1.20
	High	37	138	0.89	0.56-1.40	54	161	1.04	0.69-1.57
	P-trend				*0.15*				*0.19*
	Other	645	2580			645	2580		
1-15 ears	**Unexposed**	1304	5109	1.00	Referent	1281	5096	1.00	Referent
	Low	53	258	0.76	0.55-1.04	57	227	1.03	0.76-1.40
	Medium	24	106	0.78	0.48-1.26	31	123	1.02	0.67-1.56
	High	21	75	0.97	0.54-1.74	33	102	1.47	0.89-2.41
	P-trend				*0.49*				*0.02*
	Other	1268	5134			1268	5134		
6-20 ears	**Unexposed**	651	2517	1.00	Referent	643	2494	1.00	Referent
	Low	28	115	0.95	0.62-1.45	33	118	1.07	0.72-1.61
	Medium	13	51	1.02	0.53-1.95	13	52	0.96	0.50-1.84
	High	5	36	0.51	0.19-1.36	8	55	0.38	0.16-0.88
	P-trend				*0.48*				*0.11*
	Other	1973	7963			1973	7963		

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period
Non-genotoxic TCAs: regardless of any exposure to genotoxic TCAs
Genotoxic TCAs: regardless of any exposure to non-genotoxic TCAs

Appendix D.3: Incidence of breast cancer as a function of average daily dose of genotoxic and non-genotoxic TCA exposure by time period before diagnosis for those aged 65 years or older

eriod efore iagnosis	Average daily dose	Non-Genotoxic TCAs				Genotoxic TCAs			
		Cases N=3121	Controls N=12491	Adjusted RR*	Adjusted 95% CI*	Cases N=3121	Controls N=12491	Adjusted RR*	Adjusted 95% CI*
-5 years	**Unexposed**	2882	11566	1.00	Referent	2897	11650	1.00	Referent
	Low	111	457	0.96	0.78-1.20	89	351	1.02	0.81-1.30
	Medium	55	214	0.98	0.72-1.34	62	222	1.14	0.85-1.53
	High	73	254	1.04	0.75-1.45	73	268	1.08	0.79-1.49
	P-trend				*0.74*				*0.61*
	Other	-	-			-	-		
-10 ears	**Unexposed**	2307	9228	1.00	Referent	2303	9224	1.00	Referent
	Low	97	436	0.88	0.70-1.11	99	389	1.02	0.81-1.29
	Medium	48	167	1.13	0.80-1.60	54	201	1.02	0.74-1.42
	High	55	182	1.25	0.83-1.90	51	199	0.83	0.55-1.26
	P-trend				*0.99*				*0.69*
	Other	614	2478			614	2478		
1-15 ears	**Unexposed**	1579	6300	1.00	Referent	1563	6202	1.00	Referent
	Low	70	256	1.11	0.84-1.47	72	313	0.93	0.71-1.22
	Medium	34	106	1.23	0.81-1.88	38	148	1.01	0.69-1.49
	High	28	118	0.76	0.46-1.26	38	117	1.28	0.80-2.06
	P-trend				*0.07*				*0.06*
	Other	1410	5711			1410	5711		
6-20 ears	**Unexposed**	725	2865	1.00	Referent	730	2822	1.00	Referent
	Low	37	151	1.04	0.71-1.52	26	152	0.65	0.42-0.99
	Medium	11	65	0.70	0.36-1.37	11	91	0.46	0.24-0.88
	High	16	38	1.63	0.84-3.16	22	54	1.37	0.78-2.50
	P-trend				*0.91*				*0.40*
	Other	2332	9372			2332	9372		

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period
Non-genotoxic TCAs: regardless of any exposure to genotoxic TCAs
Genotoxic TCAs: regardless of any exposure to non-genotoxic TCAs

Appendix E.1: Incidence of prostate cancer, for those having at least 20 years of history, as a function of two exposure indices of TCA drugs: ever/never and cumulative dosage exposure

TCA exposure				Cases N=2234	Controls N=8799	RR	95% CI
Ever/Never exposed							
All combined	2-20 years		Unexposed	1841	7431	1.00	Referent
			Any	393	1368	1.17	1.03-1.32
Categorized	2-20 years		Unexposed	1841	7431	1.00	Referent
			Genotoxic	130	480	1.06	0.86-1.30
			Non-Genotoxic	164	578	1.16	0.96-1.40
			Both	99	310	1.32	1.04-1.68
Cumulative dosage exposure							
All combined	2-20 years		Unexposed	1841	7431	1.00	Referent
			Low	195	633	1.28	1.08-1.52
			High	198	735	1.09	0.92-1.30
			P-trend				*0.33*
	6-20 years		Unexposed	1901	7634	1.00	Referent
			Low	155	546	1.18	0.98-1.43
			High	178	619	1.15	0.96-1.38
			P-trend				*0.43*
	11-20 years		Unexposed	1977	7917	1.00	Referent
			Low	116	399	1.19	0.96-1.48
			High	141	483	1.18	0.97-1.44
			P-trend				*0.41*
	16-20 years		Unexposed	2078	8262	1.00	Referent
			Low	68	261	1.08	0.82-1.42
			High	88	276	1.24	0.97-1.59
			P-trend				*0.35*
Categorized	2-20 years	Genotoxic	Unexposed	1841	7431	1.00	Referent
			Low	72	257	1.12	0.86-1.48
			High	58	223	0.99	0.73-1.34
			P-trend				*0.93*
		Non-Genotoxic	Unexposed	1841	7431	1.00	Referent
			Low	106	330	1.35	1.07-1.70
			High	58	248	0.92	0.68-1.24
			P-trend				*0.29*
	6-20 years	Genotoxic	Unexposed	1901	7634	1.00	Referent
			Low	70	242	1.19	0.90-1.57
			High	54	216	0.94	0.69-1.28
			P-trend				*0.54*
		Non-Genotoxic	Unexposed	1901	7634	1.00	Referent
			Low	73	267	1.16	0.89-1.53
			High	52	194	1.07	0.78-1.47
			P-trend				*0.38*
	11-20 years	Genotoxic	Unexposed	1977	7917	1.00	Referent
			Low	53	198	1.08	0.79-1.48
			High	47	185	0.98	0.70-1.36
			P-trend				*0.38*
		Non-Genotoxic	Unexposed	1977	7917	1.00	Referent
			Low	56	173	1.38	1.01-1.89
			High	42	148	1.18	0.83-1.69
			P-trend				*0.47*

