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A POPULATION-BASED, CASE-CONTROL STUDY OF BREAST CANCER AND ALCOHOL CONSUMPTION AMONG POSTMENOPAUSAL WOMEN LIVING IN MONTREAL, QUEBEC, CANADA

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November, 2000

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfilment of the requirements of the degree of Master of Science

ABSTRACT

In the present population-based, case-control study of incident, postmenopausal breast cancer, we obtained an extensive history of alcohol consumption. Indices reflecting age-specific exposure, duration and cumulative exposure of alcohol were developed for specific types of alcoholic beverages as well as the combination of these beverages. Unconditional logistic regression, within the context of the Generalized Additive Models, was used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI). Case subjects included all new histologically-confirmed cases of malignant breast cancer among postmenopausal women, age 51-75 years, diagnosed or treated in 1996 and 1997 in all major hospitals in Montreal. Control subjects were selected randomly from other histologically-confirmed sites of cancer from the same hospitals as the cases. The response rate was 82% for cases and 75% for controls. Current drinkers of any kind of alcohol were at an increased risk of breast cancer (OR=1.47; 95%CI: 1.01-2.15). In particular, the risk of breast cancer was increased by 1.6-fold among weekly and current exclusive drinkers of wine. Other factors suggestive of an increased risk of breast cancer include early-age at first consumption of alcohol (≤30 years old) and increased number of years (>15 years) of consuming wine among women who only drank wine. We did not find, however, monotonically increasing risks with levels of consumption. Although, the associations found were relatively weak, our findings provide further support for a positive association between the risk of breast cancer and alcohol consumption, particularly wine.

ABREGÉ

Dans la population-base présente, étudiant l'incidence des sujets versus controle, du cancer du sein post-ménaupose, nous avons obtenu une importante corrélation entre ce cancer et la consommation d'alcool. Les indices reflétants l'age spécifique, la durée et la cumulation de l'exposition à l'alcool ont été développés pour un certain type de boissons alcooliques mais aussi pour la combinaison de ces boissons. Une régression logistique dans le contexte d'un Modèle Additif Généralisé á été utilisée pour ajuster les probabilités et 95% des intervalles confidents (IC). Les sujets comprennent tous les nouveaux cas de cancer du sein confirmés histologiquement au niveau des femmes ménauposées, agées de 51-75 ans, diagnostiquées et traitées entre 1996 et 1997 dans les principaux hospitaux de Montréal. Les sujets controles ont été sélectionnés au hasard à partir de résultats histologiques de cancer venant des mêmes hopitaux. Le niveau de réponse fut de 82% pour les sujets et de 75% pour les controles. Les buveurs de différents types d'alcool ont une augmentation du risque du cancer du sein (Probabilité=1.47; 95% IC: 1.01-2.15). En particulier, le risque du cancer du sein est augmenté par 1.6 parmis les buveurs de vin. D'autres facteurs suggestent une augmentation du cancer du sein parmis les jeunes buveurs de vin (< 30ans) ainsi que parmis les buveurs de longue durée (> 15 ans). Malgrés que les différences trouvées soint peu importante, notre étude permet de supporter une association positive entre le risque du cancer du sein et la consommation d'alcool et plus particulièrement la consommation de vin.

ACKNOWLEDGEMENTS

This thesis could not have been completed without the support of many people. First I would like to thank my supervisor Dr. Mark Goldberg. Most for his insightful comments and suggestions as well as his guidance throughout the entire process. I appreciate the expertise on alcohol consumption and breast cancer of my thesis committee, Drs. Marie-Élise Parent and France Lebrèche. An enormous thank you goes to Holly Lam and Marie-France Valois for their extremely generous help with the literature review and statistical analysis. To everyone in building 6 and 11 at the INRS-Institute-Armand-Frappier, thank you for giving me the proper infrastructure as well as a friendly environment for the completion of my thesis. To Janet Faith, thank you for teaching me about the finer things in Montreal and distracting me from my thesis work. I would also like to extend a thank you to my family and friends for their loving support and interest throughout the two years. Last but definitely not least, an especially big thank you to G. Grant Welstead, for his patience, not only dealing with the distance between us but also the patience to listen to every detail about alcohol consumption, breast cancer and epidemiology he never knew he wanted to know.

Acknowledgement of financial support

I gratefully acknowledge the fellowship I received from the Fondation INRS-Institute-Armand-Frappier and for the contribution made by my supervisor Dr. Mark Goldberg.

CONTRIBUTIONS OF AUTHORS

During the period between 1994 and 1997 when the study was designed and conducted, Dr. Mark Goldberg and Dr. France Labrèche designed the questionnaire, selected the control group, identified the case series, trained the interviewers and supervised data collection and data coding. Marie-France Valois was responsible for the data coding as well as cleaning the data and proved to be invaluable during my work on the analysis. I carried out the statistical analyses of the data and wrote this thesis while I was a master of science student in the Department of Epidemiology and Biostatistics at McGill University. Dr. Mark Goldberg, my supervisor, was involved with all aspects of my thesis and provided valuable advice with regards to the composition of the thesis, the decision to submit a manuscript-based thesis, the presentation of the findings, and the interpretation of the results. In addition, the two members of my committee, Drs. Marie-Élise Parent and France Labrèche, provided valuable input in the drafting of the thesis and provide useful suggestions regarding the statistical analysis.

Manuscript Title and Authors

Sarah K Lenz, Mark S Goldberg, France Labrèche, Marie-Élise Parent, Marie-France Valois: A population-based, case-control study of breast cancer and alcohol consumption among postmenopausal women living in Montreal, Quebec, Canada. To be submitted to *Epidemiology*.

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CHAPTER 1: INTRODUCTION

One of the most important public health problems in the industrialized world is female breast cancer. It is estimated that in 1999 there were about 18,700 incident cases of breast cancer and 5,400 deaths from breast cancer among Canadian women.[1] Breast cancer is the second most frequent cause of death from cancer accounting in 1999 for an estimated 18% of all cancer deaths among Canadian women.[1] One in nine Canadian women will develop the disease during their lifetime and one in 28 women will die from it.[1]

Over the last 25 years, incidence rates in Canada have increased by approximately 28%.[1] Rates have risen continuously between 1984 and 1999 (Figure 1.1),[2] with minor fluctuations during this period. The steepest increases were found in women over 50 years of age.[1] The reasons for the increase in incidence rates are largely unknown, but early detection of breast cancer may be a possible reason, especially given that death rates have remained about constant during this period of time.[3]

On a global scale, the incidence of breast cancer appears to be greatest in more industrialized countries, with the highest rates found in Western Europe, the United States, and Canada (Figure 1.2).[4] White women in the San Francisco Bay area, California, appear to have the highest incidence rates of breast cancer (104.2 per 100,000), whereas the lowest reported incidence rates are found in The Gambia (3.4 per 100,000).[4] Reasons for the international differences are uncertain, but variations in registration practices or in the ways breast cancer is defined may be a contributing factor. In addition, differences in risk factors for breast cancer (e.g., body weight, endogenous hormone levels, diet, and reproductive factors such as age at menarche, menstrual cycle lengths, parity, lactation) may also play a role in these international differences.[5] Finally, the differences may relate to yet unidentified environmental exposures.

Although world-wide incidence rates are increasing, mortality rates from breast cancer in Canada and Northern Europe are declining.[6,7] In contrast, there is a steady increase in breast cancer mortality in Japan,[8] even though incidence rates in Asia are much lower

than in North America and Europe (Figure 1.2). In the United States, rates for Caucasian women are declining but not for women of other races.[5] Furthermore, mortality rates in other countries, such as Portugal, Greece, Poland, Hungary, and Italy are still increasing.[9] These increases may be due in part to secular changes in reproductive, hormonal, and dietary risk factors. Additional contributors to increases in mortality may be poor early detection practices or inadequate management and treatment of breast cancer after diagnosis.[8] That some modest improvement has been made in preventing breast cancer deaths in certain countries while mortality rates have increased substantially in others provides the impetus to find preventative strategies.

Personal, familial and societal burdens of the disease, coupled with increased expenditures on health care[10] and the continuing increase in breast cancer incidence, of which only 25% to 40%[11] may be attributed to accepted risk factors, are important reasons to determine the causes of this disease.[1]

Risk Factors for Breast Cancer

Factors that affect the risk of disease are often divided into those that are modifiable and those that are not. Modifiable risk factors are those that can be altered by making changes to an individual's lifestyle or environment, and non-modifiable risk factors are those factors that cannot be changed, such as a person's genetic make-up. Some risk factors that may seem to be modifiable (e.g., age at first pregnancy) may not be because of current social behaviour. It is debatable whether some risk factors such as body mass index and parity (number of children) are modifiable. Chest irradiation and an oophorectomy are in principal avoidable, although in reality these procedures may be necessary in many instances. Table 1.1 shows different risk factors for breast cancer and their approximate relative risks. The most significant risk factor for breast cancer is age, as incidence increases rapidly with age.[5] Family history of breast cancer is also a very important risk factor: risks increase more than 4-fold if 1) a relative has had premenopausal bilateral breast cancer or 2) two relatives have had any form of breast cancer.[12] Benign breast disease increases the risk of breast cancer 2- to 4-fold.[5,13,14] Reproductive factors, such as age at menarche, age at first full-term pregnancy, and parity

are also important, with relative risks ranging from 1.1- to 3.[5,13,14] Other factors such as socio-economic status and body mass index may also increase risk from 10% to 100%.[5,14,15]

One modifiable risk factor that has been examined recently is consumption of alcohol. Although alcohol has been investigated in a number of studies, further information is required before a more definitive statement about its role in the etiology of breast cancer can be made. This thesis concerns estimating the association between postmenopausal breast cancer and lifetime history of alcohol consumption. The data are drawn from a population-based, case-control study of postmenopausal breast cancer conducted in Montreal in 1996 and 1997. The thesis is written in manuscript style, with one paper to be submitted for publication that describes the study population, methods, results and a discussion of the findings. In keeping with the format approved by McGill University and the Joint Departments of Epidemiology and Biostatistics and Occupational Health, a detailed review of the literature regarding the association is presented in Chapter 2, the objectives of the thesis are described in Chapter 3, the substantive paper describing the analysis of the association between postmenopausal breast cancer and consumption of alcohol is presented in Chapter 4 (copies of the letter of introduction and ethics' approval from the McGill University Institutional Review Board and the questionnaires from the study will be found in the Appendices A and B), and the conclusions and summary will be found in Chapter 5.

Figure 1.1: Age-Standardized Incidence Rates (ASIR) for Breast Cancer, Females, Canada, 1970-1999
(Rates are standardized to the age distribution of the 1991 Canadian female population)

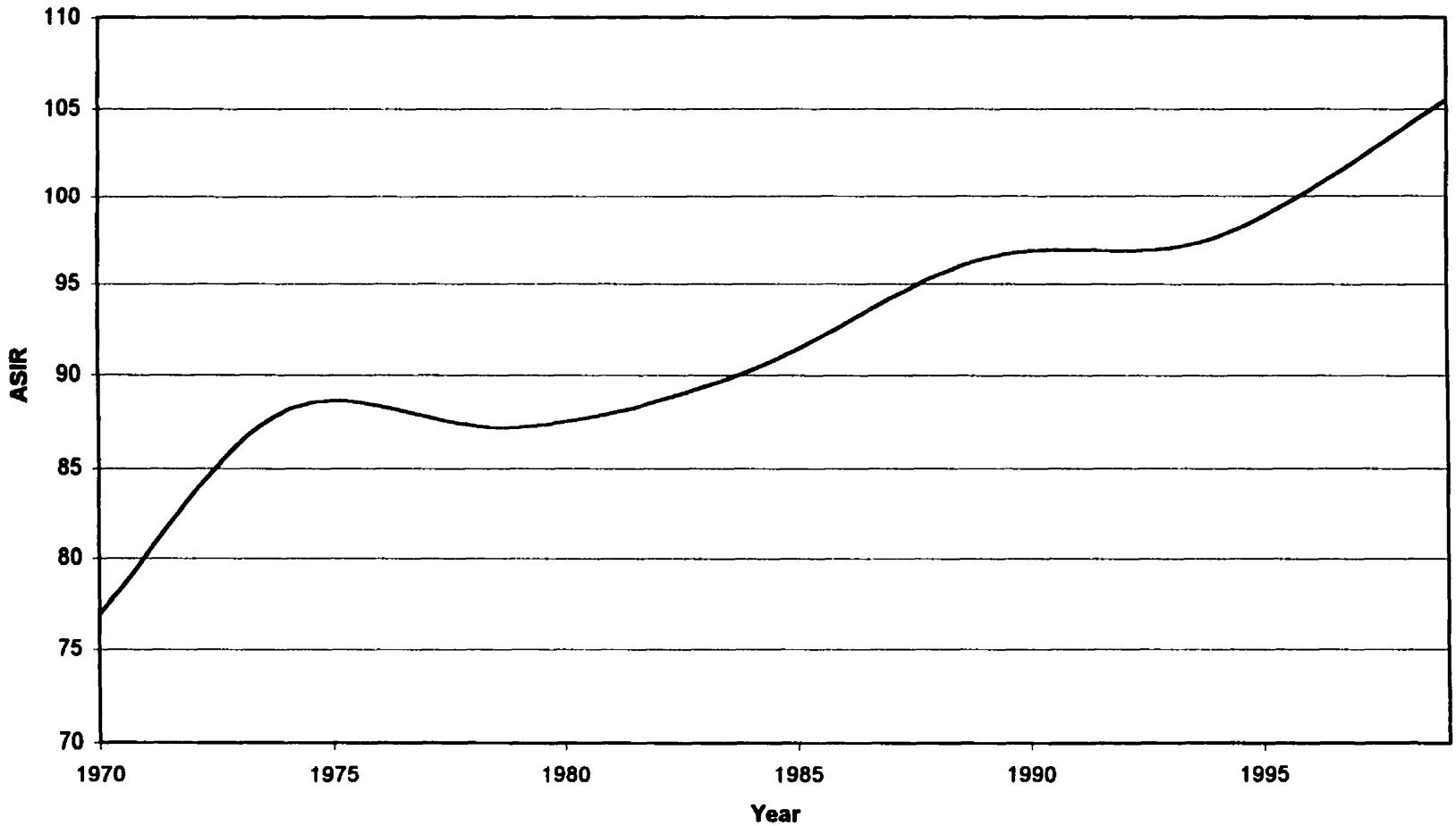

Figure 1.2 : International Comparision of Age-Standardized Incidence Rates of Breast Cancer (Rates are standardized to the age distribution of the world)

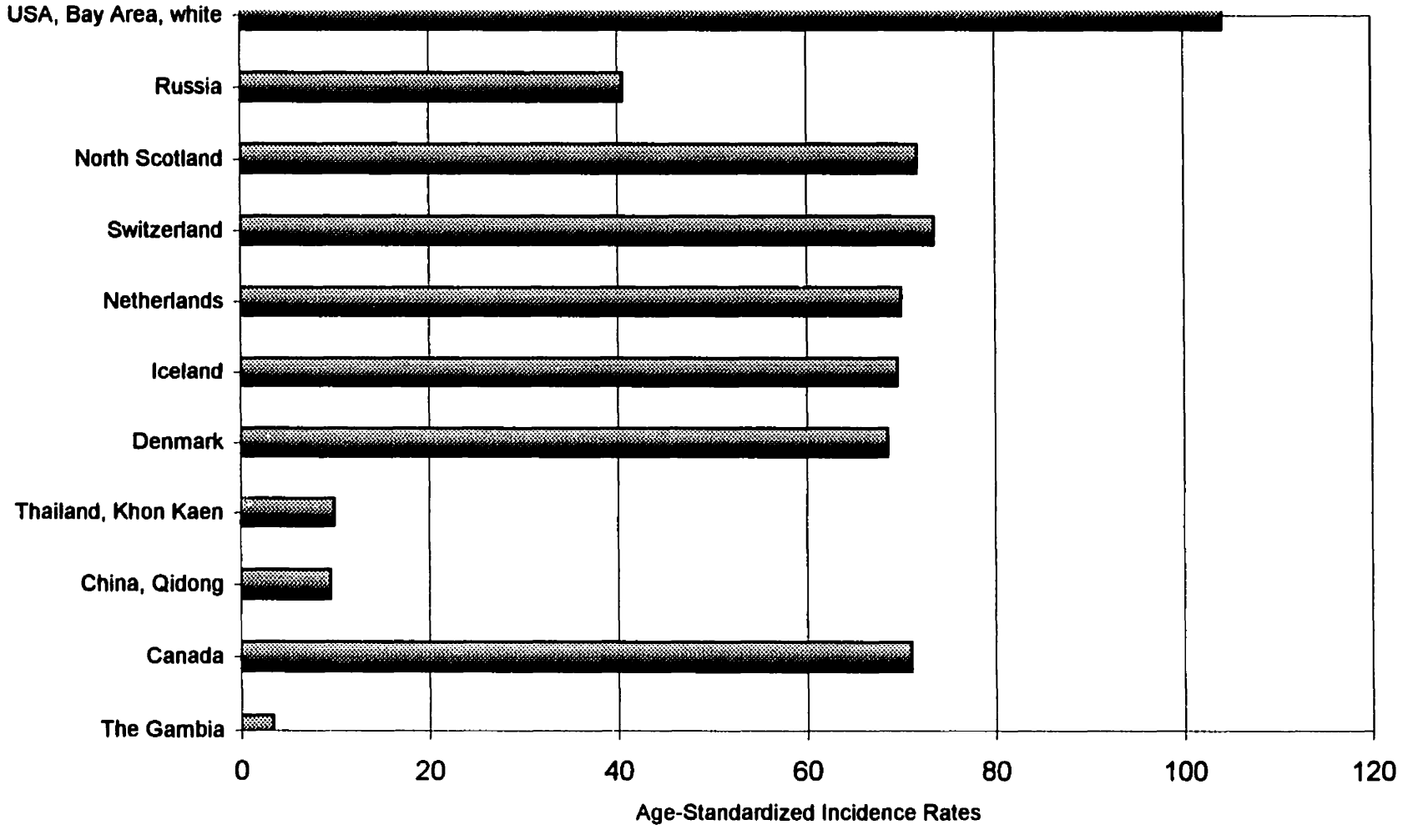

TABLE 1.1: Risk Factors for Female Breast Cancer

Risk Factor	Approximate Estimate of Risk	References
Non-modifiable Risk Factors		
Age	4 fold increase in risk (>50 years/<50 years)	5
Family history		
Relative with pre-menopausal bi-lateral breast cancer	>4 fold increase in risk (Yes/No)	14
One 1st degree relative with any form of breast cancer	2-4 fold increase in risk (Yes/No)	5,14
Two 1st degree relatives with any form of breast cancer	>4 fold increase in risk (Yes/No)	5,13,14
Country of birth	>4 fold increase in risk (North America, Northern Europe/ Asia, Africa)	5
Benign breast disease		
Atypical hyperplasia	>4 fold increase in risk (Yes/No)	13,14,16
Dense breast tissue	3-4 fold increase in risk (Yes/No)	5,14
Chest irradiation (ionizing radiation)	2-4 fold increase in risk if exposure occurs from puberty through child bearing years (High/Minimal)	5,14
Age at first full-term pregnancy	1.1-3 fold increase in risk (>30 years/<20 years)	5,13,14
Bi-lateral oophorectomy before age 40	1.1-3 fold increase in risk (No/Yes)	5,13,14
History of primary cancer of ovary or endometrium of subject	1.1-2 fold increase in risk (Yes/No)	5,14

Table 1.1 (continued)

Risk Factor	Approximate Estimate of Risk	References
Socio-economic status (income, education)	1.1-2 fold increase in risk (High/Low)	[5]
Body mass index (weight/height^2)	1.1-2 fold increase in risk in postmenopausal women (Obese/Thin)	[5,14,15]
Marital status	1.1-2 fold increase in risk (Never married/Ever married)	[5]
Place of residence	1.1-2 fold increase in risk (Urban/Rural)	[5]
Race	1.1-2 fold increase in risk (White/black)	[5]
Age at menopause	1.1-2 fold increase in risk (≥55/≤45)	[5,13]
Age at menarche	1.1-2 fold increase in risk (≤11/≥15)	[5,13]
Modifiable Risk Factors		
Parity	1.1-3 fold increase in risk (Nulliparous/ parous) Inconclusive after 1 child	[5,14]
Hormone replacement therapy	Possible modest increase in risk but restricted to women who took them for a long time, in high doses or women > 60 years old	[13,14,17]
Oral contraceptives	1.5 fold increase in risk (Current/Never) Increased risk for women with benign breast disease, women who used them at a late age >46-65 or women who used them very early <20 years and/or before the first pregnancy	[13,14]

Table 1.1 (continued)

Risk Factor	Approximate Estimate of Risk	References
Breastfeeding	Suggestive of a protective effect, especially if breast-feeding occurs for a long period of time at a young age	5,14
Alcohol consumption	Suggestive of increase in risk	18,19,71
Dietary fat	Suggestive of an increase in risk, but weak effect	14
Physical activity	Potential influence on menstrual cycle patterns and ovulatory frequency, slight risk (inactive women/active women)	5
	Strenuous exercise appears to reduce risk among post-menopausal women who do not gain sizeable amounts of weight during adulthood	20
New Emerging Hypotheses, not sufficiently evaluated		
Cigarette smoking	No estimate available	21
Extremely low frequency electromagnetic radiation and light-at-night (LAN)	No estimate available	22,23
Exposure to pesticides and organo-chlorine compounds	No estimate available	24-26
Organic solvents	No estimate available	27

CHAPTER 2: LITERATURE REVIEW- THE ASSOCIATION BETWEEN ALCOHOL CONSUMPTION AND POSTMENOPAUSAL BREAST CANCER

Materials

In keeping with the objectives of this thesis (see Chapter 3), I reviewed epidemiologic studies of postmenopausal breast cancer published in English language peer-reviewed, scientific journals. However, studies that contained both pre- and postmenopausal women subjects were included. Relevant papers were uncovered by searching the MEDLINE bibliographic database for the years 1966 to 1999. Reference lists of the retrieved papers were then consulted to discover other studies that were not identified in the electronic search. The following types of articles were excluded: letters[28-32] and abstracts,[33-35] (because they did not provide sufficient methodological details); studies of women with multiple primary cancers;[36] studies that mentioned alcohol consumption but gave no specific results;[37-39] studies for which the outcome was not incidence or mortality (i.e., breast cancer survival,[40,41] stage of breast cancer,[42,43] screening by mammography[44]); studies of alcoholic women[45-50] (because the sample sizes were small, major risk factors of breast cancer were not controlled for adequately, and there was little information on exposures); and ecological studies.[51-56] Another case-control study[57] was excluded because of its small sample size (60 subjects). Articles covering the same population were combined and considered as one study even though different results may have been reported in separate publications.[58-71] Four studies[72-75] have been updated and the results from these articles were reported in more recent articles.[76-79]

In the end, 57 studies were included in this review, comprising 42 case-control studies[58-65,76,79-115] and 15 cohort studies[66-71,77,78,116-125] for which there were reports of the association for the consumption of alcohol with postmenopausal breast cancer or with premenopausal and postmenopausal breast cancer combined. Table 2.1 provides a succinct summary of the important aspects of the design of each of these studies as well as the principal results.