16-20 years	Genotoxic	**Unexposed**	2078	8262	1.00	Referent
		Low	35	435	1.06	0.73-1.55
		High	33	111	1.22	0.82-1.81
		P-trend				*0.19*
	Non-Genotoxic	**Unexposed**	2078	8262	1.00	Referent
		Low	29	112	1.09	0.71-1.66
		High	26	82	1.20	0.77-1.88
		P-trend				*0.55*

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
All combined: both types of TCAs (genotoxic or non-genotoxic)
Genotoxic: exposure to genotoxic TCAs only
Non-genotoxic: exposure to non-genotoxic TCAs only
Both: exposure to both types of TCAs (genotoxic and non-genotoxic)

Appendix E.2: Incidence of prostate cancer, for those having at least 15 years of history, as a function of two exposure indices of TCA drugs: ever/never and cumulative dosage exposure

TCA exposure				Cases N=4693	Controls N=18655	RR	95% CI
Ever/Never exposed							
All combined	2-15 years		Unexposed	4008	16286	1.00	Referent
			Any	685	2369	1.18	1.07-1.29
Categorized	2-15 years		Unexposed	4008	16286	1.00	Referent
			Genotoxic	258	894	1.16	1.00-1.34
			Non-Genotoxic	289	990	1.20	1.04-1.38
			Both	138	485	1.17	0.96-1.42
Cumulative dosage exposure							
All combined	2-15 years		Unexposed	4008	16286	1.00	Referent
			Low	356	1114	1.32	1.16-1.50
			High	329	1255	1.07	0.94-1.22
			P-trend				*0.87*
	6-15 years		Unexposed	4173	16804	1.00	Referent
			Low	264	872	1.24	1.07-1.43
			High	256	979	1.05	0.91-1.21
			P-trend				*0.53*
	11-15 years		Unexposed	4362	17490	1.00	Referent
			Low	174	557	1.24	1.04-1.48
			High	157	608	1.05	0.88-1.26
			P-trend				*0.76*
Categorized	2-15 years	Genotoxic	Unexposed	4008	16286	1.00	Referent
			Low	150	458	1.33	1.09-1.61
			High	108	436	0.99	0.80-1.23
			P-trend				*0.36*
		Non-Genotoxic	Unexposed	4008	16286	1.00	Referent
			Low	183	585	1.29	1.08-1.53
			High	106	405	1.07	0.86-1.34
			P-trend				*0.43*
	6-15 years	Genotoxic	Unexposed	4173	16804	1.00	Referent
			Low	133	391	1.37	1.12-1.67
			High	84	386	0.87	0.68-1.11
			P-trend				*0.11*
		Non-Genotoxic	Unexposed	4173	16804	1.00	Referent
			Low	118	432	1.13	0.91-1.39
			High	79	303	1.05	0.82-1.36
			P-trend				*0.59*
	11-15 years	Genotoxic	Unexposed	4362	17490	1.00	Referent
			Low	94	275	1.34	1.06-1.71
			High	56	265	0.84	0.62-1.12
			P-trend				*0.24*
		Non-Genotoxic	Unexposed	4362	17490	1.00	Referent
			Low	75	257	1.17	0.90-1.51
			High	58	213	1.15	0.86-1.55
			P-trend				*0.75*

Appendix E.3: Incidence of prostate cancer, for those having at least 10 years of history, as a function of two exposure indices of TCA drugs: ever/never and cumulative dosage exposure

TCA exposure				Cases N=6308	Controls N=25143	RR	95% CI
Ever/Never exposed							
All combined	2-10 years		Unexposed	5621	22834	1.00	Referent
			Any	687	2309	1.21	1.10-1.32
Categorized	2-10 years		Unexposed	5621	22834	1.00	Referent
			Genotoxic	271	872	1.27	1.11-1.47
			Non-Genotoxic	311	1021	1.25	1.09-1.42
			Both	105	416	1.02	0.82-1.28
Cumulative dosage exposure							
All combined	2-10 years		Unexposed	5621	22834	1.00	Referent
			Low	351	1084	1.31	1.16-1.49
			High	336	1225	1.12	0.99-1.28
			P-trend				0.44
	6-10 years		Unexposed	5868	23618	1.00	Referent
			Low	220	691	1.29	1.10-1.50
			High	220	834	1.06	0.91-1.23
			P-trend				*0.45*
Categorized	2-10 years	Genotoxic	Unexposed	5621	22834	1.00	Referent
			Low	139	431	1.31	1.08-1.59
			High	132	441	1.24	1.02-1.52
			P-trend				*0.83*
		Non-Genotoxic	Unexposed	5621	22834	1.00	Referent
			Low	199	596	1.36	1.15-1.61
			High	112	425	1.10	0.88-1.36
			P-trend				*0.64*
	6-10 years	Genotoxic	Unexposed	5868	23618	1.00	Referent
			Low	105	295	1.44	1.15-1.81
			High	85	359	0.96	0.75-1.22
			P-trend				*0.13*
		Non-Genotoxic	Unexposed	5868	23618	1.00	Referent
			Low	110	358	1.24	1.00-1.54
			High	76	285	1.10	0.85-1.42
			P-trend				*0.67*

Appendix E.4: Incidence of prostate cancer, for those having at least 5 years of history, as a function of two exposure indices of TCA drugs: ever/never and cumulative dosage exposure

TCA exposure				Cases N=7767	Controls N=31068	RR	95% CI
Ever/Never exposed							
All combined	**2-5 years**		**Unexposed**	7230	29361	1.00	Referent
			Any	537	1707	1.28	1.16-1.41
Categorized	**2-5 years**		**Unexposed**	7230	29361	1.00	Referent
			Genotoxic	224	709	1.30	1.12-1.52
			Non-Genotoxic	259	812	1.30	1.13-1.50
			Both	54	186	1.19	0.87-1.61
Cumulative dosage exposure							
All combined	**2-5 years**		**Unexposed**	7230	29361	1.00	Referent
			Low	279	841	1.35	1.18-1.55
			High	258	866	1.22	1.06-1.41
			P-trend				*0.98*
Categorized	**2-5 years**	**Genotoxic**	**Unexposed**	7230	29361	1.00	Referent
			Low	110	347	1.29	1.04-1.60
			High	114	362	1.31	1.05-1.62
			P-trend				*0.35*
		Non-Genotoxic	**Unexposed**	7230	29361	1.00	Referent
			Low	158	465	1.39	1.16-1.68
			High	101	347	1.19	0.95-1.49
			P-trend				*0.74*

Appendix E.5: Incidence of prostate cancer as a function of average daily dose of TCA exposure by time period before diagnosis

	TCA exposure						
Period before diagnosis	**Average daily dose**	**Cases N=7767**	**Controls N=31068**	**Crude**		**Adjusted***	
				RR	**95% CI**	**RR**	**95% C**
2-5 years	**Unexposed**	7230	29361	1.00	Referent	1.00	Referen
	Low	276	835	1.34	1.17-1.54	1.31	1.14-1.5
	Medium	141	428	1.34	1.11-1.62	1.33	1.09-1.6
	High	120	444	1.10	0.90-1.35	1.20	0.94-1.5
	P-trend				*0.98*		*0.82*
	Other	-	-				
6-10 years	**Unexposed**	5868	23618	1.00	Referent	1.00	Referent
	Low	244	769	1.28	1.10-1.48	1.19	1.02-1.3
	Medium	112	381	1.19	0.96-1.47	1.05	0.84-1.3
	High	84	375	0.90	0.71-1.14	0.76	0.56-1.0
	P-trend				*0.48*		*0.08*
	Other	1459	5925				
11-15 years	**Unexposed**	4362	17490	1.00	Referent	1.00	Referent
	Low	193	620	1.25	1.06-1.47	1.18	1.00-1.4
	Medium	76	310	0.98	0.76-1.27	0.91	0.70-1.1
	High	62	235	1.06	0.80-1.40	1.04	0.74-1.4
	P-trend				*0.72*		*0.58*
	Other	3074	12413				
16-20 years	**Unexposed**	2078	8262	1.00	Referent	1.00	Referent
	Low	77	295	1.04	0.80-1.34	0.99	0.77-1.2
	Medium	50	126	1.58	1.13-2.20	1.52	1.08-2.1
	High	29	116	0.99	0.66-1.50	0.99	0.64-1.5
	P-trend				*0.33*		*0.26*
	Other	5533	22269				

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period

Appendix E.6: Incidence of prostate cancer as a function of duration of TCA exposure by time period before diagnosis

Period before diagnosis	TCA exposure Duration	Cases N=7767	Controls N=31068	Crude RR	Crude 95% CI	Adjusted* RR	Adjusted* 95% CI
2-5 years	**Unexposed**	7230	29365	1.00	Referent	1.00	Referent
	Short	230	707	1.32	1.14-1.54	1.29	1.11-1.51
	Medium	192	566	1.38	1.17-1.63	1.35	1.14-1.61
	Long	115	430	1.09	0.88-1.34	1.12	0.88-1.43
	P-trend				*0.09*		*0.13*
	Other	-	-				
6-10 years	**Unexposed**	5872	23635	1.00	Referent	1.00	Referent
	Short	251	825	1.22	1.06-1.41	1.14	0.99-1.32
	Medium	110	392	1.13	0.91-1.40	1.02	0.81-1.27
	Long	77	301	1.03	0.80-1.33	0.93	0.68-1.28
	P-trend				*0.85*		*0.27*
	Other	1457	5915				
11-15 years	**Unexposed**	4382	17565	1.00	Referent	1.00	Referent
	Short	209	710	1.18	1.01-1.38	1.11	0.95-1.31
	Medium	82	279	1.18	0.92-1.52	1.05	0.81-1.37
	Long	40	180	0.89	0.63-1.26	0.74	0.49-1.12
	P-trend				*0.64*		*0.55*
	Other	3054	12334				
16-20 years	**Unexposed**	2090	8330	1.00	Referent	1.00	Referent
	Short	93	318	1.16	0.92-1.47	1.11	0.88-1.41
	Medium	44	136	1.29	0.91-1.82	1.25	0.88-1.79
	Long	24	81	1.18	0.75-1.86	1.34	0.80-2.25
	P-trend				*0.39*		*0.28*
	Other	5516	22203				

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period

Appendix E.7: Incidence of prostate cancer, for those having at least 10 years of history, as a function of two exposure indices of SSRI drugs: ever/never and cumulative dosage exposure

SSRI exposure			Cases N=5346	Controls N=21384	RR	95% CI
Ever/Never exposed						
	2-10 years	**Unexposed**	5237	20942	1.00	Referent
		Any	109	442	0.99	0.80-1.22
Cumulative dosage exposure						
	2-10 years	**Unexposed**	5237	20942	1.00	Referent
		Low	61	266	0.92	0.69-1.22
		High	48	176	1.09	0.79-1.50
		P-trend				*0.37*
	6-10 years	**Unexposed**	5313	21252	1.00	Referent
		Low	23	90	1.03	0.65-1.63
		High	10	42	0.94	0.47-1.87
		P-trend				*0.70*

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
Unexposed: no exposure to any SSRI
Any: exposure to any SSRI

Appendix E.8: Incidence of prostate cancer, for those having at least 5 years of history, as a function of two exposure indices of SSRI drugs: ever/never and cumulative dosage exposure