Methods

In attempting to summarize the results of these studies, I sought indices of alcohol consumption that were commonly used. In the case-control studies, I found that the most common indices of alcohol consumption (in 51 of the 57 studies) were "recent" or "current" total alcohol consumption; in the cohort studies, "usual" alcohol consumption was used exclusively. This index of recent or usual or current alcohol consumption may not be the best predictor of breast cancer risk because it may be more influenced by recall bias and recent changes in drinking habits by newly diagnosed subjects. However, in few studies was past drinking habits assessed.[66,67,77,79-81,83-85,89,91,94,95,99] It was for this reason that I decided to use the recent/usual/current alcohol intake index for the purposes of summarizing the literature. Due to the potential importance of indices involving past drinking habits, the results of those studies in which past intake was assessed will be addressed in the Results section of this chapter.

In all the case-control and cohort studies, total alcohol consumption was defined as an individual's combined consumption from all types of alcoholic beverages, including varieties of beer, wine, hard liquor, spirits, ciders and fortified wines. In the case-control studies, alcohol intake was assessed either as recent or current. Recent alcohol intake was defined as average alcohol consumption for a specified period of time closely preceding the interview (this period was always less than five years) and current alcohol intake was defined as a subject's consumption at the time of the interview. Recent[58-65,76,79-81,83-104,106-108] and current total alcohol consumption[82,105,115] was assessed in 36 case-control studies.

In the cohort studies, usual alcohol intake was defined slightly differently in various studies. In most studies, it was defined as the average amount of alcohol consumed within the year before the start of the follow-up period.[66-71,77,116-121,124,125] For one study, usual alcohol intake was defined as the average amount consumed throughout the follow-up period[78] and, in the Kaiser Permanente Multiplan health study, alcohol was evaluated during the year before each examination.[122,123]

It was beyond the scope of this literature review to summarize quantitatively the published data (e.g., conduct a meta-analysis). Rather, I classified each of the 51 studies according to key design characteristics that could affect the validity of a given study, including: selection of case subjects; histological confirmation of the diagnosis of breast cancer; definition of comparison populations; response rates; adjustments for potential confounding factors; and the definition of postmenopausal status. I then calculated the proportion of studies indicating a positive association between postmenopausal breast cancer and recent, current or usual total alcohol consumption. For both case-control and cohort studies, I defined a "positive" study when it met one of the following conditions:

1) There was evidence of a monotonic increase in risk by consumption (usually if the test for linear trend was statistically significant (p-value<0.05)) or
2) The 95% confidence limits associated with the odds ratio or relative risk for the categories of highest consumption when compared to the lowest category excluded unity.

A limitation of this type of summary is that studies are given equal weight regardless of their ability to detect true excess risks (statistical power). It was not possible to assess the power of each study for two reasons: 1) there was no index, such as ever/never alcohol consumption, common to all studies and 2) in many of the articles estimates of parameters needed to calculate power were not provided.

Major variations in key design characteristics were compared by calculating the differences in binomial proportions to determine if the discrepancies were statistically significant.

Results

Table 2.1 shows the principal results from each study, according to selected characteristics of design and conduct of the studies. Results are presented for usual, recent, or current drinking, but other types of indices are also presented in the table, including: alcohol consumption at early ages; types of alcoholic beverages consumed; duration of alcohol consumption; and average lifetime consumption of alcohol. Before

presenting a summary of the results of the studies, I shall discuss some of the salient characteristics of these studies.

Description of the Key Characteristics of the Studies

Definition of Postmenopausal Status

In the analyses of 26 studies[62-69,78,79,82,83,89,90,97-99,101-103,106-108,115,116,121-125] premenopausal and postmenopausal women were combined. In 19 case-control studies,[58-61,76,80,81,84-88,91-96,100,104,105] and in six cohort studies[70,71,77,117-120] the study population was restricted to postmenopausal women at the design stage or at the analysis stage (for nested case-control or case-cohort studies).

Definitions for postmenopausal status were provided in 16 of the 25 studies in which postmenopausal breast cancer was solely investigated,[70,71,76,77,84,85,87,88,91-93,96,100,104,105,117,120] and no definitions were given in nine studies.[58-61,80,81,86,94,95,118,119] In four studies postmenopausal status was defined as twelve months without menses based on the World Health Organization definition,[84,85,92,120] and in one study postmenopausal status was defined as six months without menses prior to interview.[100] In seven other studies, an age cut-off was used (i.e., greater than age 50 or 55 at time of study),[70,71,77,87,91,104,105,117] and in four other studies, women were classified as being postmenopausal if they claimed to have had either natural menopause or surgical menopause.[76,88,93,96]

Location

Most studies were conducted in the United States (20 studies)[58,59,66-71,76,78,80,83-85,89,93,116,118,120-125] and in Europe (20 studies).[60-63,77,79,81,82,86,87,90,91,94,95,97-99,101,102,105,115,117] Investigations have also been conducted in Japan (3 studies),[96,104,106] Canada (3 studies),[64,107,119] Russia (1 study),[100] Argentina (1 study),[108] New Zealand (1 study)[88] and Australia (1 study)[92] and one study was conducted simultaneously in Canada, the U.S., and Israel.[103]

Selection of Case Subjects in Case-Control Studies

The selection of cases is defined as recruitment that is either population-based or hospital-based. The former refers to the selection of cases from all sources in a well-circumscribed geographic area over a specified interval of time, whereas the latter usually means that the cases are recruited from some hospitals within the targeted geographical area. In 23 case-control studies[58-61,76,79-92,94,99,104,106,108,115] the enrolment of case subjects was population-based and in the other 13 studies[62-65,93,95-98,100-103,105,107] it was hospital-based.

Diagnosis and Histological Confirmation of Breast Cancer

Incidence of breast cancer was the focus of the majority of the studies. However, in two cohort studies, mortality was evaluated.[116,124] Both the incidence and mortality of breast cancer of a single population was assessed in two separate American studies.[68,69] For these two study populations, I have chosen to consider only incidence because it is measured more accurately than mortality and is not affected by factors related to survival. In three studies, *in situ* breast cancer was combined with invasive breast cancer.[84,87,120] The number of subjects with *in situ* breast cancer was not provided in any of these studies, nor were separate analyses provided.

Histological confirmation of cancer considerably reduces misclassification of disease status. All cases of breast cancer were histologically confirmed in 24 case-control studies[60-63,76,79-84,86,88,90,92-95,97-99,102,106-108,115] and in two cohort studies.[117,119] At least 90% of cases were confirmed histologically in four case-control studies[85,87,91,96] and in two other cohort studies.[68,69,78] In five studies, some of the cases were verified using information from pathology reports, but the percentage of cases so identified was not stated.[58,59,77,89,103,118] No information was provided in five case-control studies[64,65,100,101,104,105] and in nine cohort studies.[66,67,70,71,116,120-125] Overall, 60% of cohort studies and 14% of case-control studies had no confirmatory evidence regarding the diagnosis of breast cancer.

Selection of Control Subjects in Case-Control Studies

Hospital controls were included in 14 studies.[58-63,79,94-100,102,104,105] Most descriptions of hospital controls included the reason for hospitalization and the percentage of control subjects with each type of illness or disease. Information on whether the diagnosis was a suspected one or a confirmed one was missing in seven of the 14 studies.[60,61,94,96,97,100,102,104] In the other seven studies, diagnosis was based on the admission diagnosis.[58,59,62,63,79,95,98,99,105] In three studies, the diseases that the controls had acquired were not described,[100,101,108] and in four studies no reasons were provided for the hospitalization of between 10% to 25% of the control subjects.[60-63,94,95] In five papers,[62,63,100-102,106] it was indicated that the control groups had diseases that were considered to be associated with alcohol consumption, but there was little indication about which diseases in particular were thought to be associated with alcohol consumption.

Patients with other sites of cancer were used in two studies.[103,104] One study[104] included controls with many sites of cancer, whereas the other study[103] included controls with only two cancer sites (endometrium or ovaries).

Non-ill subjects from the general population were included in 13 studies[76,80,82,83,85-92,115] and neighbourhood controls were included in three other studies.[64,65,84,93] In six studies, a set of two comparison groups was used in each.[81,101,103,106-108] In two studies both neighbourhood and hospital controls were included.[107,108] In two other studies, women from screening programs and hospital controls were included.[101,106] In one study, hospital controls and a separate cancer control group were included.[103] In one study that included control groups from different European countries, the controls from some countries were chosen from the population registry whereas controls from other countries were chosen from a random sample of patients from physicians' files. In two of these studies that included two separate comparison groups[81,106] the pair of control subjects were combined into one analysis; in the other four studies separate analyses were reported.[101,103,107,108]

In all of the cohort studies, internal comparisons between breast cancer case subjects and non-cases were conducted, and no external reference populations were included.[66-71,77,78,116-125]

Response Rates

Two aspects of response rates are important. Assuming that the sampling procedure is unbiased, response rates should be high to ensure the selection of a representative sample of the target population. In addition, response rates in case-control studies should be similar between cases and controls so as to minimize bias due to differential participation. Similarly, in cohort studies, losses to follow-up should be similar between cases and non-cases and censoring should be independent of exposure.

Response rates were reported in all case-control studies in which the control group included healthy subjects from the general population, as well as in 16 of 23 of the other types of case-control studies. However, the number of studies without stated response rates was greater in studies with hospital controls[58,59,62,63,97,98,104] than studies with neighbourhood controls.[64,65] Response rates greater than 90% were found in 12 case-control studies.[60,61,79,88,93,94,96,99-103,108] In another six case-control studies,[76,82,85,86,95,105] response rates were between 75% and 90%. In eleven studies, response rates either differed by more than 10% between cases and controls[80,81,84,87,89-92,107] or were under 70%.[83,115] The greatest difference in response rates between cases and controls was in the study by Royo-Bordonada *et al.*,[81] with a response rate of 86% for cases and only 41% for the population controls. Response rates were not quoted in seven case-control studies.[58,59,62-65,97,98,104,106] As expected, case-control studies with hospital controls had higher response rates[60,61,79,94-96,99,100,102] than those that included population or neighbourhood comparison groups.[76,85,86,88,93]

Final response rates in the cohort studies were more difficult to assess as one needed to know the initial rates of recruitment (the number of people who responded to the original solicitation divided by the number of eligible subjects), losses to follow-up, and the percentage of subjects included in the analysis of alcohol consumption. Response rates were stated in five studies,[66-69,77,118,121] with rates of more than 90% reported in three of

these.[68,69,118,121] However, these response rates did not account for the initial recruitment of subjects. It was possible to calculate initial rates of recruitment for eight[68-71,77,117,118 119,120,125] of the 15 cohort studies; these ranged from 21% to 87%, but half of the studies were below 70%.[117,119,120,126] For ten studies, I was also able to calculate the proportion of eligible subjects included in the analyses,[66-71,77,116-120,125] and these ranged from 20%-66%. In one study,[116] the amount of missing information on alcohol consumption was about 50% and in another study,[123] 40% of the women who responded to the questions on alcohol were not followed until the end of the period of observation.

Confounding Variables

Adequate adjustment for potential confounding factors is essential to reduce bias. Using *a priori* information, accepted and suspected risk factors for postmenopausal breast cancer should be accounted for either in the design stage or in the analysis stage. The most pertinent factors (Table 1.1) are age, family history of breast cancer, and reproductive factors (age at menarche, age at first full-term pregnancy, parity, age at menopause).

There was considerable variation regarding the number of potential confounding factors accounted for. In 19 studies age, family history of breast cancer, and all the reproductive factors were accounted for adequately.[60,61,66-69,76,79-81,84,85,88,90,91,93-95,98,117,119,120] In 22 studies,[58,59,62,63,70,71,77,78,83,86,89,92,99,101,103,105,107,115,116,118,121-125] the effects of age and some of the above confounding factors were controlled for. However, in 14 studies family history of breast cancer was not included in the analyses.[64,65,78,82,87,96,97,99,100,102,105,106,108,118,123] In nine other studies, only age was accounted for.[64,65,82,87,96,97,100,102,104,108] In one study no confounding factors were accounted for.[106]

Although, the aforementioned factors are the most important, the most common covariates assessed in these studies were education (37 studies)[58-61,66,67,70,71,76-80,87,89,95,98-103,107,115-117,119-123,125] and body mass index (36 studies).[60,61,66-71,76-78,80,81,83-91,93,94,98,99,101,103,105,107,108,115-118,120-123,125] Adjustments for breastfeeding were only performed in two studies.[58,59,80]

A potentially important risk factor may be smoking, as it is known to be highly associated with alcohol consumption, although it is unclear whether smoking causes breast cancer. Adjustments for smoking were, however, carried out in 30 studies.[58-61,68-71,76,78-81,86-89,91,93,95,101,103-105,107,116-119,121-125]

Measurement and Indices of Alcohol Consumption

Consumption of alcohol was assessed by questionnaire. Women were usually asked about their recent, current or usual alcohol consumption (e.g., number of drinks per week) for different types of alcoholic beverages and this was summed to give a value for total alcohol consumption. The implicit assumption associated with this index of total alcohol consumption is that the mechanism for induction of cancer was from sole exposure to ethanol, independent of any other constituents of the beverages. In order to summarize across all types of beverages, the number of drinks was often converted to grams of alcohol consumed, assuming a typical alcoholic content of the beverage. The conversion factors used to produce the index of grams per day varied considerably among the different studies, ranging from 10 to 13 grams for beer,[58-61,81,84,89] 9 to 12 grams for wine,[66,67,83,86] and 10 to 15 grams for hard liquor.[58,59,81,84,89]

In 30 studies, recent, current or usual consumption of total alcohol was quantified as grams of alcohol consumed per day[58,59,62-71,77,78,80,81,84-87,89-92,94,96,98,100,101,105,115,117-120,125] and in 16 studies as the average number of drinks consumed per day or per week.[60,61,76,79,83,99,107,108,116,121-124] The frequency of alcohol intake (i.e. never, occasional, daily) was the index used in five studies.[82,102-104,106]

Associations for specific types of alcoholic beverages were investigated in 22 of the 51 studies.[60-63,68,69,76,78-80,83,86-88,90,92,94,95,98,99,104,107,117,119,122] Wine (21 studies)[60-63,68,69,76,78-80,83,86-88,90,92,94,95,98,99,107,117,119,122] and beer (21 studies)[60-63,68,69,76,78-80,83,86-88,92,94,95,98,99,104,107,117,119,122] were the most common alcoholic beverages evaluated. Other types of alcoholic beverages examined were hard liquor (nine studies),[62,63,68,69,76,80,83,99,107,117,122] spirits (11 studies),[60,61,78,79,86-88,92,94,95,98,119] fortified

wines (three studies),[60-63,87] and sherry (two studies).[86,88] Amari,[94] grappa,[94] liquers,[86] aperitifs,[98] sake,[104] whiskey[104] and cider,[62,63] were each assessed once.

In six studies, the analysis for recent/current/usual total alcohol intake was restricted to postmenopausal women,[60,61,76,86,88,92,95] but the analysis of the individual beverages included both premenopausal and postmenopausal women. Longnecker *et al.*,[84] assessed the average lifetime consumption of beer, wine and hard liquor but did not report recent or current consumption of the separate beverages.

Other indices of alcohol intake have been evaluated including: the number of years of alcohol consumption,[77,79,80,89,94,95,99] the age when the subject first started to drink,[77,79-81,89,91,94,95,99] and alcohol consumption at different exposure periods, including drinking at ages earlier than 25.[66,67,83-85] Some of these analyses are important in determining whether alcohol may act as an initiator or promoter, especially given that the breast stops proliferating around the age of 35 years.[127] About half of studies that assessed past drinking habits were based on populations restricted to postmenopausal women.[77,80,81,84,85,91,94]

In four investigations, the association between lifetime alcohol consumption and the risk of breast cancer was assessed.[66,67,83-85] Freudenheim *et al.*[83] quantified lifetime alcohol consumption as a weighted average of alcohol intake at two, 10, and 20 years prior to interview. Longnecker *et al.*[84] calculated lifetime alcohol consumption as the average consumption of alcohol at age 25, age 40, and at one year before diagnosis (for cases and for controls, the corresponding case's diagnosis. Herrinton *et al.*[66,67] calculated lifetime consumption as a weighted average of the time spent in each age period: 21-30 years, 30-49 years, over 50 years and the amount of alcohol consumed. Average lifetime alcohol consumption was computed as the amount of alcohol intake from 16 years of age up to the previous age interval (30-39) for women 40-60 years old and the previous age interval (40-59) for women over sixty in another study by Longnecker *et al.*[85]

The association between alcohol consumption and the risk of breast cancer

As indicated above, there were 57 studies included in the literature review. I summarized the associations using recent or current total alcohol consumption and six case-control studies,[109-114] included in Table 2.1, were excluded from the summary (Table 2.3) because this index was not assessed. In the study by Ranstam and Olsson[109] recent alcohol intake was assessed separately for wine, beer and spirits. However, results for total alcohol were not presented. Pawlega *et al.*[110] only reported an index for ever drank vodka 20 years prior to entry into the study. In the study by Young *et al.*[111] usual weekly consumption of alcohol was evaluated in two different periods, 18-35 years old (early-age drinking) and >35 years, excluding 5 years before diagnosis. This study was excluded because usual alcohol intake excluded the five years before diagnosis whereas in the other studies usual alcohol intake was assessed five or fewer years before diagnosis. Talamini *et al,*[112] William and Horm,[113] and Katsouyanni *et al.*[114] reported average lifetime alcohol intake and therefore were excluded from the summary because the indices were not based on drinking during a specified time period prior to diagnosis.

Of these excluded studies, no association was found in two studies.[109,110] In all three studies in which average lifetime alcohol intake was investigated[112-114] associations with breast cancer risk were found. In another study,[111] late-age drinking among women age 50-60 years at the time of diagnosis and any alcohol consumption among women greater than sixty years old were positively associated with the risk of breast cancer. These studies were not evaluated by design features like the other studies so the results of these studies should be assessed carefully.

Positive associations between the risk of breast cancer and usual, recent, or current total consumption of alcoholic beverages were found in 25 of the 51 studies (49%) included in the summary of the literature (Table 2.3). Restricting results to studies in which only postmenopausal breast cancer was investigated, 10 of 25 studies (40%) showed positive associations; this percentage was slightly higher for those studies in which pre- and postmenopausal women were combined (58%). For those studies in which specific definitions for menopause were provided, positive associations were found in 80% of

studies (4 of 5 studies). However, the difference in proportions between these latter studies and those not providing concrete definitions for menopause were not statistically significant and therefore the discrepancies seen may be due to chance.

Table 2.3 summarizes the proportion of positive studies by selected characteristics of design and conduct. The studies are separated into those that were restricted to postmenopausal populations and those that were not. For each of the design features listed in Table 2.3, such as histological confirmation of breast cancer and response rates, there were minimal differences in the percent of positive studies between those populations that were restricted to postmenopausal women and those that were not.

I found that there were differences in the proportion of positive studies by type of study, with a higher proportion of cohort studies (67%) as compared to case-control studies (42%) showing positive associations. I investigated whether the proportion of positive studies changed when the analysis was limited to specific attributes of these studies.

In the case-control studies, there was little difference in the proportion of positive studies according to most of the design characteristics considered, with the following exceptions. A greater proportion of studies with no stated response rates were positive (71%) as compared to those that had ≥90% response rates (33%). A similar difference in the proportion of positive studies was found between studies for which there was no histological confirmation of cancer (60%) as compared to those with confirmation rates >90% (36%). The percentage of positive studies increased with an increase in sample size (60% of case-control studies with greater than 500 cases (n=15) as compare to 29% for studies with less than 500 cases (n=21)). Family history of breast cancer was not controlled for in 11 studies.[64,65,82,87,96,99,100,105,108] In 27% of these studies a positive association between alcohol consumption and breast cancer was indicated.[64,65,97,100] The differences in the proportion of positive studies according to these specific study characteristics listed above was within what was expected by chance ($p>0.30$).

An interesting exercise is to select those case-control studies that, theoretically, were of the highest quality (say, response rates were greater than 75%, histological confirmation was greater than 90%, and adequate statistical adjustments for age, family history of breast cancer, and reproductive variables were performed) and will be defined as "well-designed" case-control studies for the remainder of the thesis. Only nine case-control studies met these criteria of "well-designed" studies,[60,61,76,79,85,86,88,93-95] and only four were positive for recent total alcohol consumption.[60,61,79,85,86]

With regards to the cohort studies, we found that the percentage of positive studies decreased when the time to follow-up increased: all four studies[68,69,77,117,120] were positive with follow-up times less than five years, whereas three[123-125] of six studies[78,118,121,123-125] were positive with follow-up times greater than 10 years. Among the five cohort studies that had more than 500 cases[66-69,116,123,124] a positive association was suggested in each of them. In nine cohort studies,[66,67,70,71,116,120-125] no information was presented regarding the histological confirmation of breast cancer. Seventy-eight percent of these studies indicated a positive association. Conversely, only 50% of studies in which at least some of the cases were histologically confirmed showed a positive association.