SSRI exposure			Cases N=5346	Controls N=21384	RR	95% CI
Ever/Never exposed						
	2-5 years	**Unexposed**	5255	21019	1.00	Referent
		Any	91	365	1.00	0.79-1.26
Cumulative dosage exposure						
	2-5 years	**Unexposed**	5255	21019	1.00	Referent
		Low	50	220	0.91	0.67-1.24
		High	41	145	1.13	0.80-1.60
		P-trend				*0.25*

Appendix F.1: Incidence of ovarian cancer, for those having at least 20 years of history, as a function of two exposure indices of TCA drugs: ever/never and cumulative dosage exposure

TCA exposure				Cases N=241	Controls N=1008	RR	95% CI
Ever/Never exposed							
All combined	**2-20 years**		**Unexposed**	169	736	1.00	Referent
			Any	72	272	1.10	0.81-1.50
Categorized	**2-20 years**		**Unexposed**	169	736	1.00	Referent
			Genotoxic	25	71	1.33	0.81-2.20
			Non-Genotoxic	30	114	1.11	0.70-1.76
			Both	17	87	0.81	0.46-1.42
Cumulative dosage exposure							
All combined	**2-20 years**		**Unexposed**	169	736	1.00	Referent
			Low	34	147	0.97	0.64-1.49
			High	38	125	1.23	0.81-1.86
			P-trend				*0.03*
	6-20 years		**Unexposed**	178	774	1.00	Referent
			Low	32	123	1.07	0.69-1.66
			High	31	111	1.17	0.75-1.82
			P-trend				*0.19*
	11-20 years		**Unexposed**	196	826	1.00	Referent
			Low	22	97	0.92	0.56-1.51
			High	23	85	1.16	0.70-1.93
			P-trend				*0.57*
	16-20 years		**Unexposed**	210	880	1.00	Referent
			Low	19	69	1.13	0.65-1.95
			High	12	59	0.89	0.46-1.72
			P-trend				*0.96*
Categorized	**2-20 years**	**Genotoxic**	**Unexposed**	169	736	1.00	Referent
			Low	13	41	1.15	0.59-2.53
			High	12	30	1.55	0.74-3.24
			P-trend				*0.06*
		Non-Genotoxic	**Unexposed**	169	736	1.00	Referent
			Low	17	88	0.85	0.48-1.50
			High	13	26	1.87	0.85-4.08
			P-trend				*0.03*
	6-20 years	**Genotoxic**	**Unexposed**	178	774	1.00	Referent
			Low	12	41	1.08	0.55-2.13
			High	11	34	1.24	0.60-2.55
			P-trend				*0.40*
		Non-Genotoxic	**Unexposed**	178	774	1.00	Referent
			Low	16	69	0.93	0.51-1.71
			High	9	20	1.87	0.77-4.53
			P-trend				*0.07*
	11-20 years	**Genotoxic**	**Unexposed**	196	826	1.00	Referent
			Low	12	43	1.01	0.52-1.96
			High	9	28	1.24	0.55-2.80
			P-trend				*0.70*
		Non-Genotoxic	**Unexposed**	196	826	1.00	Referent
			Low	9	47	0.81	0.38-1.73
			High	8	20	1.86	0.75-4.62
			P-trend				*0.19*

		Unexposed	210	880	1.00	Referent
	Genotoxic	**Low**	9	37	0.92	0.43-1.95
		High	5	20	1.07	0.38-3.03
16-20 years		***P-trend***				*0.98*
		Unexposed	210	880	1.00	Referent
	Non-Genotoxic	**Low**	8	30	1.31	0.56-3.03
		High	3	17	0.93	0.26-3.34
		P-trend				*0.66*

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
All combined: both types of TCAs (genotoxic or non-genotoxic)
Genotoxic: exposure to genotoxic TCAs only
Non-genotoxic: exposure to non-genotoxic TCAs only
Both: exposure to both types of TCAs (genotoxic and non-genotoxic)

Appendix F.2: Incidence of ovarian cancer, for those having at least 15 years of history, as a function of two exposure indices of TCA drugs: ever/never and cumulative dosage exposure

TCA exposure				Cases N=553	Controls N=2216	RR	95% CI
Ever/Never exposed							
All combined	**2-15 years**		**Unexposed**	418	1697	1.00	Referent
			Any	135	519	1.05	0.84-1.30
Categorized	**2-15 years**		**Unexposed**	418	1697	1.00	Referent
			Genotoxic	56	153	1.41	1.01-1.97
			Non-Genotoxic	49	218	0.96	0.68-1.35
			Both	30	148	0.87	0.57-1.33
Cumulative dosage exposure							
All combined	**2-15 years**		**Unexposed**	418	1697	1.00	Referent
			Low	78	290	1.09	0.82-1.44
			High	57	229	1.03	0.75-1.42
			P-trend				*0.25*
	6-15 years		**Unexposed**	446	1800	1.00	Referent
			Low	58	232	1.01	0.74-1.39
			High	49	184	1.07	0.76-1.50
			P-trend				*0.33*
	11-15 years		**Unexposed**	483	1944	1.00	Referent
			Low	42	152	1.14	0.79-1.64
			High	28	120	0.91	0.59-1.39
			P-trend				*0.58*
Categorized	**2-15 years**	**Genotoxic**	**Unexposed**	418	1697	1.00	Referent
			Low	35	94	1.31	0.86-1.98
			High	21	59	1.60	0.94-2.75
			P-trend				*0.04*
		Non-Genotoxic	**Unexposed**	418	1697	1.00	Referent
			Low	33	161	0.89	0.59-1.34
			High	16	57	1.14	0.63-2.07
			P-trend				*0.05*
	6-15 years	**Genotoxic**	**Unexposed**	446	1800	1.00	Referent
			Low	30	82	1.39	0.89-2.15
			High	19	56	1.43	0.82-2.49
			P-trend				*0.09*
		Non-Genotoxic	**Unexposed**	446	1800	1.00	Referent
			Low	22	124	0.78	0.48-1.27
			High	14	41	1.35	0.70-2.60
			P-trend				*0.08*
	11-15 years	**Genotoxic**	**Unexposed**	483	1944	1.00	Referent
			Low	26	69	1.58	0.98-2.54
			High	13	40	1.35	0.70-2.60
			P-trend				*0.39*
		Non-Genotoxic	**Unexposed**	483	1944	1.00	Referent
			Low	14	69	0.85	0.47-1.55
			High	9	39	0.87	0.41-1.83
			P-trend				*0.64*

Appendix F.3: Incidence of ovarian cancer, for those having at least 10 years of history, as a function of two exposure indices of TCA drugs: ever/never and cumulative dosage exposure

TCA exposure				Cases N=813	Controls N=3268	RR	95% CI
Ever/Never exposed							
All combined	2-10 years		Unexposed	665	2658	1.00	Referent
			Any	148	610	0.96	0.79-1.18
Categorized	2-10 years		Unexposed	665	2658	1.00	Referent
			Genotoxic	54	201	1.02	0.74-1.40
			Non-Genotoxic	60	278	0.89	0.66-1.19
			Both	34	131	1.04	0.70-1.56
Cumulative dosage exposure							
All combined	2-10 years		Unexposed	665	2658	1.00	Referent
			Low	78	348	0.90	0.69-1.17
			High	70	262	1.06	0.80-1.41
			P-trend				*0.06*
	6-10 years		Unexposed	706	2852	1.00	Referent
			Low	55	240	0.93	0.69-1.27
			High	52	176	1.18	0.85-1.63
			P-trend				*0.03*
Categorized	2-10 years	Genotoxic	Unexposed	665	2658	1.00	Referent
			Low	33	119	1.03	0.69-1.54
			High	21	82	1.04	0.63-1.72
			P-trend				*0.67*
		Non-Genotoxic	Unexposed	665	2658	1.00	Referent
			Low	37	194	0.82	0.57-1.19
			High	23	84	1.06	0.65-1.71
			P-trend				*0.02*
	6-10 years	Genotoxic	Unexposed	706	2852	1.00	Referent
			Low	27	95	1.10	0.71-1.71
			High	15	64	0.93	0.52-1.65
			P-trend				*0.84*
		Non-Genotoxic	Unexposed	706	2852	1.00	Referent
			Low	26	129	0.86	0.56-1.33
			High	24	59	1.69	1.03-2.78
			P-trend				*0.004*

Appendix F.4: Incidence of ovarian cancer, for those having at least 5 years of history, as a function of two exposure indices of TCA drugs: ever/never and cumulative dosage exposure

TCA exposure				Cases N=1090	Controls N=4360	RR	95% CI
Ever/Never exposed							
All combined	2-5 years		Unexposed	954	3836	1.00	Referent
			Any	136	524	1.04	0.85-1.28
Categorized	2-5 years		Unexposed	954	3836	1.00	Referent
			Genotoxic	50	183	1.07	0.77-1.47
			Non-Genotoxic	61	259	0.94	0.71-1.26
			Both	25	82	1.26	0.79-2.01
Cumulative dosage exposure							
All combined	2-5 years		Unexposed	954	3836	1.00	Referent
			Low	66	297	0.89	0.67-1.17
			High	70	227	1.29	0.97-1.71
			P-trend				*0.31*
Categorized	2-5 years	Genotoxic	Unexposed	954	3836	1.00	Referent
			Low	29	110	1.01	0.66-1.53
			High	21	73	1.18	0.72-1.95
			P-trend				*0.82*
		Non-Genotoxic	Unexposed	954	3836	1.00	Referent
			Low	35	161	0.89	0.61-1.29
			High	26	98	1.08	0.69-1.68
			P-trend				*0.27*

Appendix F.5: Incidence of ovarian cancer as a function of average daily dose of TCA exposure by time period before diagnosis

	TCA exposure						
Period before diagnosis	**Average daily dose**	**Cases N=1090**	**Controls N=4360**	**Crude**		**Adjusted***	
				RR	**95% CI**	**RR**	**95% C**
2-5 years	**Unexposed**	954	3836	1.00	Referent	1.00	Referen
	Low	54	229	0.95	0.70-1.28	0.95	0.70-1.2
	Medium	34	142	0.96	0.66-1.41	0.96	0.64-1.4
	High	48	153	1.26	0.91-1.76	1.23	0.82-1.8
	P-trend				*0.31*		*0.63*
	Other	-	-				
6-10 years	**Unexposed**	706	2852	1.00	Referent	1.00	Referen
	Low	51	220	0.94	0.68-1.28	0.93	0.67-1.2
	Medium	26	109	0.97	0.63-1.49	0.97	0.61-1.5
	High	30	87	1.40	0.92-2.14	1.53	0.88-2.6
	P-trend				*0.02*		*0.01*
	Other	277	1092				
11-15 years	**Unexposed**	483	1944	1.00	Referent	1.00	Referen
	Low	39	135	1.17	0.80-1.70	1.13	0.77-1.6
	Medium	19	71	1.08	0.64-1.81	1.02	0.59-1.7
	High	12	66	0.73	0.39-1.36	0.53	0.25-1.1
	P-trend				*0.45*		*0.79*
	Other	537	2144				
16-20 years	**Unexposed**	210	880	1.00	Referent	1.00	Referen
	Low	18	67	1.13	0.65-1.95	1.13	0.65-1.9
	Medium	8	33	1.02	0.46-2.24	1.09	0.49-2.4
	High	5	28	0.75	0.29-1.95	0.88	0.32-2.4
	P-trend				*0.91*		*0.79*
	Other	849	3352				

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period

Appendix F.6: Incidence of ovarian cancer as a function of duration of TCA exposure by time period before diagnosis