In terms of response rates, cohort studies were separated into two categories: *i*) those with calculated response rates (eligible subjects included in the analysis) of less than 60% and those without a calculated response rate; and *ii*) those studies in which calculated response rates were greater than 60%. The former group had a greater number of positive studies than the latter group (80% versus 70%).

Appropriate statistical adjustments for age, family history of breast cancer, and reproductive variables were performed in only five of the 15 cohort studies.[66-69,117,119,120] Positive associations were found in four of these five studies.[66-69,117,120]

Positive associations were found in two cohort studies[68,69,124] in which improper analyses were performed. In these long-term follow-up studies, both groups used cumulative incidence instead of incidence density sampling and their results may well be biased.

Positive associations were also indicated in two studies in which over 40% of the original populations were excluded because of missing information on alcohol intake.[116,123] If the non-participants were different with respect to alcohol consumption compared to the participants, then selection bias may have occurred.

To summarize, only three cohort studies[77,117,119] had low rates of missing information for alcohol consumption, sample size greater than 200 cases, some histological confirmation of cancer cases and adequate statistical analyses controlling for essential risk factors and thus defined as "well-designed" cohort studies. Other similarities among these three studies included: follow-up times of less than ten years, use of nested case-control or case-cohort design, restriction to a population of postmenopausal women, and all of these studies were conducted outside of the United States. Two of these three "well-designed" cohort studies[77,117,119] showed positive associations[77,117] between alcohol consumption and breast cancer.

Among the studies in which past alcohol intake was examined,[66,67,77,79-81,83-85,89,91,94,95,99] in less than half of these was an association found between alcohol consumption and the risk of breast cancer. Of 13 studies, in only four case-control studies[81,89,91,95] and two cohorts studies[66,67,77] was an association found between the risk of breast cancer and early-age alcohol consumption. Duration of alcohol consumption use in years was found to be associated with breast cancer risk in two of the seven studies in which it was investigated (29%).[77,80] The duration of alcohol consumption use was associated with an increase in the percentage of positive studies when the population was restricted to postmenopausal women (67%). The differences in the proportion of positive studies was within what was expected by chance. There were only four studies[66,67,83-85] in which average lifetime consumption was evaluated and associations were found in two studies.[84,85]

In only two of the "well-designed" case-control studies[79,85] was past levels of alcohol intake investigated. Positive results for average lifetime consumption were found in one of these studies.[85] No association was found for early-age drinking or duration of alcohol

consumption, although both were investigated in the two studies.[79,85] In only one "well-designed" cohort study was past alcohol history assessed, with associations found for early-age and long duration intake of alcohol use.[77]

Discussion and Conclusions

Important differences between the case-control studies and the cohort studies were the number of positive studies (42% for case-control studies and 67% for cohort studies) and the number of studies in which the majority of the cases of breast cancer were confirmed histologically (86% for case-control studies and 40% for cohort studies).

In summary, it is difficult to determine from the current literature, whether alcohol consumption is associated with the risk of developing breast cancer. In my review, 47% of the "well-designed" (four out of nine) case-control studies showed positive results. Although a higher percentage of cohort studies indicated positive associations, the cohort studies had some important limitations that may have compromised their results. What is apparent from this review is the evidence, thus far, is not sufficient to assess the true association between alcohol intake and postmenopausal breast cancer.

It is not enough to only assess alcohol intake during a time period prior to diagnosis, what appears to be required is the measurement of a full history of patterns of alcohol consumption. A minority of researchers have investigated past alcohol intake, including measurements of alcohol consumption at different ages or the duration of alcohol use; few have examined lifetime history of alcohol consumption. Due to the small number of studies concentrating in this area, it is difficult to make inferences. Furthermore, studies of strictly postmenopausal women have rarely been investigated. Premenopausal and postmenopausal breast cancer may have different etiologies and alcohol may affect these groups differently or may only affect one group or may affect neither group. Clearly it is crucial to conduct further studies on the link between alcohol consumption and breast cancer in order to discover the true relationship so we can produce better preventive methods to battle breast cancer. The present thesis will add important information regarding the association between alcohol consumption and the risk of breast cancer

because alcohol from specific beverages as well as alcohol intake at different ages of a women's life is being investigated in a strictly postmenopausal population.

TABLE 2.1a: Summary of Case-Control Studies of the Association Between Consumption of Alcohol and the Risk of Breast Cancer

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Cade *et al.*[105] (England 1990-1992)	220 postmenopausal cases 825 postmenopausal controls who were found to be normal and referred for a routine re-screening appointment Age 50-65 years Eligibility: women who participated in the breast assessment clinics of the breast screening program in Southampton and Portsmouth, UK	87% for all subjects	Not stated	Alcohol consumption in the last year Type of beverage was not specified	**Current total alcohol intake** (Quartiles) 1: 1.00 2: 0.77 (0.49-1.21) 3: 0.97 (0.63-1.49) 4: 0.97 (0.61-1.54) P(linear trend) ≥ 0.25	Median was around one gram of alcohol for both cases and controls Unsure about the range of alcohol consumption but the 2.5th percentile is 0.00 and the 97.5th percentile is 33.5 for cases Postmenopausal women were defined with an age cut-off of 50 years	Controlled for age, age at menarche, age at first birth, social class, body mass index, smoking, iron and vitamin E Perhaps should have controlled for saturated fat (from the univariate analysis)
Ferraroni *et al.*[94] (Milan, Genoa, the provinces of Pordenone and Gorizia in Northern Italy,	1577 postmenopausal cases admitted to major teaching hospitals and general hospitals in the study areas 1745 postmenopausal hospital controls admitted to hospitals in the same catchment areas as the cases for acute conditions	Less than 4% of cases and 4% of controls did not participate	Histo-logically confirmed Diagnosed within the year before interview with no previous history of cancer	Usual consumption two years before diagnosis Type of beverage was specified	Reference group is abstainers **Recent alcohol intake** *Total alcohol (g/day)* 1.00-5.87: 1.01 (0.79-1.30) 5.88-13.40: 1.23 (0.97-1.56) 13.41-24.55: 0.98 (0.77-1.25) 24.56-27.60: 1.03 (0.81-1.30) >27.60: 1.13 (0.89-1.44) Ex-drinkers: 1.05 (0.78-1.41) P(linear trend) = 0.62	Cases and controls were not individually matched nor matched by hospital but the distributions of cases and controls were similar for age and area of residence Low power for grappa and spirit categories	Controlled for age, centre, education, age at first birth, parity, age at menarche, body mass index and family history of breast cancer Adjustments for 5-year age groups and selected dietary factors (starch, fibre,

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Ferraroni *et al.*[94] (cont'd) the provinces of Forli and Latina in central Italy and Naples 1991-1994)	(22% traumas-fractures/sprains (not alcohol related), 33% non-traumatic orthopaedic diseases, 15% surgical conditions, 18% eye diseases, 12% miscellaneous such as ear, nose, throat, skin, dental conditions) Age range unspecified			Validated food-frequency questionnaire	**Consumption only for specific beverages (g/day)** *Alcohol from wine* Non-drinkers: 0.85 (0.56-1.29) 1.00-12.76: 1.12 (0.89-1.42) 12.77-13.45: 1.13 (0.90-1.42) 13.46-26.33: 1.11 (0.88-1.41) ≥26.34: 0.99 (0.79-1.42) Ex-drinkers: 1.06 (0.79-1.42) P(linear trend) = 0.45 *Alcohol from beer* Non-drinkers: 1.00 (0.85-1.17) Drinkers: 1.12 (0.82-1.52) Ex-drinkers: 0.96 (0.72-1.28) *Alcohol from amari* Non-drinkers: 1.02 (0.87-1.19) Drinkers: 0.83 (0.51-1.34) Ex-drinkers: 0.96 (0.72-1.28) *Alcohol from grappa* Non-drinkers: 0.99 (0.84-1.16) Drinkers: 1.54 (0.99-2.41) Ex- drinkers: 0.97 (0.73-1.29) *Alcohol from spirits* Non-drinkers: 0.99 (0.85-1.16) Drinkers: 1.59 (0.94-2.67) Ex-drinkers: 0.96 (0.72-1.28)	Women admitted with diseases related to known risk factors for breast cancer were not included Menopausal status was ascertained by questionnaire but no definition was given	beta-carotene and vitamin E) did not alter the risk estimates

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Ferraroni *et al.*[94] (cont'd)					**Consumption of alcoholic beverages simultaneously adjusted for other alcoholic beverages (g/day)** Wine 1.00-12.76: 1.13 (0.89-1.42) 12.77-13.45: 1.14 (0.91-1.43) 13.46-26.33: 1.11 (0.87-1.40) ≥26.34: 0.98 (0.78-1.23) Beer: 1.08 (0.80-1.46) Grappa: 1.55 (1.00-2.41) Amari: 0.75 (0.47-1.21) Spirits: 1.57 (0.93-2.65) **Duration of alcohol use (years)** <20: 1.20 (0.74-1.93) 20-29: 0.96 (0.69-1.35) 30-39: 1.15 (0.92-1.44) ≥40: 0.91 (0.75-1.09) P(linear trend): Non-significant **Age at first drink (years)** ≤15: 0.87 (0.65-1.15) 15-19: 0.85 (0.68-1.07) 20-24: 1.05 (0.85-1.31) ≥25: 1.13 (0.91-1.40) P(linear trend): Non-significant		

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Bowlin *et al.*[80] (Long Island, NY (two counties-Nassau and Suffolk) 1984-1986)	774 postmenopausal cases used in the analysis were identified by surveillance of all Long Island hospitals' tumour registries and medical records 774 postmenopausal population controls used in the analysis were obtained through driver's licence files Matched by age (± 1 year) and by county of residence Age <79 years Exclusion: women without driver's licences	67% (cases) 41% (controls)	Incident histo-logically confirmed breast cancer	Current alcohol intake prior to diagnosis Type of beverage was specified Standardized telephone questionnaire	**Current alcohol intake (g/day)** *Total alcohol* 0: 1.00 >0-5: 1.32 (0.97-1.80) ≥5: 1.51 (1.09-2.08) *Different alcohol beverages* None: 1.00 Beer: 1.92 (0.95-3.89) Wine: 1.32 (0.94-1.85) Liquor: 1.44 (1.01-2.07) Combo: 1.52 (1.09-2.12) **Duration of alcohol use (years)** 0: 1.00 >0-<20: 1.04 (0.56-1.94) 20-<40: 1.57 (1.12-2.21) 40+: 1.37 (0.99-1.90) **Age at first drink (years)** (univariate analysis with 558 case/control pairs) 25+: 1.00 (Reference) ≤17: 0.99 (0.69-1.44) 18-24: 1.03 (0.78-1.36) **Alcohol consumption** Never: 1.00 Ever: 1.43 (1.06-1.94)	Controls who responded were younger than those who did not respond Only 23 case subjects drank beer No test for linear trend in the multivariate analysis of current total alcohol intake but the univariate analysis test for linear trend had a p value < 0.01 Menopausal status was ascertained by questionnaire but no definition was given	Controlled for age, county, marital status, family history of breast cancer, history of benign breast disease, ever pregnant, age at first live birth, total weeks spent breastfeeding, and ever smoked Religion, years of education, household income, age at menarche, menopausal status and body mass index had no relationship with breast cancer

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Nasca *et al.*[89] (New York, USA 1982-1984)	1617 cases 1617 population controls obtained from driver's licence files of the N.Y. State Department of Motor Vehicles Category matched by year of birth and county of residence Age 20-79 years Exclusions: women without a New York State driver's license and women with unlisted telephone numbers	91% (cases) 72% (controls)	Primary breast cancer identified through the diagnostic index, tumour registry, and pathology files	Usual alcohol consumption Type of beverage was specified in questionnaire Telephone interview	**Usual total alcohol intake (g/day)** None: 1.00 <1.4: 1.07 (0.83-1.36) 1.5-4.9: 1.04 (0.78-1.39) 5.0-14.9: 1.10 (0.87-1.39) ≥15.0: 1.26 (0.98-1.64) **Duration of alcohol use (years)** Never drank: 1.00 ≤20: 1.34 (1.02-1.77) 21-30: 1.09 (0.85-1.41) 31-40: 1.22 (0.96-1.54) 41+: 1.13 (0.89-1.44) P(linear trend) = 0.619 **Age at first drink (years)** Never drank: 1.00 ≤17: 1.02 (0.76-1.35) 18-21: 1.13 (0.91-1.41) 22-30: 1.33 (1.04-1.71) 31+: 1.43 (1.02-2.00) P(linear trend) = 0.003	No test for linear trend was given for current intake but the univariate test for trend was 0.009 and the multivariate was only slightly less significant	Controlled for age, race, age at first live birth, menstrual status, benign breast disease and family history of breast cancer Religion, education, marital status, age at menarche, parity, body mass index, and cigarette smoking did not alter breast cancer risk Perhaps should have adjusted for age at menopause
Royo-Bordonada *et al.*[81] EURAMIC study (Germany, North Ireland,	315 postmenopausal cases 364 postmenopausal population controls Frequency matched for age (≤5 years) and center	86% (cases) 41 % (controls)	First diagnosis of breast cancer (ICD-174) histo-logically classified as ductal carcinoma	Usual intake within the last year Type of beverage was not specified	**Current total alcohol intake** Never drinkers: 1.00 Ex-drinkers: 1.61 (0.90-2.90) Current drinkers Tertile 1: 0.87 (0.45-1.70) Tertile 2: 0.90 (0.44-1.82) Tertile 3: 0.99 (0.48-2.01) P(linear trend) = 0.78	In Germany and Switzerland random samples were obtained from local population registries, in the Netherlands, North Ireland, and Spain controls were selected by random sample through patient's general practitioner	Controlled for age, center, body mass index, smoking, parity, age at menopause, age at menarche, estrogen replacement therapy, family history of breast cancer,

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Royo-Bordonada *et al.*[81] (cont'd) Netherlands, Spain and Switzerland 1990-1992)	Age 50-74 years Cases were recruited from the surgical units of participating hospitals		with primary tumors less than 5 cm, axillary lymph nodes stage ≤N3, without any clinical indication of distant metastases at discharge		**Age at first drink among current drinkers (years)** <40: 1.36 (0.96-1.91) >40: 0.94 (0.53-1.66) **Age at first drink among ex-drinkers (years)** <40: 1.83 (1.11-3.00) >40: 1.55 (0.62-3.87)	In Germany there was no information on past drinking therefore not included in estimates of risk for ex-drinkers Menopausal status was ascertained by questionnaire but no definition was given	history of benign breast disease, age at first birth and exclusion of centers without ex-drinkers among cases and controls
Levi, F *et al.*[95] SEARCH Programme of the IARC (Lausanne, Switzerland 1990-1995)	230 cases admitted to the University Hospital (152 postmenopausal women) 507 hospital controls admitted to the same hospital (29% traumas –sprain and fractures, 11% non-traumatic orthopaedic diseases, 35% surgical conditions	Less than 15% of the partic-ipants did not have an interview	Histo-logically con-firmed, diagnosed within one year of interview	Usual alcohol consumption Type of beverage was specified in questionnaire	Reference group is non-drinkers Postmenopausal women **Usual total alcohol intake (drinks/day)** 0: 1.00 <1: 1.0 (0.6-1.7) ≥1: 1.3 (0.8-2.2) All subjects **Usual alcohol intake (drinks/day)** Total <1: 1.3 (0.8-1.9) 1-<2: 1.8 (1.1-2.9) 2-4: 1.5 (0.8-2.7) >4: 2.7(1.3-5.8) P(linear trend) < 0.01	Primary diagnosis of control subjects were unrelated to any of the known or suspected risk factors for breast cancer Menopausal status was ascertained by questionnaire but no definition was given	Controlled for age, marital status, education, age at menarche, parity, age at first birth, age at menopause, menopausal status, type of menopause, family history of breast cancer, smoking habits, oral contraceptives and hormonal replacement use

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Levi, F *et al.*[95] (cont'd)	and 25% miscellaneous other disorders (including acute medical, eye, nose and throat) All cases were matched with a cancer registry Age 27-75 years				*Wine* >0-<1: 1.2 (0.8-1.9) 1-<2: 1.7 (1.0-2.7) ≥2: 2.0 (1.2-3.2) P(linear trend) < 0.01 *Beer* ≥0.5: 2.6 (1.4-4.6) *Spirits* >0-<1: 1.8 (1.1-2.9) ≥1: 2.0 (0.9-4.7) **Duration of alcohol use (years)** <20: 1.6 (1.0-2.6) 20-29: 1.4 (0.9-2.3) ≥30: 1.5 (1.0-2.4) **Age at first drink (years)** <30: 1.8 (1.2-2.8) ≥30: 1.4 (0.9-2.0) **Alcohol Consumption** Never: 1.00 Ever: 1.5 (1.1-2.2)		
Morabia *et al.*[115] (Switzerland 1992-1993)	244 cases obtained from three private laboratories and the University Hospital Pathology Department Age <75 years	71% (cases) 70% (controls)	Pathology reports were obtained for all breast cancer cases	Alcohol intake Semi-quantitative food frequency questionnaire	**Alcohol intake (g/day)** None: 1.00 0.1-5.0: 0.7 (0.4-1.3) 5.1-10: 0.9 (0.4-2.0) >10: 0.6 (0.3-1.2)	Only 150 cases and 336 controls were used to assess alcohol intake because the food frequency questionnaire was only established during the second year of the study	Controlled for age, education, body mass index, age at menarche, age at first live birth, oral contraception, breast cancer in mother or sister, history of breast biopsy and saturated fat

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Morabia et al[115] (cont'd)	1032 population controls selected randomly from an official list of all residents Age 30-74 years Eligibility: women who were residents of Geneva, Switzerland between 1992-1993						
Männistö *et al.*[82] Kuopio Breast Cancer Study (Finland 1990-1994)	328 cases obtained from Kuopio University Hospital (196 postmenopausal) 417 (233 postmeno-pausal) community controls sampled from the population register, covering the same catchment area, individually matched by age (+/- 5 years) and type of area (urban/rural) Age 25-75 years	Particip-ation rate for controls was 77%	Histo-logically confirmed malignant tumors	Current alcohol intake Type of beverage was not specified	**Current total alcohol intake** Never: 1.00 < once a month: 0.93 (0.66-1.31) Monthly-daily: 1.02 (0.66-1.57)	Two controls who developed breast cancer during the study years were not included as cases but remained controls	Controlled for age and area, perhaps should have controlled for age at first full-term pregnancy, parity, use of oral contraceptives, first-degree family history of breast cancer, benign breast disease and smoking

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Freudenheim *et al.*[83] (Erie and Niagara Counties New York, USA 1986-1991)	740 cases identified through all major hospitals in the two counties (439 postmenopausal) 810 population controls randomly selected from lists of residents of the same two counties (494 postmenopausal) Controls less than 65 years old were obtained from the New York State driver's license records and controls ≥ 65 years old were obtained from the Health Care Finance Administration Frequency matched on age Age 40-85 years	58% (cases) 50% (controls)	Incident primary histo-logically confirmed breast cancer	Usual alcohol consumption two years prior to disease Type of beverage was specified in questionnaire At-home interview	**Total alcohol consumption** *2 years ago (drinks/month)* 0: 1.00 1-3: 0.90 (0.65-1.25) 4-16: 0.85 (0.61-1.18) 17-27: 0.91 (0.55-1.50) ≥28: 0.89 (0.62-1.30) P(linear trend) = 0.93 *10 years ago (drinks/month)* 0: 1.00 1-3: 0.99 (0.72-1.38) 4-16: 1.15 (0.82-1.61) 17-27: 0.70 (0.43-1.15) ≥28: 0.91 (0.63-1.32) P(linear trend) = 0.66 *20 years ago (drinks/month)* 0: 1.00 1-3: 0.88 (0.64-1.20) 4-16: 0.92 (0.67-1.27) 17-27: 0.73 (0.44-1.20) ≥28: 0.74 (0.51-1.07) P(linear trend) = 0.25 *At 16 years of age (drinks/month)* 0: 1.00 1-3: 0.91 (0.63-1.31) 4-16: 0.93 (0.57-1.51) 17-27: 0.24 (0.06-0.94) ≥28: 0.72 (0.22-2.40) P(linear trend) = 0.89	Postmenopausal status was defined as those women who had ceased menstruating because of natural menopause Women who had ceased menstruating because of medical intervention were considered postmenopausal if they were <50 years of age and neither ovary was functioning (bilateral oophorectomy or irradiation to the ovaries) or if they were >50 years of age Results for premenopausal and postmenopausal women were similar so they were combined in the analysis controlling for menopausal status	Controlled for age, education, menopausal status, age at menarche, age at first pregnancy, family history of breast cancer, previous benign breast disease, body mass index, intake of kcal, fat, carotenoids, vitamin C, α-tocopherol, folic acid and dietary fibre

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Freudenheim *et al.*[83] (cont'd)	Eligibility: residents of one of the counties, alert, fluent in English, sufficiently good health, and Caucasian				**Wine consumption** *2 years ago (drinks/month)* 0: 1.00 1-2: 0.97 (0.75-1.26) 3-27: 0.90 (0.67-1.21) ≥28: 0.80 (0.51-1.25) P(linear trend) = 0.04 *10 years ago (drinks/month)* 0: 1.00 1-2: 1.21 (0.94-1.55) 3-27: 0.93 (0.69-1.26) ≥28: 1.03 (0.62-1.69) P(linear trend) = 0.96 *20 years ago (drinks/month)* 0: 1.00 1-2: 1.13 (0.89-1.44) 3-27: 0.99 (0.73-1.34) ≥28: 0.74 (0.38-1.42) P(linear trend) = 0.53 *At 16 years of age (drinks/month)* 0: 1.00 1-2: 1.08 (0.66-1.77) 3-27: 1.07 (0.42-2.69) ≥28: 0.31 (0.03-3.48) P(linear trend) = 0.99		