Period before diagnosis	TCA exposure: Duration	Cases N=1090	Controls N=4360	Crude RR	Crude 95% CI	Adjusted* RR	Adjusted* 95% C
2-5 years	**Unexposed**	954	3838	1.00	Referent	1.00	Referen
	Short	43	189	0.92	0.66-1.29	0.93	0.66-1.3
	Medium	43	185	0.93	0.66-1.31	0.97	0.68-1.3
	Long	50	148	1.36	0.98-1.90	1.38	0.92-2.0
	P-trend				*0.33*		*0.55*
	Other	-	-				
6-10 years	**Unexposed**	706	2852	1.00	Referent	1.00	Referen
	Short	58	224	1.05	0.78-1.42	1.05	0.77-1.4
	Medium	22	112	0.79	0.50-1.26	0.76	0.46-1.2
	Long	27	80	1.37	0.88-2.15	1.27	0.69-2.3
	P-trend				*0.29*		*0.59*
	Other	277	1092				
11-15 years	**Unexposed**	484	1946	1.00	Referent	1.00	Referen
	Short	40	142	1.14	0.79-1.64	1.10	0.76-1.6
	Medium	17	82	0.83	0.49-1.42	0.78	0.44-1.3
	Long	13	51	1.02	0.55-1.89	0.77	0.35-1.6
	P-trend				*0.87*		*0.34*
	Other	536	2139				
16-20 years	**Unexposed**	212	885	1.00	Referent	1.00	Referen
	Short	19	72	1.10	0.64-1.87	1.11	0.64-1.9
	Medium	6	40	0.62	0.26-1.48	0.66	0.27-1.6
	Long	6	18	1.42	0.55-3.67	1.39	0.49-3.9
	P-trend				*0.61*		*0.52*
	Other	847	3345				

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period

Appendix F.7: Incidence of ovarian cancer, for those having at least 10 years of history, as a function of two exposure indices of SSRI drugs: ever/never and cumulative dosage exposure

SSRI exposure			Cases N=672	Controls N=2688	RR	95% CI
Ever/Never exposed						
	2-10 years	**Unexposed**	648	2582	1.00	Referent
		Any	24	106	0.90	0.57-1.42
Cumulative dosage exposure						
	2-10 years	**Unexposed**	648	2582	1.00	Referent
		Low	16	67	0.97	0.56-1.70
		High	8	39	0.79	0.36-1.72
		P-trend				*0.44*
	6-10 years	**Unexposed**	663	2660	1.00	Referent
		Low	5	22	0.90	0.34-2.39
		High	4	6	2.59	0.73-9.19
		P-trend				*0.14*

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
Unexposed: no exposure to any SSRI
Any: exposure to any SSRI

Appendix F.8: Incidence of ovarian cancer, for those having at least 5 years of history, as a function of two exposure indices of SSRI drugs: ever/never and cumulative dosage exposure

SSRI exposure			Cases N=672	Controls N=2688	RR	95% CI
Ever/Never exposed						
	2-5 years	**Unexposed**	652	2597	1.00	Referent
		Any	20	91	0.87	0.53-1.44
Cumulative dosage exposure						
	2-5 years	**Unexposed**	652	2597	1.00	Referent
		Low	12	54	0.91	0.48-1.72
		High	8	37	0.84	0.38-1.84
		P-trend				*0.70*

Appendix G.1: Incidence of non-Hodgkin's lymphoma, for those having at least 20 years of history, as a function of two exposure indices of TCA drugs: ever/never and cumulative dosage exposure

TCA exposure				Cases N=502	Controls N=1970	RR	95% CI
Ever/Never exposed							
All combined	2-20 years		Unexposed	403	1534	1.00	Referent
			Any	99	436	0.84	0.66-1.09
Categorized	2-20 years		Unexposed	403	1534	1.00	Referent
			Genotoxic	35	135	1.02	0.68-1.52
			Non-Genotoxic	38	186	0.68	0.46-1.01
			Both	26	115	0.79	0.50-1.23
Cumulative dosage exposure							
All combined	2-20 years		Unexposed	403	1534	1.00	Referent
			Low	49	227	0.82	0.58-1.16
			High	50	209	0.84	0.60-1.18
			P-trend				*0.70*
	6-20 years		Unexposed	421	1598	1.00	Referent
			Low	43	194	0.85	0.60-1.22
			High	38	178	0.77	0.53-1.13
			P-trend				*0.82*
	11-20 years		Unexposed	435	1693	1.00	Referent
			Low	37	147	0.96	0.65-1.40
			High	30	130	0.85	0.55-1.29
			P-trend				*0.32*
	16-20 years		Unexposed	465	1786	1.00	Referent
			Low	19	96	0.73	0.44-1.21
			High	18	88	0.78	0.46-1.32
			P-trend				*0.71*
Categorized	2-20 years	Genotoxic	Unexposed	403	1534	1.00	Referent
			Low	19	79	0.98	0.58-1.68
			High	16	56	1.08	0.60-1.94
			P-trend				*0.29*
		Non-Genotoxic	Unexposed	403	1534	1.00	Referent
			Low	24	128	0.68	0.42-1.09
			High	14	58	0.72	0.37-1.41
			P-trend				*0.29*
	6-20 years	Genotoxic	Unexposed	421	1598	1.00	Referent
			Low	15	76	0.70	0.39-1.26
			High	14	57	0.90	0.49-1.66
			P-trend				*0.85*
		Non-Genotoxic	Unexposed	421	1598	1.00	Referent
			Low	22	104	0.82	0.50-1.34
			High	6	44	0.38	0.14-1.09
			P-trend				*0.22*
	11-20 years	Genotoxic	Unexposed	435	1693	1.00	Referent
			Low	16	62	0.93	0.52-1.64
			High	12	49	0.88	0.46-1.68
			P-trend				*0.61*
		Non-Genotoxic	Unexposed	435	1693	1.00	Referent
			Low	18	73	0.98	0.57-1.69
			High	4	27	0.47	0.14-1.58
			P-trend				*0.42*

		Unexposed	465	1786	1.00	Referent
	Genotoxic	**Low**	7	43	0.56	0.25-1.27
		High	8	40	0.73	0.34-1.58
16-20 years		***P-trend***				*0.64*
		Unexposed	465	1786	1.00	Referent
	Non-Genotoxic	**Low**	10	46	0.84	0.42-1.71
		High	3	17	0.81	0.23-2.88
		P-trend				*0.95*

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
All combined: both types of TCAs (genotoxic or non-genotoxic)
Genotoxic: exposure to genotoxic TCAs only
Non-genotoxic: exposure to non-genotoxic TCAs only
Both: exposure to both types of TCAs (genotoxic and non-genotoxic)

Appendix G.2: Incidence of non-Hodgkin's lymphoma, for those having at least 15 years of history, as a function of two exposure indices of TCA drugs: ever/never and cumulative dosage exposure

TCA exposure				Cases N=1030	Controls N=4054	RR	95% CI
Ever/Never exposed							
All combined	2-15 years		Unexposed	833	3285	1.00	Referent
			Any	197	769	1.03	0.86-1.22
Categorized	2-15 years		Unexposed	833	3285	1.00	Referent
			Genotoxic	76	282	1.08	0.83-1.41
			Non-Genotoxic	68	301	0.91	0.69-1.21
			Both	53	1886	1.10	0.79-1.52
Cumulative dosage exposure							
All combined	2-15 years		Unexposed	833	3285	1.00	Referent
			Low	98	386	1.02	0.81-1.30
			High	99	383	1.05	0.82-1.33
			P-trend				*0.20*
	6-15 years		Unexposed	881	3456	1.00	Referent
			Low	73	298	0.97	0.74-1.28
			High	76	300	1.02	0.78-1.34
			P-trend				*0.24*
	11-15 years		Unexposed	928	3677	1.00	Referent
			Low	53	205	1.07	0.78-1.47
			High	49	172	1.16	0.83-1.62
			P-trend				*0.17*
Categorized	2-15 years	Genotoxic	Unexposed	833	3285	1.00	Referent
			Low	43	158	1.06	0.75-1.50
			High	33	124	1.15	0.76-1.72
			P-trend				*0.01*
		Non-Genotoxic	Unexposed	833	3285	1.00	Referent
			Low	42	197	0.86	0.61-1.23
			High	26	104	1.00	0.64-1.58
			P-trend				*0.10*
	6-15 years	Genotoxic	Unexposed	881	3456	1.00	Referent
			Low	32	134	0.90	0.61-1.34
			High	33	113	1.17	0.78-1.75
			P-trend				*0.09*
		Non-Genotoxic	Unexposed	881	3456	1.00	Referent
			Low	33	139	0.97	0.65-1.45
			High	12	81	0.59	0.32-1.10
			P-trend				*0.12*
	11-15 years	Genotoxic	Unexposed	928	3677	1.00	Referent
			Low	29	101	1.16	0.76-1.78
			High	24	68	1.45	0.90-2.33
			P-trend				*0.03*
		Non-Genotoxic	Unexposed	928	3677	1.00	Referent
			Low	20	94	0.90	0.55-1.47
			High	7	53	0.54	0.24-1.21
			P-trend				*0.22*

Appendix G.3: Incidence of non-Hodgkin's lymphoma, for those having at least 10 years of history, as a function of two exposure indices of TCA drugs: ever/never and cumulative dosage exposure

TCA exposure				Cases N=1541	Controls N=6200	RR	95% CI
Ever/Never exposed							
All combined	**2-10 years**		**Unexposed**	1305	5279	1.00	Referent
			Any	236	921	1.04	0.89-1.21
Categorized	**2-10 years**		**Unexposed**	1305	5279	1.00	Referent
			Genotoxic	93	343	1.08	0.85-1.37
			Non-Genotoxic	100	383	1.07	0.85-1.35
			Both	43	195	0.88	0.62-1.24
Cumulative dosage exposure							
All combined	**2-10 years**		**Unexposed**	1305	5279	1.00	Referent
			Low	122	480	1.04	0.84-1.29
			High	114	441	1.04	0.83-1.29
			P-trend				*0.15*
	6-10 years		**Unexposed**	1390	5590	1.00	Referent
			Low	80	319	0.99	0.77-1.28
			High	71	291	0.97	0.74-1.28
			P-trend				*0.14*
Categorized	**2-10 years**	**Genotoxic**	**Unexposed**	1305	5279	1.00	Referent
			Low	53	188	1.09	0.80-1.49
			High	40	155	1.04	0.73-1.50
			P-trend				*0.02*
		Non-Genotoxic	**Unexposed**	1305	5279	1.00	Referent
			Low	57	252	0.95	0.70-1.29
			High	43	131	1.31	0.91-1.88
			P-trend				*0.87*
	6-10 years	**Genotoxic**	**Unexposed**	1390	5590	1.00	Referent
			Low	33	135	0.92	0.62-1.36
			High	32	117	1.05	0.70-1.57
			P-trend				*0.13*
		Non-Genotoxic	**Unexposed**	1390	5590	1.00	Referent
			Low	39	153	1.04	0.73-1.50
			High	24	94	1.02	0.64-1.61
			P-trend				*0.72*

Appendix G.4: Incidence of non-Hodgkin's lymphoma, for those having at least 5 years of history, as a function of two exposure indices of TCA drugs: ever/never and cumulative dosage exposure

TCA exposure				Cases N=1980	Controls N=7920	RR	95% CI
Ever/Never exposed							
All combined	2-5 years		Unexposed	1765	7214	1.00	Referent
			Any	215	706	1.25	1.06-1.47
Categorized	2-5 years		Unexposed	1765	7214	1.00	Referent
			Genotoxic	84	284	1.20	0.93-1.54
			Non-Genotoxic	102	316	1.34	1.06-1.69
			Both	29	106	1.19	0.78-1.82
Cumulative dosage exposure							
All combined	2-5 years		Unexposed	1765	7214	1.00	Referent
			Low	106	350	1.25	1.00-1.57
			High	109	356	1.28	1.03-1.61
			P-trend				*0.31*
Categorized	2-5 years	Genotoxic	Unexposed	1765	7214	1.00	Referent
			Low	42	146	1.14	0.80-1.61
			High	42	138	1.26	0.88-1.80
			P-trend				*0.39*
		Non-Genotoxic	Unexposed	1765	7214	1.00	Referent
			Low	56	188	1.26	0.93-1.72
			High	46	128	1.47	1.04-2.07
			P-trend				*0.34*