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Freudenheim *et al.*[83] (cont'd)					**Beer consumption** *2 years ago (drinks/month)* 0: 1.00 1-2: 0.93 (0.71-1.21) 3-27: 1.02 (0.74-1.41) ≥28: 1.37 (0.83-2.25) P(linear trend) = 0.08 *10 years ago (drinks/month)* 0: 1.00 1-2: 0.92 (0.70-1.21) 3-27: 1.04 (0.76-1.42) ≥28: 1.24 (0.78-1.96) P(linear trend) = 0.09 *20 years ago (drinks/month)* 0: 1.00 1-2: 1.07 (0.80-1.43) 3-27: 1.02 (0.75-1.38) ≥28: 1.21 (0.78-1.88) P(linear trend) = 0.41 *At 16 years of age (drinks/month)* 0: 1.00 1-2: 1.02 (0.59-1.75) 3-27: 0.64 (0.37-1.12) ≥28: 0.02 (0.000002-149.73) P(linear trend) = 0.06 **Hard liquor consumption** *2 years ago (drinks/month)* 0: 1.00 1-2: 0.87 (0.68-1.11)		

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Freudenheim *et al.*[83] (cont'd)					3-27: 0.75 (0.56-1.00) ≥28: 0.84 (0.52-1.38) P(linear trend) = 0.85 *10 years ago (drinks/month)* 0: 1.00 1-2: 0.83 (0.64-1.07) 3-27: 0.79 (0.60-1.05) ≥28: 1.03 (0.47-1.28) P(linear trend) = 0.50 *20 years ago (drinks/month)* 0: 1.00 1-2: 0.76 (0.59-0.98) 3-27: 0.73 (0.55-0.97) ≥28: 0.71 (0.43-1.17) P(linear trend) = 0.04 *At 16 years of age (drinks/month)* 0: 1.00 1-2: 0.94 (0.56-1.57) 3-27: 1.70 (0.72-4.03) ≥28: 1.59 (0.10-26.34) P(linear trend) = 0.36 **Total number of drinks in the past 20 years** *All alcoholic beverages* 0-479: 1.00 480-1300: 1.13 (0.84-1.53) 1301-4560: 0.99 (0.73-1.35) 4561-6719: 0.95 (0.59-1.52) ≥6720: 0.86 (0.61-1.21) P(linear trend) = 0.76		

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Alcohol Status	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Freudenheim *et al.*[83] (cont'd)					*Wine* 0: 1.00 1-240: 1.01 (0.76-1.34) 241-1300: 1.05 (0.77-1.44) 1301-6719: 0.80 (0.57-1.14) ≥6720: 0.94 (0.53-1.69) P(linear trend) = 0.24 *Beer* 0: 1.00 1-240: 1.14 (0.85-1.53) 241-1300: 0.94 (0.67-1.30) 1301-6719: 1.30 (0.81-2.08) ≥6720: 1.25 (0.78-2.00) P(linear trend) = 0.11 *Hard Liquor* 0: 1.00 1-240: 0.90 (0.68-1.20) 241-1300: 0.85 (0.63-1.16) 1301-6719: 0.74 (0.53-1.04) ≥6720: 0.70 (0.42-1.18) P(linear trend) = 0.37		
Hirose *et al.*[96] Aichi Cancer Centre Hospital (Japan 1988-1992)	445 natural postmenopausal cases from the Aichi Cancer Center Hospital 6215 natural postmenopausal non-cancer	98% for both cases and controls	Histo-logically confirmed	Usual alcohol intake prior to the presentation of symptoms Type of beverage was not specified	**Current total alcohol intake (go/day)** Non-drinker: 1.00 Drinker: 0.88 (0.67-1.15) Occasional: 0.92 (0.67-1.26) ≤1 go/day: 0.73 (0.43-1.24) >1 go/day: 1.26 (0.58-2.77) Go = the unit of Japanese sake	Data was collected from patients prior to their diagnosis Definition of natural menopause was not given	Controlled for age and first-visit year Perhaps should have adjusted for body mass index, age at first full-term pregnancy, smoking and physical activity

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Hirose *et al.*[96] (cont'd)	outpatient controls (44.3% free of disease, 13.1% benign tumour and/or non-neoplastic polyp, 7.5% mastitis, 4.1% digestive disease, 4.1% benign gynecological disease-based on a 10% random sample of all the controls) Age range unspecified			Self administered questionnaire		Prevalent cases Ten controls were categorized as having natural menopause at the age of <39, including two at <29	
Longnecker *et al.*[84] SEER program (Los Angeles 1987-1989)	1425 invasive and 161 in situ postmenopausal breast cancer cases identified through the Cancer Surveillance Program 1510 postmenopausal population controls, individually matched by age (±3 years), ethnicity and neighborhood	64% (cases) 80% (controls)	First diagnosis of histo-logically confirmed breast cancer Both in situ and invasive cancer were included	Recent intake (1 year before diagnosis) Lifetime alcohol consumption was estimated as the average alcohol consumed at ages 25, 40 and recent intake	**Recent total alcohol intake (g/day)** 0: 1.00 >0-5: 0.90 (0.71-1.14) 6-11: 0.73 (0.55-0.96) 12-18: 1.31 (0.96-1.79) 19-32: 1.28 (0.93-1.76) 33-45: 1.56 (0.94-2.59) ≥46: 1.36 (0.79-2.35) P(linear trend) = 0.02 **Alcohol intake at 25 years (g/day)** 0: 1.00 >0-5: 1.20 (0.97-1.52) 6-11: 0.96 (0.72-1.28) 12-18: 1.17 (0.78-1.77) 19-32: 1.11 (0.67-1.83) 33-45: 2.17 (0.89-5.29)	The number of matched pairs in the analysis that are in situ or invasive breast cancer is unspecified Postmenopausal women were defined as those women with no menstrual period in the reference year or women with menstrual periods but used hormone replacement therapy	Controlled for age, age at menarche, education, benign breast disease, family history, body mass index, parity, age at first full-term pregnancy, age at menopause and ethnicity

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Longnecker *et al.*[84] (cont'd)	1431 matched pairs used in analysis restricting to postmenopausal women Eligible participants were English speaking, non-Hispanic whites or Hispanic, residents of LA county, born in the US, Canada or West Europe Age 55-64 years			Type of beverage was specified At-home interview	≥46: 0.99 (0.44-2.20) P(linear trend) = 0.25 **Alcohol intake at 40 years (g/day)** 0: 1.00 >0-5: 1.00 (0.81-1.23) 6-11: 1.01 (0.79-1.28) 12-18: 1.21 (0.89-1.65) 19-32: 1.28 (0.92-1.80) 33-45: 2.32 (1.27-4.25) ≥46: 1.11 (0.70-1.77) P(linear trend) = 0.03 **Lifetime consumption of alcohol (g/day)** 0: 1.00 >0-5: 1.01 (0.84-1.22) 6-11: 1.21 (0.95-1.55) 12-18: 0.94 (0.69-1.29) 19-32: 1.63 (1.14-2.33) 33-45: 2.45 (1.22-4.93) ≥46: 0.94 (0.46-1.93) P(linear trend) = 0.01 **Different beverage types (13g/day)** Beer: 0.91 (0.71-1.17) Wine: 1.04 (0.79-1.36) Spirits: 1.22 (1.04-1.42) **Per 13 g/day at age 40** 1.14 (1.04-1.24)	Identified housing units where the case lived by a predefined walking pattern Spirit intake did not alter risk significantly from the other beverages	

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Longnecker *et al.*[85] (Maine, Massachusetts (excluding Boston), New Hampshire and Wisconsin 1988-1991)	6163 (4563 postmenopausal) cases reported to one of the four state-wide cancer registries 8480 (5733 postmenopausal) population controls Controls younger than 65 were randomly chosen from state driver's license lists and subjects 65-74 were obtained from the Health Care Financing Administration's list of Medicare beneficiaries Age <75 years	80% (cases) 84% (controls)	Cancer registry had histo-logically confirmed breast cancer for 98% of the inter-viewed cases	Average consumption of alcohol prior to diagnosis and during five age interval, 16-19, 20-29, 30-39, and 40-59 Type of beverage was specified in questionnaire Telephone interview	Postmenopausal women **Average alcohol consumption in the last age interval (g/day)** 0: 1.00 >0-5: 1.14 (1.00-1.31) 6-18: 1.20 (1.02-1.41) 19-32: 1.76 (1.36-2.26) ≥33: 2.13 (1.52-2.97) per 13 g/d: 1.26 (1.12-1.42) P(linear trend)<0.001 **Average alcohol consumption before age 30 (g/day)** 0: 1.00 >0-5: 0.89 (0.78-1.01) 6-18: 0.88 (0.73-1.05) 19-32: 1.15 (0.78-1.68) ≥33: 1.11 (0.64-1.94) per 13 g/d: 1.03 (0.88-1.20) P(linear trend)=0.75 All subjects **Average alcohol consumption in lifetime (g/day)** 0: 1.00 >0-5: 1.13 (1.01-1.26) 6-11: 1.24 (1.08-1.42) 12-18: 1.39 (1.16-1.67) 19-32: 1.69 (1.36-2.10) 33-45: 2.30 (1.51-3.51) ≥46: 1.75 (1.16-2.64) per 13 g/d: 1.31 (1.20-1.43) P(linear trend)<0.0001	Postmenopausal women were defined as those women without menses for 12 months and women who had had a hysterectomy and who had at least one remaining ovary if the reference age was in the highest decile of age at natural menopause For postmenopausal women, looking at drinking between 30-39 or 40-59 because all postmenopausal women should be over 40 Eligibility: residents of one of the four areas, a listed telephone number or one available through directory assistance, fluency in English, for those younger than 65 a self-reported possession of a driver's licence	Controlled for age, state, age at first full-term pregnancy, parity, body mass index, age at menarche, education, benign breast disease, age at menopause and family history of breast cancer Oral contraceptive use and hormone replacement therapy were not associated with alcohol, hence not considered true confounders and not looked at further in the analysis

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Ranstam and Olsson[109] (Lund, Sweden 1981-1984)	216 postmenopausal cases 254 postmenopausal population controls randomly selected through a national population register, of the same age and geographic location as the cases Age ≥44 years	90% (cases) 80% (controls)	Not defined	Frequency of recent alcohol intake Type of beverage was specified in the questionnaire Mailed questionnaire	**Recent alcohol intake** *Beer (bottles/week)* <1: 1.0 1-3: 0.9 (0.6-1.4) ≥4: 0.4 (0.1-1.3) *Wine (times/week)* Never: 1.0 Occasionally: 0.4 (0.3-0.7) Once a week: 0.4 (0.2-0.8) More often: 0.2 (0.1-0.5) *Spirits (times/week)* Never: 1.0 Occasionally: 0.6 (0.4-0.9) Once a week: 0.4 (0.2-1.3) More often: --	Cases were enrolled and interviewed from 1981 to 1984 whereas all controls were interviewed in 1984 Menopausal status was ascertained by questionnaire but no definition was given Only four subjects found in the "More often" category of Spirits intake	Controlled for age, age at menarche, age at first full-time pregnancy, parity and age at menopause Smoking status did not change breast cancer risk results
Katsouyanni *et al.*[114] (Athens, Greece 1989-1991)	820 cases (550 postmenopausal) 795 orthopaedic patients (43% had fractures, 28% had arthroplasty, 29% had other orthopaedic conditions) 753 hospital visitor controls excluding first-degree relatives and women who had breast cancer	94% (cases) 96% (hospital controls) 93% (visitor controls)	Histo-logically confirmed	Frequency of alcohol consumption per day, week or month, before the age of 30, between age 30 and 50 and over 50 years Type of beverage was specified in questionnaire	**Alcohol consumption before age of 30 years** Non-drinker: 1.00 Any: 1.06 (0.88-1.27) Wine: 0.89 (0.70-1.14) Beer: 1.32 (1.04-1.69) p-value = 0.02 Spirits: 0.95 (0.75-1.20) **Lifetime alcohol consumption** Non-drinker: 1.00 Any: 1.17 (0.95-1.42) Wine: 0.93 (0.72-1.20) Beer: 1.34 (1.05-1.71) p-value = 0.02 Spirits: 0.88 (0.71-1.09)	Conditional and unconditional logistic regression was used for the 680 triplets, results were the same so unconditional logistic regression was used for all cases and controls Menopausal status was ascertained by questionnaire but no definition was given Only results for consumption before 30	Controlled for age, place of birth, parity, age at first pregnancy, age at menarche, menopausal status, body mass index and total energy intake Dietary macronutrients do not change the breast cancer risk Exogenous estrogens are rarely used in

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Katsouyanni *et al.*[114] (cont'd)	(1041 post-menopausal controls in total) Individually matched on same hospital, +/- 5 years and residency Mean age of cases: 56.4 Mean age of controls: 54.4			Hospital interview	**Type of alcoholic beverage throughout life (number of drinks)** Non-drinkers: 1.00 Beer Only: 1.51 (0.92-2.47) Beer and other: 1.24 (0.99-1.55) Other only: 1.03 (0.74-1.44)	and consumption throughout life are given No fractures were associated with alcohol	Greece, so oral contraceptive use and hormone replacement therapy use were not controlled for
Landa *et al.*[97] (Navarra, Spain 1987-1988)	100 cases (84% are postmenopausal) from the hospital of Navarra 100 hospital controls (orthopaedic, ophthalmologic, and ear and nose disorders)	Not stated	Histo-logically confirmed	Average alcohol consumption before onset of disease Type of beverage was specified in questionnaire	**Current total alcohol intake (monthly tertiles)** Low: 1.00 Medium: 0.6 High: 2.0 P-value < 0.05	Does not give range of alcohol consumption Few cases and controls in middle tertile Control subjects could be related to alcohol Menopausal status was ascertained by questionnaire but no definition was given	Controlled for age Perhaps should have controlled for urban residence, family history of breast cancer, weight, and age at menopause
Martin-Moreno *et al.*[86] (Spain 1990-1991)	762 cases (515 postmenopausal) 988 population controls (632	89% (cases) 82% (controls)	Histo-logically con-firmed, first	Usual alcoholic intake in the year prior to diagnosis	Postmenopausal women only **Current total alcohol intake (g/day)** 0: 1.00 <1.81: 1.2 (0.8-1.7) 1.81-6.60: 1.6 (1.1-2.4)	Lifetime alcohol consumption could not be calculated	Controlled for age group, geographical region (province), socio-economic status, body mass

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Martin-Moreno *et al.*[86] (cont'd)	postmenopausal) obtained from random samples of the municipal rolls that corresponded to the catchment areas where the cases were detected Frequency matched by age (<5 years) Age 18-75 Eligibility: women listed on the municipal rolls as residents of one of five Spanish provinces		diagnosis of breast cancer	Type of beverage was specified in questionnaire Interviewer-administered, semi-quantitative food frequency questionnaire	6.61-18.80: 1.8 (1.3-2.7) >18.80: 1.9 (1.3-2.8) P(linear trend) = 0.01 All subjects *Wine (g/day)* 0: 1.00 <0.7: 1.2 (0.9-1.7) 0.70-5.12: 1.0 (0.8-1.4) 5.13-18.00: 1.8 (1.3-2.3) >18.00: 1.5 (1.0-2.5) P(linear trend) = 0.02 *Sherry (g/day)* 0: 1.00 <0.09: 1.2 (0.8-1.8) 0.09-0.20: 1.2 (0.8-1.8) 0.21-0.50: 1.2 (0.8-1.8) >0.50: 2.0 (1.3-3.2) P(linear trend) = 0.03 *Beer (g/day)* 0: 1.00 <0.76: 1.2 (0.9-1.6) 0.77-3.28: 1.2 (0.9-1.6) 3.29-6.55: 1.2 (0.8-1.8) >6.55: 1.2 (0.9-1.7) P(linear trend) = 0.37 *Liqueurs* 0: 1.00 <0.19: 0.8 (0.5-1.3) 0.19-0.58: 1.5 (1.0-2.5) 0.59-2.30: 1.1 (0.7-1.7)	Menopausal status was ascertained by questionnaire but no definition was given	index, family history of breast cancer, age at menarche, age at menopause, age at first full-term pregnancy and total energy intake Menopausal status was controlled for in the specific types of alcohol beverage analyses Oral contraceptive use, hormone replacement therapy use and regular smoking habit did not alter breast cancer risk History of benign breast disease was not controlled for because it is thought to be an intermediate factor (did not change the risk that much when controlled for)

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Martin-Moreno *et al.*[86] (cont'd)					>2.30: 1.5 (0.9-2.4) P(linear trend) = 0.15 *Spirits* 0: 1.00 <0.46: 1.0 (0.6-1.6) 0.46-1.38: 1.0 (0.6-1.7) 1.39-5.98: 1.3 (0.8-2.0) >5.98: 2.2 (1.1-4.2) P(linear trend) = 0.07		
Harris *et al.*[58,59] American Health Foundation (New York 1987-1989)	412 postmenopausal cases 336 postmenopausal hospital controls (18% leukaemia or lymphomas, 15% benign lesions excluding breast lesions, 11% benign haematological conditions, 10% infectious diseases, 10% minor surgical procedures, 9% other non-malignant chronic diseases, 8% other gastro-intestinal tract cancers, 7% traumatic injuries, 6% skin cancers,	Not stated	Diagnosis of primary breast cancer confirmed on the basis of review of the medical records and pathology reports	Recent intake of alcohol prior to illness Type of beverage was specified in questionnaire	**Recent total alcohol intake (g/day)** 0: 1.00 1-15: 1.1 (0.8-1.6) >15: 0.8 (0.5-1.3)	Controls with diseases related to alcohol or tobacco were excluded from the study Menopausal status was ascertained by questionnaire but no definition was given	Controlled for age, family history of breast cancer, age at menarche, parity, age at first pregnancy, breastfeeding, age at menopause, cigarettes smoked per day and oral contraceptive use Education did not alter breast cancer risk

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Harris *et al.*[58,59] (cont'd)	5% other cancers of the genitourinary tract, 1% central nervous system lesions) Frequency matched on age (<5 years), month of diagnosis and hospital of interview Age >40						
Kato *et al.*[106] (Japan 1990-1991)	908 cases (~420 postmenopausal) from 10 large hospitals in Japan 244 screening controls (70% breast cancer screening, 30% other) 664 hospital controls (45% no clinical finding, 20% benign breast disease, 12% cervical cancer, 8% digestive cancer, 2% other cancers,	Not stated	Histo-logically diagnosed	Frequency of alcohol consumption Type of beverage was not specified	**Usual total alcohol intake** None: 1.00 Occasional: 0.99 (0.80-1.22) Daily: 0.97 (0.71-1.33)	Controls could be related to alcohol Controls were excluded if they had hormone-related cancers	Only crude odds ratios are shown Should have controlled for family history of breast cancer, marital status, body mass index, parity, and age at first full-term pregnancy

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Kato *et al.*[106] (cont'd)	9% gynaecologic disease, 4% other non-malignant disorders) For each case, one hospital or screening control was selected (matched to the case by sex and age within three years at the same hospital) Age ≥20 years						
Pawlega[110] (Cracow, Poland 1987)	94 postmenopausal cases 180 postmenopausal population controls randomly selected from the general population using electoral roll and systematic sampling Each case was matched by age (+/- 5 years) and place of residence with two controls Age >50 years	75% cases 74% controls	Histo-logically confirmed carcinoma of the breast	Alcohol consumption 20 years ago Type of beverage was specified Mailed self-administered questionnaire	**Vodka consumption 20 years earlier** Never drinkers: 1.00 Ever drinkers: 1.2 (0.8-2.6)	Non-response required un-matched analysis Postmenopausal status was defined as women over 50 years old	Controlled for age, education, social class, marital status, number of person in household, body mass index, and previous 20 year habit of smoking

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Ewertz[87] (Denmark 1983-1984)	1486 cases (833 postmenopausal, 383 that were >60 years old) identified from the files of a nation-wide, clinical breast-cancer trial of the Danish Breast Cancer Co-operative Group and Danish Cancer Registry 1336 population controls (786 postmenopausal), who were an age stratified random sample selected from the general population identified from the Central Population Register Age <70 years	88% cases 78% controls	Histo-logically confirmed in all but five cases	Usual consumption of alcoholic beverages in the year before diagnosis Type of beverage was specified Self-administered questionnaires	**Current alcohol intake** Women > 60 years old *Total (g/day)* 0: 1.0 1-23 : 0.73 (0.50-1.06) ≥24: 0.95 (0.44-2.07) P(linear trend) = 0.60 All subjects *Beer (bottles/week)* 0: 1.00 <3: 0.94 (0.79-1.13) 3-6: 0.99 (0.72-1.35) 7: 0.84 (0.58-1.22) >7: 1.27 (0.78-2.07) *Table wine (glasses/week)* 0: 1.00 <3: 1.00 (0.81-1.23) 3-6: 0.99 (0.74-1.32) 7: 1.01 (0.67-1.53) >7: 1.30 (0.87-1.94) *Fortified wine (glasses/week)* 0: 1.00 <3: 1.03 (0.86-1.23) 3-6: 1.73 (0.98-3.03) >6: 1.29 (0.76-2.17) *Spirits (glasses/week)* 0: 1.00 <3: 0.96 (0.81-1.15) 3-6: 1.19 (0.84-1.67) >6: 0.89 (0.59-1.27)	There was 15%-25% missing values for each type of beverage 32 of the original 1694 cases invited to participate had a carcinoma in situ, it is unclear how many of them were included in the analysis	Controlled for age For women over 60, the analysis was controlled for age at diagnosis, parity and fat intake Place of residence (urban/rural), education, ever smokers, oral contraceptive use and body mass index did not alter breast cancer risk