Appendix G.5: Incidence of <u>non-Hodgkin's lymphoma</u> as a function of <u>average daily dose</u> of <u>TCA</u> exposure by time period before diagnosis

	TCA exposure						
Period before diagnosis	**Average daily dose**	**Cases N=1980**	**Controls N=7920**	**Crude**		**Adjusted***	
				RR	**95% CI**	**RR**	**95% CI**
2-5 years	**Unexposed**	1765	7214	1.00	Referent	1.00	Referent
	Low	95	302	1.29	1.02-1.63	1.33	1.04-1.6
	Medium	57	194	1.20	0.89-1.62	1.26	0.92-1.7
	High	63	210	1.23	0.92-1.65	1.37	0.96-1.9
	P-trend				*0.31*		*0.25*
	Other	-	-				
6-10 years	**Unexposed**	1390	5590	1.00	Referent	1.00	Referent
	Low	76	307	1.00	0.77-1.29	0.93	0.71-1.2
	Medium	39	160	0.98	0.69-1.40	0.87	0.60-1.2
	High	36	143	1.01	0.70-1.46	0.74	0.46-1.1
	P-trend				*0.14*		*0.54*
	Other	439	1720				
11-15 years	**Unexposed**	928	3677	1.00	Referent	1.00	Referent
	Low	51	200	1.01	0.74-1.38	1.03	0.75-1.4
	Medium	28	107	1.05	0.68-1.61	1.10	0.70-1.7
	High	23	70	1.31	0.81-2.11	1.57	0.87-2.8
	P-trend				*0.16*		*0.09*
	Other	950	3866				
16-20 years	**Unexposed**	465	1786	1.00	Referent	1.00	Referent
	Low	19	96	0.75	0.46-1.25	0.73	0.44-1.2
	Medium	8	48	0.64	0.30-1.36	0.58	0.27-1.2
	High	10	40	0.96	0.48-1.92	0.69	0.32-1.5
	P-trend				*0.75*		*0.85*
	Other	1478	5950				

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period

Appendix G.6: Incidence of non-Hodgkin's lymphoma as a function of duration of TCA exposure by time period before diagnosis

	TCA exposure						
Period before diagnosis	**Duration**	**Cases N=1980**	**Controls N=7920**	**Crude**		**Adjusted***	
				RR	**95% CI**	**RR**	**95% C**
2-5 years	**Unexposed**	1765	7218	1.00	Referent	1.00	Referen
	Short	73	250	1.19	0.92-1.56	1.23	0.94-1.6
	Medium	76	251	1.24	0.96-1.61	1.31	1.00-1.7
	Long	66	201	1.35	1.02-1.80	1.44	1.01-2.0
	P-trend				*0.04*		*0.06*
	Other	-	-				
6-10 years	**Unexposed**	1390	5593	1.00	Referent	1.00	Referen
	Short	82	337	0.98	0.76-1.26	0.91	0.70-1.1
	Medium	33	162	0.82	0.56-1.20	0.70	0.47-1.0
	Long	36	109	1.32	0.90-1.93	0.96	0.58-1.5
	P-trend				*0.37*		*0.47*
	Other	439	1719				
11-15 years	**Unexposed**	930	3690	1.00	Referent	1.00	Referen
	Short	57	225	1.01	0.75-1.36	1.03	0.76-1.4
	Medium	27	94	1.15	0.74-1.78	1.19	0.74-1.9
	Long	19	58	1.31	0.78-2.20	1.34	0.71-2.5
	Short				*0.31*		*0.44*
	Other	947	3853				
16-20 years	**Unexposed**	471	1806	1.00	Referent	1.00	Referen
	Short	21	103	0.78	0.48-1.26	0.75	0.46-1.2
	Medium	8	57	0.54	0.25-1.14	0.48	0.22-1.0
	Long	8	27	1.14	0.52-2.51	0.76	0.31-1.8
	P-trend				*0.59*		*0.19*
	Other	1472	5927				

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
*: Adjustment for the exposure in the other periods was carried out for each period
Other: subjects with incomplete information during the specified period

Appendix G.7: Incidence of non-Hodgkin's lymphoma, for those having at least 10 years of history, as a function of two exposure indices of SSRI drugs: ever/never and cumulative dosage exposure

SSRI exposure			Cases N=1243	Controls N=4972	RR	95% CI
Ever/Never exposed						
	2-10 years	Unexposed	1208	4805	1.00	Referent
		Any	35	167	0.83	0.57-1.21
Cumulative dosage exposure						
	2-10 years	Unexposed	1208	4805	1.00	Referent
		Low	23	102	0.90	0.57-1.42
		High	12	65	0.70	0.38-1.30
		P-trend				*0.48*
	6-10 years	Unexposed	1233	4918	1.00	Referent
		Low	7	39	0.71	0.32-1.61
		High	3	15	0.80	0.23-2.76
		P-trend				*0.33*

P-trend was based on the continuous data rather than the categorical data
RR: rate (incidence) ratio
Unexposed: no exposure to any SSRI
Any: exposure to any SSRI

Appendix G.8: Incidence of non-Hodgkin's lymphoma, for those having at least 5 years of history, as a function of two exposure indices of SSRI drugs: ever/never and cumulative dosage exposure

SSRI exposure			Cases N=1243	Controls N=4972	RR	95% CI
Ever/Never exposed						
	2-5 years	**Unexposed**	1214	4833	1.00	Referent
		Any	29	139	0.83	0.55-1.25
Cumulative dosage exposure						
	2-5 years	**Unexposed**	1214	4833	1.00	Referent
		Low	19	87	0.89	0.54-1.46
		High	10	52	0.73	0.37-1.44
		P-trend				*0.60*