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Ferraroni *et al.*[98] (Milan, Italy 1982-1985)	214 cases (105 postmenopausal) 215 hospital controls (99 postmenopausal) (46% had orthopaedic illnesses, 22% for acute surgical conditions, 32% for other conditions such as peripheral venous disease and benign tumors) Age 30-65	Not stated	Primary carcinoma of the breast (T1-2, N0-1, M0)	Usual weekly consumption in the past 12 months (if diet had recently changed they were asked to think about the previous 12 months' consumption) Type of beverage was specified	**Current alcohol intake (g/day)** Total None: 1.00 0.11-5.31: 1.1 (0.5-2.2) 5.32-13.10: 1.5 (0.8-2.8) 13.11-24.34: 1.2 (0.6-2.4) 24.35+: 2.1 (1.1-3.9) P(linear trend) = 0.035 *Wine* None: 1.00 0.11-5.82: 1.3 (0.6-2.5) 5.83-11.94: 1.0 (0.5-2.1) 11.95-23.49: 1.8 (0.8-3.8) 23.50+: 1.7 (0.9-3.2) P(linear trend) = 0.067 *Beer* None: 1.00 0.14-0.77: 0.6 (0.2-1.5) 0.78+: 0.6 (0.2-1.4) P(linear trend) > 0.10 *Spirits* None: 1.00 0.23-2.03: 0.6 (0.3-1.3) 2.04+: 0.9 (0.5-1.8) P(linear trend) > 0.25 *Aperitifs* None: 1.00 Yes: 1.7 (0.8-3.6) P(linear trend) > 0.15	Controls admitted for malignant tumours and hepatic, vascular and metabolic diseases were excluded	Controlled for age, parity, family history of breast cancer, education, age at first birth, age at menarche, age at menopause, body mass index

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Franceschi *et al.*[99] (Friuli-Venezia Giulia Region, Italy 1986-1987)	132 cases (~75 postmenopausal) 499 hospital controls-inpatients for acute conditions (40% for traumatic and non-traumatic orthopaedic conditions, 33% for surgical conditions, and 27% for other (ear, nose, throat, skin or teeth disorders)) Recruited from the Aviano Cancer Center and all other general hospitals of the Pordenone province Age <75	3 cases and 13 controls refused to participate	Histo-logically confirmed	Habitual alcohol consumption Type of beverage was specified in questionnaire	**Habitual alcohol intake** *Total alcohol (drinks/day)* 0: 1.00 1: 1.3 (0.7-2.6) 2: 1.4 (0.8-2.7) ≥3: 1.7 (0.9-3.2) P(linear trend) = 0.12 *Wine (drink/day)* 0: 1.00 1: 1.2 (0.7-2.4) 2: 1.4 (0.7-2.4) 3: 1.9 (0.9-3.9) 4: 1.6 (0.7-3.6) P(linear trend) = 0.09 *Beer (drink/day)* 0: 1.00 ≥1: 1.5 (0.6-3.5) *Hard Liquors (drinks/day)* 0: 1.00 ≥1: 0.6 (0.2-1.5) **Duration of alcohol use (years)** Never drinkers: 1.00 <20: 1.4 (0.7-3.0) 20-29: 2.1 (1.0-4.3) 30-39: 1.1 (0.5-2.1) ≥40: 1.6 (0.8-3.2) P(linear trend) = 0.30	Very low power in ≥1 drinks/day category for both beer and hard alcohol Too small for subgroup analysis Controls were excluded if their disease was related to alcohol or smoking consumption or those with a malignant disorder, endocrine or gynaecolgical disorder	Controlled for age, age at first birth, meat and vegetable intake, education, occupation, body mass index, reproductive and menstrual factors did not alter breast cancer risk

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Franceschi *et al.*[99] (cont'd)					Age at first drink (years) Never drinkers: 1.00 >30: 1.5 (0.7-3.1) 20-29: 1.7 (0.9-3.1) <20: 1.3 (0.7-2.5) P(linear trend) = 0.46		
Richardson *et al.*[61] (Montpellier, France 1983-1987)	409 cases (~265 postmenopausal) from the Paul Lamarque Center which is the main cancer treatment center in the area 515 hospital controls (~309 postmenopausal) admitted for the first time to neurological, neurosurgical or general surgery (30% admitted for neurosurgery-sicatic neuritis, traumatism or benign tumors, 8% abdominal surgery-gynaecological or digestive, 19% neurological conditions-peripheral paresis, paresthesia, epilepsy, 12% neurological disease-Multiple sclerosis and Parkinson's disease, 14% with slight psychological disorders, 12% admitted for headaches, asthenia and sleep disorders, 3% cardiovascular and 2% diagnoses were unknown) Age 28-66 years	100% cases 98% controls	Histo-logically confirmed primary carcinoma of the breast	Usual alcohol consumption within the last year unless habits had changed due to onset of disease Type of beverage was specified in questionnaire Face to face interview	<u>Only postmenopausal women</u> **Current alcohol intake** *Total (glasses/week)* None: 1.00 1-7: 4.6 (2.2-9.6) >7: 6.0 (2.6-13.9) <u>All subjects</u> **Current alcohol intake** *Total (glasses/week)* None: 1.00 1-7: 3.1 (1.8-5.4) >7: 4.0 (2.2-7.3)	Control subjects' conditions are not related to nutritional factors Controls were excluded if they were admitted for neoplastic or cardiovascular diseases Menopausal status was ascertained by questionnaire but no definition was given	Controlled for age, age at menopause, family history of breast cancer, past history of benign breast disease, age at menarche, parity, age at first full-term pregnancy, education level, body mass index and menopausal status

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Richardson *et al.*[60] (Montpellier France 1983-1986)	349 cases from the Paul Lamarque Center which is the main cancer treatment center in the area (161 postmenopausal) 459 hospital controls (199 postmenopausal) admitted for the first time for 30.3% surgical neurology (sciatic neuritis, traumatism and benign tumors), 11.5% for general surgery (gynaecological, digestive or orthopaedic), 30.5% for neurological syndromes (fainting, migraine, intracranial haemorrhage, meningitis, epilepsy, medical neuropathy, 12.9% suffered neurological diseases (multiple sclerosis, Parkinson's disease), 12.6% slight psychological disorders (depression, other disorders), 10% were unknown diagnoses Age 25-65 years	100% cases 98% controls	Histo-logically confirmed primary carcinoma of the breast	Usual alcohol consumption within the last year unless habits had changed due to onset of disease Type of beverage was specified in questionnaire Face to face interview	**Current alcohol intake** Reference group consists of women who drink less than one drink a week *Total (drinks/week)* 1-2: 1.8 (1.2-2.8) 3-9: 1.9 (1.3-2.7) 10-17: 2.3 (1.4-3.6) >17: 3.5 (2.0-6.1) P(linear trend) = 10^{-6} *Beer (drinks/week)* ≥1: 1.6 (0.9-2.8) *Wine (drinks/week)* 1-7: 2.2 (1.6-3.0) Fortified wines *(drinks/week)* 1: 2.0 (1.3-3.1) Spirits *(drinks/week)* >1: 3.6 (2.1-6.2)	Even though this is not as recent as the other article by Richardson *et al.*, the alcohol information is more complete	Adjustment for age, family history, benign breast disease, age at menopause, age at menarche, parity, age at first full-term pregnancy, education level, smoking, oral contraceptive use and body mass index did not modify the odds ratios
Sneyd *et al.*[88] (New Zealand 1983-1987)	891 cases (~285 postmenopausal cases) from the National Cancer Registry or the Auckland Breast Cancer Study Group 1864 population controls (~425 postmenopausal controls)	95% (cases) 90% (controls)	Histo-logically confirmed	Usual alcohol consumption within the last year and in the last 5 years Type of alcohol was specified	<u>Postmenopausal (natural) women</u> **Recent total alcohol consumption (drinks/week)** Never or <1: 1.0 1-7: 0.57 ≥8: 0.96 Ex-drinkers: 1.5	Data was not complete (complex) enough to look at dose-response for particular beverages, alcohol consumption at	Controlled for age, parity, social class, smoking and age at menarche Age at first full-term pregnancy, menopausal status,

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Sneyd *et al.*[88] (cont'd)	randomly selected from electoral rolls Age 25-54 Exclusions: women who were not in a current electoral roll and women whose telephone number could not be found			Telephone interview	Postmenopausal (artificial) women **Recent total alcohol consumption (drinks/week)** Never or <1: 1.0 1-7: 0.58 ≥8: 0.84 Ex-drinkers: 0.64 All subjects **Recent alcohol intake** *Total (drinks/week)* Never: 1.0 <1: 1.1 (0.69-1.8) 1-3: 0.88 (0.53-1.5) 4-7: 0.91 (0.54-1.5) 8-14: 0.91 (0.51-1.6) >14: 1.8 (0.87-3.8) P(linear trend) = 0.37 *Different alcoholic beverages* Never drinkers: 1.00 Only sherry: 0.78 (0.42-1.5) Only wine: 0.99 (0.57-1.7) Only beer: 1.00 (0.52-1.9) Only spirits: 0.78 (0.44-1.4) **Alcohol Consumption** Never drinkers: 1.00 Ex-drinkers: 1.3 (0.74-2.5) Current drinkers: 1.0 (0.64-1.7)	specific ages or duration Menopausal status was ascertained by questionnaire but no definition was given for natural or artificial menopause If alcohol was drank only before the 5 year period women were considered ex-drinkers	family history of breast cancer, history of benign breast disease, body mass index, ethnic group, years of education, geographical area, hypertension, diabetes, gall-bladder disease and ever use of oral contraceptives did not alter breast cancer risk

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Zaridze *et al.*[100] (Moscow, Russia 1987-1989)	81 postmenopausal cases 85 postmenopausal hospital controls with minor complaints only Matched on age (< 2 years) and neighborhood (catchment areas for local polyclinics) Age range unspecified	Only two potential cases and nine potential controls did not participate	Newly diagnosed cases, none with distant metastases	Average frequencies during the year prior to diagnosis Type of beverage was not specified	**Recent total alcohol intake (g/week)** 0: 1.00 <0.93: 2.26 (0.66-7.76) 0.93-2.12: 7.06 (1.70-29.40) 2.13-6.46: 3.10 (0.83-11.55) 6.47+: 0.74 (0.06-8.89) P(linear trend) = 0.003 **Alcohol consumption** Never: 1.00 Ever: 3.39 (1.37-8.38)	Postmenopausal status was defined as having no menstrual cycle within the six months prior to diagnosis for cases and interview for controls Controls could be related to alcohol	Controlled for age, education and age at menarche Perhaps should have controlled for age at menopause, length of menstrual cycle, age at first birth and some dietary factors (p-value < 0.09)
Rosenberg *et al.*[107] (Toronto, Canada 1982-1986)	607 cases (~300 postmenopausal) 1214 neighbourhood controls obtained through Toronto voting and census records within the same decade of age (~600 postmenopausal) 249 hospital controls (22% had gastrointestinal disorders, 20% had infections, 14% had disk and other musculoskeletal disorders and 44% were miscellaneous) Age <70 years	76% (cases) 65% (neigh-bourhood controls) Not stated for hospital controls	Histo-logically confirmed first occurrence of breast carcinoma	Usual alcohol consumption in the year prior to interview and three years earlier Type of beverage was specified in questionnaire Face to face, at-home interview	Reference group is women who drank <1 drink per month <u>Cases and neighbourhood controls</u> **Recent alcohol intake** *Total (number of drinks)* 1-3/month: 0.6 (0.4-0.8) 1-3/wk: 1.0 (0.7-1.4) 4-6/wk: 0.8 (0.6-1.2) 1/day: 0.8 (0.5-1.1) ≥2/day: 1.0 (0.7-1.5) Variable: 0.6 (0.4-1.0) Ex-drinker: 0.6 (0.3-1.1) *Beer (number of drinks)* 1-6/wk: 1.00 (0.6-1.7) ≥1/day: 1.7 (0.9-3.3)	Controls were admitted for conditions unrelated to alcohol consumption Controls were obtained from different hospitals (four) than the cases (one)	Controlling for age at menarche, age at first birth, parity, menopausal status, body mass index, history of breast cancer in mom or sister, history of fibrocystic breast disease, duration of oral contraceptive use, duration of supplemental estrogen use, cigarette smoking, years of education,

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Rosenberg *et al.*[107] (cont'd)	Eligibility: lived in metropolitan Toronto and spoke English with no history of breast cancer				*Wine* 1-6/wk: 1.00 (0.7-1.3) ≥1/day: 0.7 (0.5-1.0) *Liquor* 1-6/wk: 0.7 (0.5-1.0) ≥1/day: 1.1 (0.7-1.8) <u>214 cases and 428 neighbourhood controls</u> **Recent alcohol intake** *Total(number of drinks)* 1-3/month: 0.4 (0.2-0.7) 1-6/wk: 0.9 (0.6-1.5) ≥1/day: 0.8 (0.5-1.4) <u>214 cases and 249 hospital controls</u> **Recent alcohol intake** *Total(number of drinks)* 1-3/month: 0.8 (0.4-1.8) 1-6/wk: 1.3 (0.8-2.3) ≥1/day: 1.1 (0.6-2.1)	Postmenopausal status excludes those women who became menopausal because of hysterectomy with retention of one or both ovaries Only the results from three years prior are shown but results were similar	religion and dietary fat intake did not change breast cancer risk
Chu *et al.*[76] Cancer and Steroid Hormone Study	3,498 cases from population based registries in eight SEER centers (1170 postmenopausal) 3,157 population controls (1800 postmenopausal) obtained through random digit dialling who were residents of the same geographic area as the cases and	82% (cases) 81% (controls)	Histologically confirmed	Average alcohol consumption in the last five years Type of alcohol was specified	The reference group was women who had not drank in the past five years <u>Postmenopausal women (natural)</u> **Recent alcohol intake (drinks/week)** Total <1: 0.9 1-7: 0.9		Controlled for age, parity, menopausal status, age at first full-term pregnancy, age at menarche, family history of breast cancer, history of benign breast disease and pack-years of cigarette smoking

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Chu *et al.*[76] (cont'd) (metropolitan areas of Atlanta, Detroit, San Francisco, Seattle and the states of Connecticut, Iowa, and New Mexico and the four urban counties of Utah 1981-1982)	frequency-matched on age Age 20-54 years				≥8: 1.0 <u>Postmenopausal women (surgical)</u> **Recent alcohol intake (drinks/week)** *Total* <1: 1.0 1-7: 1.0 ≥8: 1.1 <u>All subjects</u> **Recent alcohol intake (drinks/week)** *Total* Ever: 1.0 (0.9-1.2) <1: 1.0 (0.8-1.1) 1-3: 1.0 (0.8-1.2) 4-7: 0.9 (0.7-1.1) 8-14: 1.1 (0.9-1.3) 15-21: 1.0 (0.8-1.4) 22+: 1.2 (0.9-1.6) P(linear trend) = 0.51 *Beer (cans/week)* Ever drinkers: 1.00 <1: 1.0 1-7: 1.0 ≥8: 1.0 P(linear trend) = 0.99		Body mass index, total months of breastfeeding, years of education and region of residence did not alter the risk of breast cancer

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Chu *et al.*[76] (cont'd)					*Wine (glasses/week)* Ever drinkers: 0.9 <1: 0.9 1-7: 0.9 ≥8: 1.2 P(linear trend) = 0.31 *Hard Liquor (drinks/week)* Ever drinkers: 0.9 <1: 0.9 1-7: 0.9 ≥8: 1.1 P(linear trend) = 0.26		
Iscovitch *et al.*[108] (La Plata, Argentina 1984-1985)	150 cases admitted to eight general hospitals 150 neighborhood controls (from same block) 150 hospital controls (in and out patients seen at same hospital as case, within three months of case's diagnosis) Controls matched to cases by age (+/- 5 years) Mean age of cases: 56 years old	98% (cases)	Histo-logically confirmed	Usual alcohol consumption in the last five years but not six months prior to onset of disease Type of beverage was specified in questionnaire	<u>Cases and neighborhood controls</u> **Recent total alcohol intake** 1: 1.0 2: 0.37 p-value <0.05 3: 1.1 4: 0.60 <u>Hospital controls</u> **Recent total alcohol intake** 1: 1.0 2: 0.40 p-value <0.05 3: 1.1 4: 1.2	Does not say how many women are postmenopausal Levels for each index are determined by the distribution of the neighborhood control group, frequency mean was 210 for cases (assumed to be number of drinks) Hospital controls were not specified but those with malignant disease or any conditions related to a special long-term diet were eliminated	Controlled for age, residential area, hospital, age at first full-term birth, husband's occupation and body mass index

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Kato *et al.*[104] (Japan 1980-1986)	1,740 cases (934 postmenopausal) 8,920 cancer controls (stomach (30.7%), large intestine (18.8%), uterus other than corpus (17.4%) and lung (7.2%), pancreas, biliary tract, hematopoietic tissue, urinary organs, thyroid, skin and other (4.4%)) All cancers were obtained from the Aichi Cancer Registry Age >20 years	Not stated	Not stated	Frequency of alcohol Type of beverage was specified in question-naire	<u>Women ≥ 50 years</u> **Usual alcohol intake** *Total* Current vs. None: 1.34 (1.06-1.68) Daily versus Less: 1.77 (1.19-2.64) Occasional versus None: 1.19 (0.91-1.57) Daily versus None: 1.80 (1.21-2.67) *Sake* None: 1.00 Current: 0.80 (0.49-1.30) *Beer* None: 1.00 Current: 1.56 (1.08-2.24) *Whisky* None: 1.00 Current: 1.22 (0.33-4.47) <u>All subjects</u> **Recent total alcohol intake** Daily vs. Less: 1.35 (1.01-1.80) p-value <0.05	Controls were excluded if the cancer was known to be related to alcohol (mouth, pharynx, eso-phagus and liver), if the cancer was of an ill-defined site or if the primary site was unknown Low power for whisky No definition given for postmenopausal status-assumed to be ≥ 50 years old There was no information on age at menarche, age at menopause, age at first full-term pregnancy, parity, use of exogenous hormones, body mass index, history of disease and nutritional intake	Controlled for age, smoking, marital status, residence, occupation and family history of breast cancer Analysis for women ≥50 years was only controlled for age

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
La Vecchia *et al.*[79] (Northern Italy 1983-1988)	2402 cases (~1363 postmenopausal) admitted to the National Cancer Institute and Ospedale Maggiore of Milan 2220 hospital controls from the same group of hospitals as the cases (32% had traumas, 29% non-traumatic orthopaedic conditions, 16% acute surgical conditions, 23% miscellaneous such as skin, eye, nose, throat or dental disorders) Matched on age by decades Age 21-74 years	Less than 3% of cases and controls did not participate	Histo-logically confirmed, diagnosed within one year before interview	Average alcohol con-sumption Type of beverage was specified	**Usual alcohol intake (drinks/day)** *Total* 0: 1.00 <1: 1.3 (1.1-1.6) 1-<2: 1.3 (1.1-1.5) 2-3: 1.4 (1.2-1.7) >3: 2.2 (1.7-2.7) P(linear trend) = 0.001 *Wine* 0: 1.00 <1: 1.2 (1.0-1.5) 1-<2: 1.3 (1.1-1.5) 2-3: 1.4 (1.2-1.6) >3: 2.2 (1.7-2.8) P(linear trend) = 0.001 *Beer* 0: 1.00 <0.5: 1.4 (1.1-1.8) 2-3: 1.5 (1.0-2.3) P(linear trend) = 0.002 *Spirits* 0: 1.00 <0.5: 1.4 (1.0-1.9) 2-3: 2.0 (1.3-3.1) P(linear trend) = 0.001	Controls were not included if their primary diagnosis was thought to be related to alcohol consumption	Controlled for age, geographical area, marital status, education, smoking, age at menarche, menopausal status, age at menopause, nulliparity, age at first birth, oral contraceptive and oestrogen replacement use, family history, nutrition and diet indicators

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
La Vecchia *et al.*[79]					**Duration of alcohol use (years)** Never: 1.00 <20: 1.6 (1.3-2.0) 20-29: 1.7 (1.4-2.0) 30-39: 1.7 (1.4-2.0) ≥40: 1.3 (1.1-1.6) **Age at first drink (years)** Never: 1.00 <30: 1.4 (1.2-1.7) >30: 1.4 (1.1-1.7)		
Meara *et al.*[101] (United Kingdom 1980-1984)	998 married cases from eight hospitals in London and Oxford 998 married hospital controls matched on age (5 years) Age 25-59 118 cases from a screening clinic in Edinburgh 118 controls selected among the normal screenees Age 45-69	100%	Diagnosed at the mammographic breast cancer screening clinic	Usual alcohol consumption before onset of breast cancer Type of beverage was not specified	**Recent total alcohol intake (g/day)** <u>Hospital study (age 25-44)</u> None: 1.00 <3: 1.0 (0.6-1.6) 3-12: 1.2 (0.7-2.1) 13-27: 0.7 (0.3-1.4) ≥28: 0.7 (0.3-1.7) <u>Hospital study (age 45-59)</u> None: 1.00 <3: 1.1 (0.8-1.6) 3-12: 1.0 (0.7-1.5) 13-27: 1.1 (0.6-1.7) ≥28: 1.1 (0.7-1.9) <u>Screening study</u> None: 1.00 <3: 1.2 (0.4-3.6) 3-12: 1.1 (0.3-3.5) 13-27: 1.1 (0.2-2.9) ≥28: 1.2 (0.1-9.4)	Controls were judged to have conditions which were not associated with breast cancer or with contraceptive practices but could be associated with alcohol	Controlled for age, menopausal status, age at first term pregnancy, age at menarche, family history of breast cancer of first degree relatives, duration of oral contraceptive use, body mass index, smoking and education

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Toniolo *et al.*[90] (Northern Italy 1983-1986)	250 cases from all major hospitals in the province of Vercelli 499 population controls (an age stratified random sample of the province's female residents obtained from electoral rolls) Age <75 years	91% (cases) 79% (controls)	Histo-logically confirmed adeno-carcinomas	Usual alcohol intake Type of beverage was not specified At-home face to face interview	**Usual alcohol intake (g/day)** *Total* 0: 1.00 >0-10: 0.9 (0.5-1.5) >10-20: 1.2 (0.7-1.9) >20-30: 1.0 (0.7-1.6) >30-40: 1.2 (0.6-2.4) >40: 1.6 (0.9-2.9) P(linear trend) linear model = 0.165 P(linear trend) quadratic model = 0.078 *Wine alone* 0: 1.00 >0-10: 0.9 (0.5-1.5) >10-20: 1.2 (0.8-1.9) >20-30: 1.0 (0.6-1.5) >30-40: 1.3 (0.6-2.5) >40: 1.8 (1.0-3.3) P(linear trend) linear model = 0.149 P(linear trend) quadratic model = 0.098	Interviewers were aware of case/control status Duration of exposure was not obtained Cases were identified from 1983-1984 while controls were recruited throughout the study period	Controlled for age, body mass index, menopausal status and energy intake (excluding calories from alcohol) Controlling for family history of breast cancer, history of breast lumps or breast surgery, age at menarche, age at menopause, marital status, parity and age at first full-term pregnancy did not alter breast cancer risk
Van't Veer *et al.*[91] (Nether-lands 1985-1987)	73 postmenopausal cases 79 postmenopausal population controls sampled from the muni-cipal population registry in the catchment area of the 17 hospitals Age 55-64 years	80% cases 55% controls	Histo-logically confirmed for 96% of the cases	Current alcohol consumption for the year prior to diagnosis Type of beverage was specified	**Recent total alcohol intake (g/day)** None: 1.00 1-4: 0.8 (0.3-2.3) 5-14: 1.0 (0.3-3.6) 15-29: 1.1 (0.3-4.3) ≥30: 0.9 (0.2-4.5) **Frequency (times/wk)** ≤3: 1.0 ≥4: 1.7 (0.6-4.8)	Very low power once stratified Postmenopausal women defined as those women over the age of 55	Controlled for age, region, season, reproductive history, level of education, first degree familial history, smoking habits, body mass index, energy per cent and fat intake

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Van't Veer *et al.*[91] (cont'd)				At-home face to face interview	**Dose (g/day)** 1-14: 1.0 ≥15: 0.4 (0.2-1.2) **Age at first drink (years)** Never: 1.00 ≤25: 1.8 (0.6-1.7) 26-35: 0.6 (0.2-2.2) 36-50: 0.7 (0.2-2.3) 55-64: 0.8 (0.2-3.5) **Age at first drink (years)** >26: 1.00 ≤25: 2.4 (1.0-5.6)		Controlling for age at menarche, benign breast disease and oral contraceptive use did not alter risk
Young[111] (Wisconsin, USA 1981-1982)	277 cases 372 population controls obtained from the 10 year file of motor vehicle operator licensees 433 cancer controls other than breast including colon (n=206), lung and bronchus (n=39), connective tissue and skin (n=15), uterus (n=109), ovary (n=33), thyroid (n=8), lymphatic (n=21) and endocrine (n=2) Age 35-89 years	64% (cases) 61% (cancer controls) 57% (population controls)	Histologically confirmed cases	Usual consumption of alcohol in two life periods, age 18-35 and age>35, excluding 5 years before diagnosis Type of beverage was not specified Mail-back questionnaire	Population controls **Early age (18-35) (drinks/week)** 0: 1.00 1-5: 1.74 (1.37-2.21) ≥6: 3.17 (2.20-4.57) **Later age (>35) (drinks/week)** 0: 1.00 1-5: 1.13 (0.87-1.46) ≥6: 2.67 (1.91-3.71) *Age at entry to study 50-60 years* Early age: 1.79 (0.82-3.91) Later-age: 2.29 (1.05-5.02) *Age of entry to study >60* Early age: 2.64 (1.20-5.78) Later-age: 1.96 (1.16-3.22)	Cancer controls were believed to not be related to alcohol	Controlled for age Education, mother with history of breast cancer, body mass index, use of estrogens, oral contraceptives, marital status, number of children, coffee, cigarette smoking and diet were controlled for and alcohol still remained significant (p-value < 0.05)

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Young[111] (cont'd)					Cancer controls **Early age (18-35) (drinks/week)** 0: 1.00 1-5: 1.49 (1.18-1.88) ≥6: 2.35 (1.68-3.29) **Later age (>35) (drinks/week)** 0: 1.00 1-5: 1.17 (0.91-1.51) ≥6: 1.93 (1.42-2.62) *Age at entry to study 50-60* Early age: 1.65 (0.83-3.27) Later-age: 1.36 (0.80-2.31) *Age at entry to study >60* Early age:2.51 (1.24-5.08) Later-age: 1.64 (1.04-2.57)		
Rohan and McMichael [92] (Adelaide, South Australia 1982-1984)	451 cases (281 postmenopausal) from a population-based South Australian Central Center Registry 451 population controls (288 controls) individually matched on age (within one year) and selected randomly from the electoral roll Age 20-74 years Eligibility: residents of the Adelaide metropolitan area	81% cases 70% controls	Histo-logically confirmed first diagnosis of breast cancer	Usual alcohol intake disregarding any recent changes in habit due to disease	Postmenopausal women **Current total alcohol intake (g/day)** 0: 1.0 <2.51: 0.84 (0.46-1.53) 2.51-9.30: 1.12 (0.59-2.15) >9.30: 1.27 (0.69-2.33) P(linear trend) = 0.388 All subjects **Current alcohol intake (g/day)** *Total* 0: 1.0 <2.51: 0.80 (0.51-1.27) 2.51-9.30: 1.16 (0.73-1.85)	Pairs were not matched on menopausal status so there were more postmenopausal controls than postmenopausal cases There were 262 pairs that were concordant on post-men status, but the analysis was done on all post-	Controlled for age, family history of breast cancer, history of benign breast disease, history of bilateral oophorectomy, age at first menstrual period, age at first live birth, age at last menstrual period, practice of breast self exam, ever use of oral contraceptives,

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Rohan and McMichael[92] (cont'd)	registered on the electoral roll			Type of beverage was specified Self-administered questionnaire	>9.30: 1.57 (0.99-2.51) P(linear trend) = 0.038 *Beer* 0: 1.0 <2.51: 1.06 (0.57-1.95) 2.51-9.30: 1.28 (0.66-2.47) >9.30: 1.12 (0.53-2.35) P(linear trend) = 0.511 *Wine* 0: 1.0 <2.51: 0.84 (0.55-1.29) 2.51-9.30: 1.20 (0.74-1.93) >9.30: 1.28 (0.78-2.08) P(linear trend) = 0.300 *Spirits* 0: 1.0 <2.51: 0.83 (0.50-1.38) 2.51-9.30: 1.79 (0.96-3.32) >9.30: 2.01 (1.01-4.00) P(linear trend) = 0.024	menopausal subjects Little power in highest category of spirits Postmenopausal women were defined as those women with no menstrual period within the last 12 months or women who had undergone a bilateral oophorectomy or women who had undergone a hysterectomy before the natural cessation of menstruation and who had retained at least one ovary but only if they were older than 56 years	ever use of replacement estrogens, history of cigarette smoking and years of education
O'Connell *et al.*[93] (North Carolina, USA 1977-1978)	276 cases (196 postmenopausal) admitted to Duke University, Durham County General and Cabarrus County Memorial Hospital	93% cases 88% controls	Histologically confirmed primary breast cancer	Habitual alcohol consumption	**Habitual total alcohol intake (drinks/week)** Postmenopausal women <1: 1.00 ≥1: 1.17 (0.70-1.97)	Cases interviewed in the hospital and controls interviewed at home	Controlled for age, race, estrogen use, oral contraceptives, and cigarette smoking

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
O'Connell *et al.*[93] (cont'd)	1519 community controls, (842 postmenopausal) obtained from a stratified sample of households within a region of North Carolina that served as the catchment area of the hospitals from where the cases were identified Age >30 years			Type of beverage was not specified	All subjects <1: 1.0 ≥1: 1.45 (0.99-2.12)	Menopausal status was ascertained by questionnaire but no definition was given for natural or surgical menopause	Controlling for family history of breast cancer, benign breast disease, age at first birth, menopausal status, type of menopause (surgical or natural), parity, years of education, age at menarche, body mass index, history of diabetes, history of gallbladder disease and history of hypertension did not alter risk
Katsouyanni *et al.*[102] (Greater Athens Area, Greece 1983-1984)	120 cases from two teaching hospitals in the Greater Athens area which admit a little more than half of the breast cancer cases in the area 120 hospital controls (37% had traumatic fractures, 10% had other trauma, 25% had osteoarthrosis and related disorders and 28% had other orthopaedic conditions) Age range unspecified	92% (cases) 92% (controls)	Histologically confirmed, 57 were localized, 59 had regional spread, and 4 had distant metastases	Average alcohol consumption in period prior to disease onset by frequency: never, rarely, at least once a month, at least twice a week, every day Type of beverage was not specified	No association	Controls were not selected from the same hospital as the cases Article had only distributions not odds ratios Half of the cases and controls were in the first two frequency levels, no subject drank every day Control conditions could be associated with alcohol	Controlled for age, interviewer, and length of schooling

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Lê *et al.*[62,63] (Paris, France 1976-1980)	1010 (~690 postmenopausal) cases from 66 private surgical clinics 1950 (~1300 postmenopausal) hospital controls requiring surgery for non-malignant disease (21% gynecologic disorders, 32% abdominal disorders, 10% cardiovascular, 8% musculoskeleteral or orthopaedic disorders, 9% traumatisms, 5% benign tumors excluding gynecologic or breast tumors, 14% other or unspecified disorders, 1% healthy) 940 cases were matched to two controls and 70 cases were matched to one control on age and clinic Mean age of cases = 58.2 Mean age of controls = 58.0	Not stated	Histo-logically confirmed primary breast cancer	Recent alcohol consumption Type of beverage was specified	**Recent alcohol intake (g/week)** *Total* None: 1.00 1-79: 1.0 (0.7-1.4) 80-159: 1.4 (1.0-2.0) 160-239: 1.5 (1.0-2.1) ≥240: 1.2 (0.7-2.0) *Cider* Never: 1.00 <10: 0.78 ≥10: 0.63 P(linear trend) = Non-significant *Beer* Never: 1.00 <80: 1.29 ≥80: 2.78 P(linear trend) = 0.02 *Wine* Never: 1.00 <80: 1.19 80-159: 1.77 ≥160: 1.32 P(linear trend) = 0.02	Some of the control conditions may be related to alcohol Cider and liquor may have low power Original group may have 50% missing information because analysis was performed on 500 cases and 945 controls with detailed information on alcohol consumption	Controlled for age, clinic, patient's occupation, history of breast cancer death of mother or sisters, age at menarche, history of surgery for benign breast disease, parity, age at first birth and induced or spontaneous menopause

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Lê *et al.*[62,63] (cont'd)					*Hard Liquors* Never: 1.00 <10: 0.86 ≥10: 0.46 P(linear trend) = Non-significant *Fortified wines* Never: 1.00 <10: 1.08 ≥10: 1.28 P(linear trend) = Non-significant **Alcoholic beverage with meals (1986)** No: 1.00 Yes: 1.9 (1.4-2.6) P(linear trend) = 10^{-6} **Alcoholic beverage with meals (1984)** No: 1.00 Yes: 1.47		
Talamini *et al.*[112] (Pordenone, Italy 1980-1983)	368 cases (~275 postmenopausal) from the General Hospital of Pordenone, more than 90% of cancer patients in the area are admitted to this hospital 373 hospital controls (~246 postmenopausal) due to 32% trauma	Less than 1% did not participate	Histo-logically confirmed diagnosis made within the previous year	Type of beverage was specified in questionnaire as well as lifelong average quantity *pro die*	**Alcohol beverage consumption** None: 1.00 Wine only, beer only, or spirits only: 2.3 (1.6-3.5) Combined: 7.6 (3.8-15.2) *Current wine intake (litres/day)* None: 1.00 ≤0.5: 2.4 (1.6-3.5) >0.5: 16.7 (3.1-89.7) P(linear trend) < 0.001	60% of cases and controls were interviewed by one interviewer and 40% were inter-viewed by a second one The category of >0.5 litres of wine	Controlled for education, occupation, marital status, food intake, age, body mass index, parity, age at first birth, age at menarche and at menopause, oral contraceptive and

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Talamini *et al.*[112] (cont'd)	(fractures and sprains), 9% acute infections, 6% dermatological disorders, 6% acute abdominal disorders, 14% ear, nose, throat, otitis media or sinusitis. Frequency matched on age (<5 years) Age 26-79				**Alcohol consumption** Never: 1.00 Ever: 2.5 (1.7-3.7)	had only 11 exposed cases and two exposed controls Controls were excluded if they had diseases that were malignant, hormonal or gynaecological but could be related to alcohol	other female hormone use, cigarette smoking and methlxanthine consumption
Rosenberg *et al.*[103] (USA, Canada, Israel 1976-1980)	1152 cases 519 cancer controls (64% endometrial cancer, 36% ovarian cancer) 2702 hospital controls (35% disc disorder, 18% acute infection or appendicitis, 14% uterine fibroids, 12% benign skin disorder, 8% haemorrhoids, 8% hernia, 5% ovarian cyst) Age 30-69	About 6% of the patients or their physicians declined an interview	Diagnosed during the year before admission based on discharge summary or pathology reports	Usual alcohol consumption during the year before admission Type of beverage was specified in questionnaire	**Current alcohol intake (days/wk)** Cancer controls Never: 1.00 Ex-drinkers: 1.3 (0.7-2.3) <4: 1.5 (1.1-2.1) ≥4: 2.0 (1.3-2.0) Non-malignant hospital controls Never: 1.00 Ex-drinkers: 1.6 (1.1-2.4) <4: 1.9 (1.5-2.4) ≥4: 2.5 (1.9-3.4) **Alcohol consumption** Cancer controls Never: 1.00 Ever: 1.4 (1.0-2.0) Non-malignant hospital controls Never: 1.0 Ever: 1.9 (1.5-2.4)	Type of beverage was specified in questionnaire but 649 cases, 376 cancer controls and 1610 hospital controls were excluded because they were ex-drinkers, did not specify preferred drink or did not drink only one type of alcoholic beverage	Controlled for age, geographical area of admitting hospital, year of interview, number of previous hospital admissions, years of education, cigarette smoking, religion, history of obesity, history of breast biopsy, age at menopause, age at first pregnancy, parity and history of breast cancer in the patient's mother or sisters

Table 2.1a (continued)

Reference (Place and year)	Study Population	Response Rate	Diagnosis of Breast Cancer	Measures of Alcohol Intake	Odds Ratio (95% confidence interval)	Comments	Adjustment for Confounding Factors
Miller *et al.*[64 65] (Saskatchewan, Winnipeg, Toronto, and Sherbrooke 1973-1976)	100 cases and 100 controls from each of the four areas = 400 matched pairs (112 were postmenopausal) Matched on age (<5 years), marital status and residence Age 35-74	Not stated	Newly diagnosed malignant breast cancer	Usual intake of alcohol during the immediate past two months and if different the intake of alcohol during a two month period, six months prior to the time of interview Type of beverage was not specified	**Recent total alcohol intake (g/day)** 0: 1.00 >0-<10: 0.93 10-<20: 1.50 20-<30: 0.99 30-<40: 0.22 ≥40: 1.41		Controlled for age and marital status
Williams and Horm[113] Third National Cancer Survey (United States 1969-1971)	"Intercancer comparison" of one cancer site with controls from other cancer sites Age ≥35	Not stated	Breast cancer death 95% of those inter-viewed had a report of the histo-logy of their cancer	Quantitative lifetime drinking history (at least once a week for a whole year) Type of alcohol was specified	**Lifetime alcohol intake** *Wine level (glass-years)* 1: 1.67 p-value < 0.01 2: 1.08 *Beer level (can-years)* 1: 1.18 2: 1.35 *Hard Liquor level (jigger-years)* 1: 1.43 p-value < 0.01 2: 1.44 p-value < 0.05 *Total alcohol level (ounce-years)* 1: 1.28 p-value < 0.05 2: 1.55 p-value < 0.01	Reference group were those women not exposed to alcohol Specific beverages were not adjusted for the use of other alcoholic beverages Control groups associated with alcohol were not used	Controlled for age, race and smoking Controlling for education, marital status and geo-graphical location did not alter breast cancer risk

TABLE 2.1b: Summary of Cohort Studies of the Association Between Consumption of Alcohol and the Risk of Breast Cancer

Reference (Place and year)	Study Population	Period of Follow-up	Number of Cases	Measure of Alcohol Consumption	Relative Risk (95% confidence interval)	Comments	Adjustment for Confounding Factors
Zhang *et al.*[78] Framingham Heart Study (Massachusetts, USA)	2873 women in original cohort in 1948 Age 28-62 years 2641 women in offspring cohort in 1971 Age 12-60 years An on-going population-based cohort study to evaluate risk factors for cardiovascular disease in the town of Framingham, Massachusetts with examinations every two years The population consisted of any one 30-59 years of age as of January 1, 1950 and the sample was chosen randomly by family	Median follow-up: Original cohort: 34.3 years (1948-1993) Offspring cohort: 19.3 years (1971-1993)	221 in original cohort (96% of cases occurred after menopause) 66 in offspring cohort (82% of cases occurred after menopause) Pathologically confirmed for 98% for original cohort and 100% for offspring cohort Response rate was not stated	Average alcohol consumption during follow-up period based on number of drinks consumed per month for the first two examinations of the original cohort and then per week for the remainder of the exams Type of beverage was specified	Original cohort **Usual alcohol intake** *Total (g/day)* None: 1.0 0.1-<5.0: 0.9 (0.6-1.2) 5.0-<15: 0.7 (0.5-1.1) ≥15: 0.7 (0.5-1.1) *Wine (drinks/week)* None: 1.0 0.1-<1.0: 0.9 (0.6-1.4) 1.0-<3.0: 0.7 (0.3-1.7) ≥3: 1.0 (0.7-1.5) *Beer (drinks/week)* None: 1.0 0.1-<1.0: 1.0 (0.7-1.4) 1.0-<3.0: 0.7 (0.3-1.6) ≥3: 1.0 (0.4-2.6) *Spirits (drinks/week)* None: 1.0 0.1-<1.0: 0.8 (0.5-1.4) 1.0-<3.0: 0.9 (0.4-1.9) ≥3: 0.7 (0.5-1.0) Offspring cohort **Usual alcohol intake** *Total (g/day)* Non-drinker: 1.0 0.1-<5.0: 0.7 (0.3-1.4)	Low power in high categories of beer consumption Results for combined analysis show similar results Information on family history of breast cancer and benign breast disease were not collected Many sick people did not respond to initial study	Controlled for age, education, height, body mass index, physical activity index, age at first pregnancy (original cohort only), parity, age at menarche (offspring cohort only), age at menopause, average number of cigarettes smoked and postmenopausal estrogen use

Table 2.1b (continued)

Reference (Place)	Study Population	Period of Follow-up	Number of Cases	Measure of Alcohol Consumption	Relative Risks (95% confidence interval)	Comments	Adjustment for Confounding Factors
Zhang *et al.*[78] (cont'd)					5.0-<15: 0.7 (0.3-1.6) ≥15: 1.0 (0.4-2.2) *Wine (drinks/week)* None: 1.0 0.1-<1.0: 1.0 (0.5-2.1) 1.0-<3.0: 0.7 (0.4-1.4) ≥3: 0.7 (0.3-1.5) *Beer (drinks/week)* None: 1.0 0.1-<1.0: 1.6 (0.7-3.6) 1.0-<3.0: 1.2 (0.6-2.6) ≥3: 0.9 (0.3-3.1) *Spirits (drinks/week)* None: 1.0 0.1-<1.0: 0.9 (0.4-2.0) 1.0-<3.0: 0.9 (0.4-1.7) ≥3: 0.7 (0.5-2.4)		
Thun *et al.*[116] Cancer Prevention Study II (United States)	676, 536 women in original cohort 251, 420 women used in analysis American Cancer Society volunteers in all 50 states recruited friends, relatives or neighbors (those they knew well because	1982-1991	691 breast cancer deaths In 1988 2.2% had been lost to follow-up In 1991, 12% of the cohort had died; death certificates available for 98%	Current alcohol consumption and duration of time drinking at baseline People who claimed change in drinking habits in the last ten years were asked about previous consumption	**Usual total alcohol intake (drinks/day)** None: 1.00 Less than daily: 1.1 (0.9-1.3) 1: 1.2 (1.0-1.6) 2-3: 1.5 (1.2-1.9) ≥4: 1.0 (0.7-1.4) P(linear trend) = 0.02	One fifth of the cohort completed a more detailed dietary questionnaire in 1992, the answers were similar to those obtained at baseline Subjects were more likely to	Controlled for exact age at enrolment, race, education, body mass index, smoking, fat consumption, estrogen replacement therapy, family history of breast cancer in mother or sister,

Table 2.1b (continued)

Reference (Place)	Study Population	Period of Follow-up	Number of Cases	Measure of Alcohol Consumption	Relative Risk (95% confidence interval)	Comments	Adjustment for Confounding Factors
Thun *et al.*[116] (cont'd)	they had to keep track of them) to complete a mailed questionnaire Age >30 years		Deaths obtained through personal inquiries by volunteers Participation rate: 37%	Type of beverage was not specified	**Usual total alcohol intake (drinks/day)** None: 1.00 Less than daily: 1.1 (0.9-1.3) ≥1: 1.3 (1.1-1.6) P(linear trend) = 0.006	be college-educated, married, middle class and white 55% of original cohort had missing alcohol information	total number of sisters, age at menarche, age at first birth, age at menopause, use of oral-contraceptives and presence of breast cysts
Garfinkel *et al.*[124] Cancer Prevention Study I (United States)	581,321 women Age >30 years but mostly population was over 45 Efforts were made to include all segments of the population in 25 states except migrant workers and those who could not easily be traced	12 years (1960-1972) 6,139,265 person years	2933 breast cancer deaths based on death certificates 92.2% of subjects accounted for by 68,000 volunteers who collected the questionnaires and reported periodically whether subjects were dead or alive	Average alcohol consumption at baseline, determined in whiskey equivalents (WE) Type of beverage was not specified	**Usual total alcohol intake (WE/day)** None: 1.00 Occasional: 0.96 (0.82-1.13) 1: 1.18 (1.03-1.36) 2: 1.06 (0.86-1.30) 3: 1.28 (0.95-1.74) 4: 1.36 (0.90-2.07) 5: 2.10 (1.18-3.72) 6+: 1.60 (1.00-2.56)	Drinking status was classified according to the 1959 baseline questionnaire and changes in habit over the following decade were not taken into account	Controlled for age, education, age at first pregnancy, family history of breast cancer, meat consumption and cigarette smoking
Fuchs *et al.*[68] Harvard Nurses' Health Study (11 large US states)	121, 700 registered female nurses completed a mailed questionnaire in 1976 Age 30-55 years	1980-1992	350 breast cancer deaths, 93% from pathology reports 1, 010, 209 person years	Usual alcohol intake during the previous 12 months in 1980 Type of beverage was not specified	**Usual total alcohol intake (g/day)** None: 1.00 0.1-1.4: 0.67 (0.45-1.01) 1.5-4.9: 0.85 (0.61-1.16) 5.0-14.9: 0.96 (0.71-1.32) 15.0-29.9: 1.37 (0.96-1.96) ≥30: 1.67 (1.10-2.53)	Age at menarche, parity, age at first full-term pregnancy, benign breast disease and family history of breast cancer could not be	Controlled for age, smoking status, body mass index, regular aspirin use, regular vigorous exercise, high plasma cholesterol level, diabetes, hyper-,

Table 2.1b (continued)

Reference (Place)	Study Population	Period of Follow-up	Number of Cases	Measure of Alcohol Consumption	Relative Risk (95% confidence interval)	Comments	Adjustment for Confounding Factors
Fuchs *et al.*[68] (cont'd)			Response rate to initial question-naire: 71% Participation Rate: 53% 89, 538 women used in analysis			controlled for because the original study objective was total mortality so specific cancer risk factors were not collected	tension, myocardial infarction in a parent past or present oral-contraceptive use, menopausal status, past or present post-menopausal hormone use, energy adjusted intake of dietary fibre and saturated fat
Willet *et al.*[69] Harvard Nurses' Health Study (11 large US states)	89 538 registered female nurses with no history of breast cancer Age 34-59 years In 1976, mailed questionnaires were sent to all married female registered nurses age 30-55 years residing in one of 11 larger US states	1980-1984	601 cases (including 40 women whose pathology reports had not yet been obtained) 80 303 in cohort in analysis but the number 89 538 was used in the denominator Response rate: 90%	Two questionnaires were given in the four year period At each interview women were asked how often on average over the past year alcohol was consumed. It was also asked if alcohol use had greatly increased, decreased or stayed the same over the previous ten years Type of beverage was specified	**Usual alcohol intake** *Total (g/day)* None: 1.00 <1.5: 1.0 (0.8-1.3) 1.5-4.9: 0.9 (0.7-1.2) 5.0-14.9: 1.3 (1.0-1.6) ≥15: 1.6 (1.3-2.0) P(linear trend) < 0.0001 *Total (drinks/day)* None: 1.00 <0.25: 1.0 (0.8-1.3) 0.25: 0.8 (0.6-1.2) 0.50: 1.3 (1.0-1.6) 1.0: 1.4 (1.1-1.8) >1.0: 1.5 (1.2-2.0) *Beer (g/day)* None: 1.00 <5.0: 1.3 (1.0-1.6) ≥5.0: 1.4 (1.1-1.8)		Controlled for age, menopausal status, age at first birth, age at menarche, maternal history of breast cancer and parity Family history of breast cancer, age at menopause, smoking, benign breast disease and nutrient intake did not alter breast cancer risk

Table 2.1b (continued)

Reference (Place)	Study Population	Period of Follow-up	Number of Cases	Measure of Alcohol Consumption	Relative Risk (95% confidence interval)	Comments	Adjustment for Confounding Factors
Willet *et al.*[69] (cont'd)					*Wine (g/day)* None: 1.00 <5.0: 0.9 (0.7-1.0) ≥5.0: 1.1 (0.8-1.4) *Liquor (g/day)* None: 1.00 <5.0: 1.1 (0.9-1.3) ≥5.0: 1.4 (1.1-1.7)		
Holmberg *et al.*[77] Sweden Mammography Cohort (Uppsala and Vastmanland County, Sweden)	61, 471 women Age 40-74 years Eligibility for nested case control study: participants must be members of the original screening cohort Original screening cohort: all women age 40-70 years old from Uppsala country and all women age 40-74 years old from	1987-1990	222 post-menopausal cases (invasive breast cancer either at the first screening, at a subsequent screen or independent of the mammography program) identified through pathology reports and cancer registries at screening centers 355 postmenopausal controls, frequency matched on month of diagnosis, age (<5 years) and county of residence 87% of the eligible women accepted the invitation and were	Usual alcohol consumption during the most recent six months before the first screening Telephone interview six months after screening or cancer diagnosis to examine "dietary periods" (times of constant eating patterns) Type of beverage was not specified Self-administered questionnaire	**Alcohol use** Never: 1.00 Ever: 1.9 (1.2-2.7) **Age at first drink (years)** Never: 1.0 15-27: 1.8 (1.2-2.7) ≥28: 1.7 (1.0-2.7) **Duration of alcohol use (years)** Never: 1.00 ≤10: 1.5 (0.9-2.5) 11-20: 1.8 (1.1-3.0) ≥21: 1.8 (1.2-3.0) **Currency of use** Never: 1.0 Stopped (>2 years): 1.6 (1.0-2.6) Current: 1.8 (1.2-2.8)	Postmenopausal status was defined with an age cut-off of >50 years	Controlled for age, county of residence, month of mammography, family history of breast cancer, parity, age at first birth, educational level and body mass index

Table 2.1b (continued)

Reference (Place)	Study Population	Period of Follow-up	Number of Cases	Measure of Alcohol Consumption	Relative Risk (95% confidence interval)	Comments	Adjustment for Confounding Factors
Holmberg *et al.*[77] (cont'd)	Vastmanland county were invited to receive a mammography		screened at least once Response rates were 73% for cases and 86% for controls		**Mean alcohol dose for overall period (g/day)** Never: 1.0 ≤0.75: 1.4 (0.9-2.3) 0.76-2: 2.1(1.3-3.4) ≥2 : 1.8 (1.1-2.9)		
Van den Brandt[117] Netherlands Cohort Study (Netherlands)	62 573 postmenopausal women Age 55-69 years A sub-cohort of 1812 women was randomly sampled from the cohort after baseline exposure measurements were taken Subjects originated from the general population and were sampled from the municipal population registries	3.3 years (1986-1989)	422 cases and 1579 sub-cohort members with complete alcohol data were used in the analysis Microscopically confirmed incident breast cancer cases Incident cancer cases identified by record linkage to cancer registries and a pathology register Completeness of cancer follow-up was estimated to be 95% Response rate to initial questionnaire: 36.6%	Current consumption of alcohol beverages during the year before the start of the study Type of beverage was specified A validated self-administered questionnaire	The reference group is total non-drinkers **Usual alcohol intake (g/day)** *Total alcohol* <5: 1.30 (0.96-1.75) 5-14: 1.29 (0.89-1.85) 15-29: 1.28 (0.81-2.03) ≥30: 1.72 (0.90-3.28) P(linear trend) = 0.047 *Alcohol from beer* Non-drinkers: 1.31 (1.00-1.73) Beer drinker: 1.27 (0.79-2.04) *Alcohol from wine* Non-drinkers: 1.28 (0.64-2.56) <5: 1.30 (0.97-1.75) 5-14: 1.30 (0.89-1.91) 15-29: 1.31 (0.80-2.16) ≥30: 1.64 (0.69-3.89) P(linear trend) = 0.039 *Alcohol from liquor* Non-drinkers: 1.25 (0.94-1.65) <15: 1.51 (1.00-2.29) ≥15: 1.96 (0.95-4.05) P(linear trend) = 0.005	Case-cohort analysis Short follow-up Post-menopausal women defined as those >55 years old (subjects were assumed to be post-menopausal) 10% of cases and 8% of sub-cohort had missing alcohol information	Controlled for age, history of benign breast disease, maternal breast cancer, breast cancer in sisters, age at menarche, age at menopause, oral contraceptive use, parity, age at first birth, body mass index, education, current cigarette smoking, and intake of energy

Table 2.1b (continued)

Reference (Place)	Study Population	Period of Follow-up	Number of Cases	Measure of Alcohol Consumption	Relative Risk (95% confidence interval)	Comments	Adjustment for Confounding Factors
Herrinton *et al.*[66] Breast Cancer Detection Demonstration Project (United States)	280, 000 women from different centres across the USA Age 35-74 The Breast Cancer Detection Demonstration Project is a screening program involving more than 280, 000 females at 29 centers Women were recruited for a five year program of annual breast exams	Enrolment 1973-1975 Follow up: 5 year period This study is based on women who had their breast cancer detected during the fifth year of the screening services	Nested case control analysis: 1799 cases (~730 postmenopausal cases) and 2208 controls selected from women who had not been recommended for or did not undergo a biopsy during screening Controls were stratified to cases on center, race, age (5 years), time of entry and length of participation 266 cases and 301 controls were used in the analysis because resources were available only for a small subset of the study participants Response rate: 74% cases 90% controls Breast cancer detected through screening program	Recent alcohol consumption before entry into screening program and during three age periods, less than 30 years of age, 30-49 years or 50 years and older Lifetime intake was also assessed using a weighted average of the time spent in each of the three periods, from age 21 to reference date Type of beverage was not specified Home interviews averaging five years after diagnosis	**Lifetime total alcohol intake (g/week)** Never: 1.00 Infrequent: 0.8 (0.5-1.3) 14-51 : 0.6 (0.3-1.1) ≥52: 0.9 (0.6-1.6)		Controlled for age at entry, age at first birth and parity Menopausal status, age at menopause, type of menopause, age at menarche, family history of breast cancer in a first-degree relative, educational attainment, oral contraceptives, hormone replacement therapy, number of breast biopsies, height, weight and body mass index did not alter breast cancer risk Perhaps should have controlled for age at menarche based on descriptive table

Table 2.1b (continued)

Reference (Place)	Study Population	Period of Follow-up	Number of Cases	Measure of alcohol consumption	RR (95% confidence interval)	Comments	Adjustment for confounding factors
Harvey *et al.*[67] Breast Cancer Detection Demonstration Project (United States)	280, 000 volunteer women from centres across the United States invited for breast cancer screening services for five years Age 35-74	Enrolment 1973-1975 Follow up: 5 year period This study looks at women whose breast cancer was detected between 1977-1980 (in the fifth year of the screening service)	1799 cases (~730 postmenopausal cases) and 2208 controls selected from women who had not been recommended for or did not undergo a biopsy during screening Controls were stratified to cases on center, race, age (5 years), time of entry and length of participation 1524 cases and 1896 controls in the analysis, limited to white subjects with complete alcohol information and no previous breast cancer Response rates were 74% cases and 90% controls Breast cancer detected through screening program	Ever consumption of beer, wine or liquor, and if so the number of servings per week during three age periods, less than 30 years of age, 30-49 years, or 50 years and older obtained by home interviews averaging five years after diagnosis	**Usual total alcohol intake (g/week)** Non drinkers: 1.00 Ever drank: 1.14 (1.0-1.3) 0.1-13: 1.12 (0.9-1.3) 14-91: 1.06 (0.9-1.3) 92-182: 1.31 (1.0-1.7) ≥183: 1.66 (1.2-2.4) P(linear trend) = 0.04 <u>Women entering at age >50</u> **Consumption age <30** <14 : 1.00 14-91: 1.15 92-182: 1.53 (<0.05) ≥183: 1.95 **Consumption age 30-49** <14 : 1.00 14-91: 0.91 92-182: 0.96 ≥183: 1.45 **Consumption age ≥50** <14 : 1.00 14-91: 0.92 92-182: 0.90 ≥183: 0.90	Nested case control analysis Matched analyses were performed but due to the similarity in the results only unmatched estimates are presented	Age at entry, age at first birth, parity, menopausal status, age at menopause, type of menopause, age at menarche, family history of breast cancer in a first-degree relative, educational attainment, oral contraceptives, hormone replacement therapy, the number of breast biopsies, height, weight and body mass index did not alter breast cancer risk

Table 2.1b (continued)

Reference (Place)	Study Population	Period of Follow-up	Number of Cases	Measure of Alcohol Consumption	Relative Risk (95% confidence interval)	Comments	Adjustment for Confounding Factors
Barrett-Connor and Friedlander[118] (California, USA)	619 women Age 40-79 at baseline Residents of Rancho Bernardo, CA (a white middle-upper class community)	1972-1987 7600 person years	44 postmenopausal cases based on self report and confirmed by hospital report and/or pathology report Only 15 of the 44 were used in the analysis because their breast cancer was diagnosed at least 1 year after the baseline evaluation and dietary recall (29 were excluded-15 died without knowing date of onset, 14 were diagnosed within a year or less of the baseline dietary evaluation), 575 women without breast cancer were used as the comparison group Response rate to initial survey: 82% Participation rate: ~66% Nonfatal breast cancer was ascertained by three morbidity questionnaires or interviews Breast cancer listed anywhere on death certificate was accepted as an endpoint	A single 24 hour recall dietary recall at baseline Type of beverage was not specified	**Alcohol (per 18g):** 0.59 (0.27-1.30)	Only a single recall questionnaire Definition of post-menopausal women was not given	Controlled for age, age at menopause, parity, body mass index, and total calories Exercise, exogenous estrogens and cigarettes did not differ between cases and controls

Table 2.1b (continued)

Reference (Place)	Study Population	Period of Follow-up	Number of Cases	Measure of Alcohol Consumption	Relative Risk (95% confidence interval)	Comments	Adjustment for Confounding Factors
Friedenreich *et al.*[119] The Canadian National Breast Screening Study (Canada 1982-1987)	56 837 women participating in a multicenter, randomized controlled trial Age 40-59	5.5 years (1982-1987)	284 histologically confirmed postmenopausal cases and 691 postmenopausal controls Matched on age (<1 year), screening center and time of completion of the diet questionnaire Response rate to initial diet questionnaire: 69%	Current alcohol intake based on the previous month's consumption at baseline Type of alcoholic beverage was specified Self-administered food frequency questionnaire	**Usual alcohol intake (g/day)** *Total* 0: 1.00 >0-<10: 1.02 (0.72-1.43) ≥10-<20: 0.77 (0.47-1.26) ≥20-<30: 1.16 (0.64-2.12) ≥30: 0.86 (0.46-1.59) P(linear trend) = 0.19 *Beer* 0: 1.00 <10: 0.90 (0.63-1.27) ≥10: 0.58 (0.23-1.46) *Wine* 0: 1.00 <10: 0.88 (0.65-1.18) ≥10: 1.10 (0.62-1.94) *Spirits* 0: 1.00 <10: 1.11 (0.81-1.51) ≥10: 1.00 (0.64-1.56)	Nested case-control analysis No definition given for menopausal status Menopausal status was determined only at entry into the study therefore those classified as pre-menopausal could have been postmenopausal or peri-menopausal at diagnosis of breast cancer The cohort was volunteers	Controlled for age, ever smoker, family history of breast cancer, parity, and total calories besides those from alcohol Age at menarche, age at first full-term pregnancy, marital status, benign breast disease, education, total fat and saturated fatty acids did not alter breast cancer risk
Gapstur *et al.*[120] Iowa Women's Health Study (Iowa, USA)	41 837 women 37 105 women were in the "at risk" cohort Age 55-69 years	4 years (1986-1989) 140 704 person years	493 incident breast cancer cases identified through the Health Registry of Iowa including 48 that were carcinomas in situ	Current alcohol intake during the year before baseline Type of alcohol was specified	**Usual total alcohol intake (g/day)** 0: 1.00 <1.5: 1.18 (0.86-1.61) 1.5-4.9: 1.20 (0.93-1.56) 5.0-14.9: 1.25 (0.93-1.68) ≥15: 1.46 (1.04-2.04) P(linear trend) = 0.04	Excluding in situ carcinomas did not change results Only 3.8% of cohort was missing	Controlled for age, body mass index, age at menarche, age at first live birth, family history of breast cancer

Table 2.1b (continued)

Reference (Place)	Study Population	Period of Follow-up	Number of Cases	Measure of Alcohol Consumption	Relative Risk (95% confidence interval)	Comments	Adjustment for Confounding Factors
Gapstur *et al.*[120] (cont'd)	The cohort was selected randomly from the 1985 Iowa Department of Transportation driver's license list (~94% of all age-eligible women in Iowa)		Response rate to initial questionnaire: 43% Participation rate: 39%	Harvard semi-quantitative food frequency questionnaire		information on alcohol variables Postmenopausal women were defined as those women who were not menstruating in the previous year	Education, age at menopause, parity, use of oral contraceptives, and use of non-contraceptive estrogens did not alter risk
Graham *et al.*[70,71] New York State Cohort (New York, USA)	18 475 women Age 50-93 years Original cohort: chosen from a mailing list consisting of persons who had resided at the same address with the same phone number in New York state for at least 18 years Eligibility: white women who filled out the initial questionnaire and did not have cancer by 1980	7 years (1980-1987)	367 primary invasive breast cancer cases identified from the New York State registry Response rate to initial mailed questionnaire: 21.1% Participation rate: 20%	Typical alcohol intake at baseline	**Usual total alcohol intake (g/day)** Non-drinkers: 1.00 >0-<1.5: 0.89 (0.67-1.19) 1.5-<5.0: 0.76 (0.53-1.09) 5.0-<15.0: 0.93 (0.63-1.38) 15.0-<30.0: 0.69 (0.39-1.21) 30.0-<60.0: 1.28 (0.63-2.59) ≥60.0: 4.16 (0.71-24.39) P(linear trend) = 0.53	Cohort was more likely to be white, have a higher socio-economic status and be older than the general population Women over 50 were assumed to be post-menopausal	Controlled for age, age at menarche, age at birth of first child, menopausal status at diagnosis, postmenopausal hormone use, oral contraceptive use, history of benign breast disease, history of breast cancer in mother or sister, smoking status, education, body mass index, height, fat intake, fibre intake and energy intake

Table 2.1b (continued)

Reference (Place)	Study Population	Period of Follow-up	Number of Cases	Measure of Alcohol Consumption	Relative Risk (95% confidence interval)	Comments	Adjustment for Confounding Factors
Simon *et al.*[121] Tecumseh Community Health Study (Michigan, USA)	2420 women in original cohort who responded in the first data collection of 1959-1960, and provided information regarding alcohol consumption were mailed a question-naire to determine history of cancer 2299 women responded to questions about history of cancer Age ≥21 9 500 in target population	28 years (1959-1987)	In total, 87 women developed breast cancer (64 women during their post-menopausal follow-up) 1954 women were used in the analysis of which 1706 women contributed follow-up time after menopause 95% response rate	Current alcohol consumption for the year before baseline (If greater amounts of alcohol were consumed over a specific time period, the frequency and amount were determined for that time and prorated over the entire year)	**Usual total alcohol intake (drinks/day)** Never: 1.00 Ex-drinkers: 0.93 (0.40-2.18) 0-<1: 1.08 (0.64-1.82) 1-<2: 1.23 (0.49-3.10) ≥2: 1.12 (0.25-5.01) <u>Post-menopausal women only</u> **Alcohol consumption** Never: 1.00 Ever: 0.94 (0.53-1.67) **Current ethanol consumption (ounce/week)** No: 1.00 Yes: 1.04 (0.96-1.14) **Current or past consumption of ethanol (ounce/week)** No: 1.00 Yes: 1.04 (0.95-1.13)	Not a very thorough analysis-not much to it Less than 2% were excluded due to missing alcohol information Older and less well to do people were under represented	Controlled for age, body mass index, subscapular and triceps skinfolds, education level, cigarette use, family history of breast cancer, age at menarche, mother's age at first live birth and parity
Hiatt *et al.*[122] California Health Plan-Kaiser Permanente Medical Care Program (San Francisco Bay Area, California, USA)	68 674 insured women who voluntarily completed a multiphasic health exam from 1978-1984 Age >15	1978-1984	303 (~225 postmenopausal) cases identified through hospital discharge records from a cohort of 58 347 women Analysis used 10% of a random	Recent alcohol intake within the last year of the multiphasic exams as well as age the range of ages subjects drank the most	Reference group is women who are lifelong abstainers **Usual alcohol intake (drinks/day)** Past drinkers: 2.17 (1.21-3.87) <1: 1.21 (0.86-1.69) 1-2: 1.50 (0.98-2.29) 3-5: 1.47 (0.78-2.79) 6+: 3.30 (1.18-9.28)	Type of analysis probably resulted in lower relative risks than using the full cohort Only 4 women in 6+ category	Controlled for age, race, body mass index and smoking Other variables not associated with breast cancer and alcohol were not included in the model-

Table 2.1b (continued)

Reference (Place)	Study Population	Period of Follow-up	Number of Cases	Measure of Alcohol Consumption	Relative Risk (95% confidence interval)	Comments	Adjustment for Confounding Factors
Hiatt *et al.*[122] (cont'd)	182 357 members of all races and sex were in plan originally in 1968 Exclusions: women who were not white, black or Hispanic were excluded from the multivariate analysis because of the small number of cases		sample of all non cases Response rate not stated (but loss to follow up may be high)	Type of beverage was specified in questionnaire	*Wine* Infrequent: 0.91 (0.51-1.60) Regular: 1.36 (0.86-2.17) *Liquor* Infrequent: 1.10 (0.66-1.85) Regular: 1.46 (0.93-2.29) *Beer* Infrequent: 1.21 (0.82-1.80) Regular: 1.37 (0.76-2.47) Postmenopausal women ≥6: 4.2 (1.5-11.5)	Well to do and indigent women may be under-represented as well as people with drinking problems Cases in the two studies are independent of each other-those cases used in the first study were not used in the second	menopausal status, family history of breast cancer, lump in breast, breast surgery, education, age at first full-term pregnancy and marital status Perhaps should have controlled for menopausal status, lump in breast and breast surgery
Hiatt and Bawol[123] Kaiser Foundation Health Plan of Northern California (California,US)	96, 179 women without a history of breast cancer who had had a multiphasic health check-up >15 years old Identified women who had breast cancer in the area and traced back to find out which ones had regular health check-ups	1964-1977 668 334 person years	694 cases identified through hospital discharge records (654 women used in analysis because they at least answered partially to the alcohol questions, restricted to white and black women over 30 years of age who had their first multiphasic	Recent alcohol intake within the last year of multiphasic examinations Type of beverage was specified	**Usual total alcohol intake (drinks/day)** None: 1.00 ≤2: 0.98 3-5: 1.41 6+: 1.24 P(linear trend) = 0.167 3+ vs. none : 1.38 P-value = 0.035	Among women with responses to the alcohol consumption questions, 40.1% were not followed until the end of the study but there was no difference between participation and non-participation for heavy drinkers	Controlled for age, race, education, smoking, body mass index, cholesterol level, menopausal status, parity and age at menarche

Table 2.1b (continued)

Reference (Place)	Study Population	Period of Follow-up	Number of Cases	Measure of Alcohol Consumption	Relative Risk (95% confidence interval)	Comments	Adjustment for Confounding Factors
Hiatt and Bawol[123] (cont'd)			examination in 1965 or later 3, 595 non cases (five controls per case were selected randomly from the cohort without breast cancer)			Could not control for family history of breast cancer or history of benign breast cancer	
Schatzkin *et al.*[125] National Health and Nutrition Examination Survey Epidemiology Follow-up Study (United States)	8596 women in original cohort, a probability sample of the US population excluding people who were institutionalized Age 25-74 years	Entry 1971-1975 Follow up until 1981-1984 Median: 10 year follow-up	121 cases identified through hospital records, death certificates or both (76 postmenopausal), 88 cases with complete covariate information were used in analysis 7188 women used in analysis Response rate to initial exam: ~70% Participation rate: 61%	Current alcohol intake in year before baseline Type of alcohol beverage was specified but not the quantity	**Usual total alcohol intake (g/day)** None: 1.00 Any: 1.6 (1.0-2.5) >0-1.2: 1.4 (0.8-2.5) 1.3-4.9: 1.6 (0.9-3.1) ≥5: 2.0 (1.1-3.7)	Only at the base-line interview was information on alcohol collected, early age drinking information was obtained at the follow-up interview, but the women with breast cancer who gave this information were too few to use in analysis Could not adjust for benign breast disease	Controlled for age, education, body mass index, total dietary fat, age at first parturition, age at menarche, parity, positive family history, premenopausal status and smoking

TABLE 2.2: Number of Positive Associations among Studies that Restricted the Analysis of Usual/Current or Recent Alcohol Intake, by Postmenopausal Status

Analysis of Usual/Recent/ Current Alcohol Intake	References: Case-Control Studies	References: Cohort Studies	Number of Case-control/ Cohort Studies	Percent Positive Total (Case-control/ Cohort studies)
Restricted to postmenopausal women	58-61,76,80,81,84-88,91-96,100,104,105	70,71,77,117-120	19/6	40% (37%/50%)
Standard definition (e.g. World Health Organization)	84,85,92,100	120	4/1	80% (75%/100%)
Age cut-off	87,91,104,105	70,71,77,117	4/3	43% (25%/67%)
Defined by type of menopause (e.g. natural/surgical)	76,88,93,96		4/-	0%
No definition given	58-61,80,81,86,94,95	118,119	7/2	33% (43%/0%)
Not restricted to postmenopausal women	62-65,79,82,83,89,90,97-99,101-103,106-108,115	66-69,78,116,121-125	17/9	58% (47%/78%)
All studies			36/15	49% (42%/67%)

TABLE 2.3: Percent Distribution of Studies with Positive Associations for Usual/Current or Recent Consumption of Alcoholic Beverages by Important Methodological Variables

	References		All studies		Postmenopausal studies only	
	Case-Control Studies	Cohort Studies	Number of Case-control/ Cohort Studies	Percent Positive (Case-control/ Cohort studies)	Number of Case-control/ Cohort Studies	Percent Positive (Case-control/ Cohort studies)
All Studies						
Location of Study						
United States	58,59,76,80,83-85,89,93	66-71,78,116,118,120-125	8/12	60% (50%/67%)	6/3	44% (50%/33%)
Europe	60-63,79,81,82,86,87,90,91, 94,95,97-99,101,102,105,115	77,117	18/2	45% (39%/100%)	8/2	40% (25%/100%)
Other	64,65,88,92,96,100,103,104,106-108	119	10/1	36% (40%/0%)	5/1	33% (40%/0%)
Type of Study						
Case-Control	58-65,76,79-108,115		36/NA	42%	19/NA	37%
Cohort		66-71,77,78,116-125	NA/15	67%	NA/6	50%

Table 2.3 (continued)

	References	All studies		Postmenopausal studies only	
	Case-Control Studies	Number of Studies	Percent Positive	Number of Studies	Percent Positive
Case-Control Studies					
Selection of case subjects					
Population	58-61,76,79-92,94,99,104,106,108,115	23	39%	14	43%
Hospital	62-65,93,95-98,100-103,105,107	13	46%	5	20%
Selection of control subjects					
Non-ill subjects from the general population	76,80,82,83,85-92,115	13	38%	8	38%
Neighborhood	64,65,84,93	3	67%	2	50%
Hospital	58-63,79,94-100,102,104,105	14	50%	8	38%
Other Cancer Sites	103,104	2	100%	1	100%

Table 2.3 (continued)

	References	All studies		Postmenopausal studies only	
	Case-Control Studies	Number of Studies	Percent Positive	Number of Studies	Percent Positive
Studies with type of hospital controls not specified	62,63,94,95,100,101,108	7	43%	4	50%
More than one type of control used	81,101,103,106-108	6	17%	1	0%
Studies with controls possibly related to alcohol	62,63,100-102,106	5	40%	1	100%
Response Rates					
≥90%	60,61,79,88,93,94,96,99-103,108	12	33%	6	33%
75-89%	76,82,85,86,95,105	6	33%	5	40%
Low (<70%)	83,115	2	0%	-	-
At least 10% difference between case and control subjects	80,81,84,87,89-92,107	9	44%	6	33%
Not stated	58,59,62-65,97,98,104,106	7	71%	2	50%

Table 2.3 (continued)

	References	All studies		Postmenopausal studies only	
	Cohort Studies	Number of Studies	Percent Positive	Number of Studies	Percent Positive
Cohort Studies					
Calculable response rates					
≥60	[66,67,77,118,119,125]	5	60%	3	33%
<60	[68-71,116,117,120]	5	80%	3	67%
Not calculable	[78,121-124]	5	60%	-	-
Follow-up time for cohort studies					
<5 years	[68,69,77,117,120]	4	100%	3	100%
5-10 years	[66,67,70,71,116,119,122]	5	60%	2	0%
10-20 years	[118,123-125]	4	75%	1	0%
≥20 years	[78,121]	2	0%	-	-

Table 2.3 (continued)

	References	All studies		Postmenopausal studies only	
	Cohort Studies	Number of Studies	Percent Positive	Number of Studies	Percent Positive
Study design used in cohort studies					
Nested case-control	[66,67,77,119]	3	67%	2	50%
Case-cohort	[117]	1	100%	1	100%
Full cohort analysis	[68-71,78,116,118,120-125]	11	64%	3	33%
Method of analysis in cohort studies					
Cox proportional hazards	[70,71,78,116,118,120-123,125]	9	56%	3	33%
Logistic regression					
Nested case-control or case-cohort	[66,67,77,117,119]	4	75%	3	67%
Cumulative incidence	[68,69,124]	2	100%	-	-

Table 2.3 (continued)

	References		All studies		Postmenopausal studies only	
	Case-Control Studies	Cohort Studies	Number of Case-control/ Cohort Studies	Percent Positive (Case-control/ Cohort studies)	Number of Case-control/ Cohort Studies	Percent Positive (Case-control/ Cohort studies)
All Studies						
Sample size-number of cases						
<200 cases	91,95,97,99,100,102,108	118,121,125	7/3	30% (29%/33%)	3/1	25% (33%/0%)
200-<500 cases	58-61,64,65,81,82,87,88,90, 92,93,96,98,105,115	71,77,78,117,119,120,122,128	14/7	38% (29%/57%)	9/5	29% (11%/60%)
500-<1000 cases	80,83,86,101,106,107	68,69,116,123	6/3	56% (33%/100%)	2/-	100%
≥1000 cases	62,63,76,79,84,85,89,94,103, 104	66,67,124	9/2	82% (78%/100%)	5/-	60%

Table 2.3 (continued)

	References		All studies		Postmenopausal studies only	
	Case-Control Studies	Cohort Studies	Number of Case-control/ Cohort Studies	Percent Positive (Case-control/ Cohort studies)	Number of Case-control/ Cohort Studies	Percent Positive (Case-control/ Cohort studies)
Histological Confirmation of Breast Cancer of Cases						
100%	60-63,76,79-84,86,88,90,92-95,97-99,102,106-108,115	117,119	24/2	38% (38%/50%)	11/2	38% (36%/50%)
>90-99%	85,87,91,96	68,69,78	4/2	33% (25%/50%)	4/-	25%
Some cases identified by pathology reports (percent not stated)	58,59,89,103	77,118	3/2	60% (67%/50%)	1/2	33% (0%/50%)
Not stated	64,65,100,101,104,105	66,67,70,71,116,120-125	5/9	71% (60%/78%)	3/2	60% (67%/50%)

Table 2.3 (continued)

	References		All studies		Postmenopausal studies only	
	Case-Control Studies	Cohort Studies	Number of Case-control/ Cohort Studies	Percent Positive (Case-control/ Cohort studies)	Number of Case-control/ Cohort Studies	Percent Positive (Case-control/ Cohort studies)
Degree of Control for Confounding						
Adjustment for age, family history and all reproductive factors	60,61,76,79-81,84,85,88,90,91, 93-95,98	66-69,117,119,120	14/5	58% (50%/80%)	11/3	43% (36%/67%)
Adjustment for age and some of the above factors	58,59,62,63,83,86,89,92,99,101, 103,105,107,115	70,71,77,78,116,118,121-125	12/10	45% (33%/60%)	4/3	29% (25%/33%)
Adjustment only for age	64,65,82,87,96,97,100,102,104, 108		9/-	44%	4/-	50%
No adjustment for age, family history or reproductive factors	106		1/-	0%	-/-	-
Adjustment for smoking	58-61,76,79-81,86-89,91,93,95, 101,103-105,107	68-71,78,116-119,121-125	18/12	47% (39%/58%)	13/4	29% (31%/25%)

Table 2.3 (continued)

	References		All studies		Postmenopausal studies only	
	Case-Control Studies	Cohort Studies	Number of Case-control/ Cohort Studies	Percent Positive (Case-control/ Cohort studies)	Number of Case-control/ Cohort Studies	Percent Positive (Case-control/ Cohort studies)
Adjustment for education	58-61,76,79,80,83-85,87-89,91-95,98-103,107,115	66,67,70,71,77,78,116,117,119-125	24/13	49% (38%/69%)	14/5	42% (36%/60%)
Adjustment for body mass index	60,61,76,80,81,83-91,93,94,98,99,101,103,105,107,108,115	66-71,77,78,116-118,120-123,125	23/13	50% (39%/69%)	13/5	44% (38%/60%)
No adjustment for family history	64,65,82,87,96,97,99,100,102,105,106,108	78,118,123	11/3	29% (27%/33%)	4/1	20% (25%/0%)
Alcohol Measurement						
Drinks per week or day	60,61,76,79,83,88,93,95,97,99,107,108	116,121-124	11/5	43% (18%/80%)	5/-	20%
Grams per week or day	58,59,62-65,80,81,84-87,89-92,94,96,98,100,101,105,115	66-71,77,78,117-120,125	20/10	53% (50%/60%)	13/7	40% (38%/43%)
Frequency	82,102-104,106		5/-	40%	1/-	100%

Table 2.3 (continued)

	References		All studies		Postmenopausal studies only	
	Case-Control Studies	Cohort Studies	Number of Case-control/ Cohort Studies	Percent Positive (Case-control/ Cohort studies)	Number of Case-control/ Cohort Studies	Percent Positive (Case-control/ Cohort studies)
Type of Alcohol specified						
Wine	60-63,76,79,80,83,86-88,90,92, 94,95,98,99,107	68,69,78,117,119,122	16/5	43% (50%/20%)	3/2	20% (0%/50%)
Beer	60-63,76,79,80,83,86-88,92,94, 95,98,99,104,107	68,69,78,117,119,122	16/5	29% (31%/20%)	3/2	20% (33%/0%)
Spirits	60,61,79,86-88,92,94,95,98	78,119	9/2	45% (56%/0%)	2/1	0%
Hard Liquor	62,63,76,80,83,99,107	68,69,117,122	6/3	33% (17%/67%)	1/1	100%
Fortified Wines	60-63,87		3/-	33%	1/-	0%
Sherry	86,88		2/-	50%	-/-	-
Amari	94		1/-	0%	1/-	0%
Grappa	94		1/-	100%	1/-	100%
Liqueurs	86		1/-	0%	-/-	-

Table 2.3 (continued)

	References		All studies		Postmenopausal studies only	
	Case-Control Studies	Cohort Studies	Number of Case-control/ Cohort Studies	Percent Positive (Case-control/ Cohort studies)	Number of Case-control/ Cohort Studies	Percent Positive (Case-control/ Cohort studies)
Aperitifs	[98]		1/-	0%	-/-	-
Sake	[104]		1/-	0%	1/-	0%
Whiskey	[104]		1/-	0%	-/-	0%
Cider	[62,63]		1/-	0%	-/-	-
Other alcohol measures						
Early age consumption	[79-81,83-85,89,91,94,95,99]	[66,67,77]	11/2	46% (36%/100%)	6/1	43% (33%/100%)
Duration	[79,80,89,94,95,99]	[77]	6/1	29% (17%/100%)	2/1	67% (50%/100%)
Average lifetime consumption	[83-85]	[66,67]	3/1	50% (67%/0%)	1/-	100%

N/A, not applicable

*A positive association is one in which there was evidence of a monotonic increase or decrease in risk by exposure (usually if the test for linear trend was statistically significant (p-value<0.05)) or if the 95% confidence limit for the association (odds ratios or relative risks) did not include unity.

Six studies were excluded from this table because recent or current or usual total alcohol consumption was not assessed.[109-114]

Some studies have double article references.[58-69,71,128]

References[122] and[123] are shown as separate studies but it is difficult to decipher whether the two studies are truly independent.

CHAPTER 3: OBJECTIVES

The present thesis is based on an occupational, population-based, case-control study of primary, invasive breast cancer among postmenopausal women living in Montreal, Quebec, Canada. The original objective of this study was to determine whether there was an association between postmenopausal breast cancer and exposure to organic solvents and other chemical and physical agents in the workplace.[27]

The main objective of this thesis was to determine within this study population whether past and current consumption of alcohol was associated with postmenopausal breast cancer.

The specific objectives were:

1. to determine whether alcohol consumption at different ages and the type of alcohol beverage consumed have an effect on the risk of developing postmenopausal breast cancer; and
2. to determine whether indices of cumulative lifetime consumption of alcohol are associated with postmenopausal breast cancer.

The following chapter, written as a manuscript to be submitted for publication in a peer-reviewed scientific journal, meets the above objectives of the thesis by describing the study design and methods, the study population, and the principal results, as well as discussing these findings in terms of methodology and the scientific literature. Certain details that are not suitable for inclusion in the paper are presented in Appendices A-D.

CHAPTER 4: A POPULATION-BASED, CASE-CONTROL STUDY OF BREAST CANCER AND ALCOHOL CONSUMPTION AMONG POSTMENOPAUSAL WOMEN LIVING IN MONTREAL, QUEBEC, CANADA

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Abstract

The available epidemiologic evidence suggests that only 25-40% of breast cancer cases can be attributed to known risk factors. One possible risk factor for breast cancer, alcohol consumption, has been investigated using both case-control and cohort studies. Conflicting results from these studies, however, call for continued examination of the relationship between alcohol consumption and breast cancer. In the present population-based, case-control study of incident postmenopausal breast cancer we obtained an extensive history of alcohol consumption, including the frequency of use of beer, wine and hard liquor/spirits at ages 20, 30, 40, and 50 years. Indices reflecting specific types, total and age-specific alcohol consumption were developed and unconditional logistic regression, within the context of the Generalized Additive Models, was used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI). Case subjects included all new histologically confirmed cases of malignant breast cancer among postmenopausal women, age 51-75 years, diagnosed in 1996 and 1997 in Montreal. Control subjects were selected randomly from other histologically confirmed sites of cancer. The response rate was 82% for cases and 75% for controls. Current drinkers of any kind of alcohol were at an increased risk of breast cancer (OR=1.47; 95%CI: 1.01-2.15). In particular, the risk of breast cancer was increased by 1.6 fold among weekly and current exclusive drinkers of wine. Other factors suggestive of an increased risk of breast cancer include early-age at first consumption of alcohol (≤30 years old) and increased number of years (>15 years) of consuming wine among women who only drank wine. We did not find, however, monotonically increasing risks with levels of consumption. Although, the associations found were relatively weak, our findings provide further support for a positive association between the risk of breast cancer and alcohol consumption, particularly wine.

Introduction

Female breast cancer is a major public health concern in the industrialized world. It is the second most common cause of death from cancer, accounting in 1999, for an estimated 18% of all cancer deaths among Canadian women.[1] Although mortality rates are declining, the incidence of breast cancer continues to rise.[6,7] Only 25% to 40% of the incidence of breast cancer is attributable to accepted risk factors.[11] Many of the risk factors that are now accepted as modifiable risk factors are particularly important as they may lead to non-invasive preventive measures. One of these modifiable risk factors, alcohol consumption, has been investigated in a number of case-control studies[58-65,76,79-115] and cohort studies.[66-71,77,78,116-125] Although a slight increased risk in breast cancer has been suggested in one meta-analysis,[19] a detailed analysis of the characteristics of these studies suggests that some findings may not be as robust as suggested by this meta-analysis. One possible reason for the inconsistencies may be from combining premenopausal and postmenopausal women together; if alcohol only affects one of these groups then relative risks for both populations will be attenuated. In addition, if the different groups have different risk factors, then statistical adjustments may only partially account for confounding bias, and this may also lead to inconsistent estimates of risk. Moreover, there have been few investigations of early-age consumption, duration of consumption, and cumulative alcohol intake restricted to a population of postmenopausal women.[77,80,81,84,85,91,94] To investigate these different aspects of alcohol consumption, we obtained detailed alcohol consumption information from a case-control study of postmenopausal breast cancer.

Subjects and Methods

This study was designed as a population-based case-control study. Eligible case subjects were women, age 50 to 75 years at time of diagnosis, who were residents of the greater Montreal area and who were diagnosed between 1996 and 1997 with an incident, primary, malignant breast cancer (ICD-9 174) that was confirmed histologically. Subjects were identified from records of pathology departments and cancer registries

from all of the 18 major hospitals in the area that treated breast cancer, thus ensuring almost complete coverage of all cases.

About an equal number of control subjects, having 32 other selected sites of incident, histologically-confirmed, cancer were selected randomly from the same set of hospitals from which the cases were recruited. The control series were approximately frequency-matched to the cases by age and interviewed during the same window of time following diagnosis of disease. As the primary objective of the original study was to investigate occupational causes of breast cancer, certain sites of cancer (liver and intrahepatic bile duct (ICD-9 155), pancreas (ICD-9 157), lung, bronchus and trachea (ICD-9 162), brain and nervous system (ICD-9 191-192) and leukemias (ICD-9 204-208)) were excluded because they may be associated with particular chemical or physical exposures. Non-melanoma skin cancer (ICD-9 173) was also excluded because it is mostly diagnosed outside a hospital setting. We therefore included subjects who had a histologically-confirmed diagnosis of cancers of the stomach (ICD-9 151), small intestine (ICD-9 152), colon (ICD-9 153) and rectum (ICD-9 154), gall bladder and extra-hepatic bile ducts (ICD-9 156), peritoneum (ICD-9 158), nasal cavity (ICD-9 160), bone (ICD-9 170), connective tissue (ICD-9 171), skin melanoma (ICD-9 172), reproductive and genital system (ICD-9 179-184), bladder (ICD-9 188), kidney (ICD-9 189), eye (ICD-9 190), thyroid (ICD-9 193), lymph nodes (ICD-9 196), and lymphatic and hematopoietic tissue (ICD-9 200-203). For the purposes of the present analysis, we excluded women with cancers of the oral cavity (ICD-9 141-149), esophagus (ICD-9 150), and larynx (ICD-9 161) because these sites of cancer are believed to be associated with the consumption of alcohol.[129]

Definition of Menopausal Status

As the focus of this study was on postmenopausal breast cancer, we recruited women 50 years of age and over. At the time of analysis, we only included women who met the World Health Organization definition of menopause:[130] women over the age of 50 who ceased menstruation naturally in the twelve months prior to interview or who ceased menstruating because of a medical intervention (bilateral oophorectomy). Women were

also considered postmenopausal if, four years or more prior to date of diagnosis, they were still menstruating at the date of diagnosis but started hormonal replacement therapy (HRT) to alleviate symptoms of menopause (hot flashes, irregular periods etc.) or if they had a simple hysterectomy without bilateral oophorectomy and reported using HRT to alleviate symptoms of menopause.[131,132]

Questionnaire and Interview

Institutional review boards from all participating hospitals and/or universities approved the procedures for the fieldwork. For subjects willing to participate, interviews were conducted by telephone or in-person one to three months after diagnosis. For subjects who died or were unable to participate, surrogate subjects (mostly next-of-kin) were interviewed. Interviewers were unaware of the cancer site of the subject, although in many instances they may have learned about their cancer status as the interview progressed.

The interviewers administered two structured questionnaires (Appendix B). One questionnaire was used to determine details regarding each occupation that the subject had had in her working lifetime and the other questionnaire was used to elicit information on non-occupational risk factors. The latter included questions on sociodemographic characteristics (age, height, weight, ethnic group, usual language spoken, marital status, education), menstrual and reproductive history, lactation history, medical history, family history of breast cancer, use of oral contraceptives, estrogens and progesterones, smoking history, and a detailed history of alcohol consumption.

Assessment of Alcohol Consumption

Subjects were asked to provide information regarding their average consumption of typical servings of beer, wine or cider, and hard liquor or spirits at specific time points in their life. Subjects who never drank any of these three types of alcohol at least once a month were considered "non-drinkers". Subjects who reported ever drinking at least one of the three types of alcohol for at least once a month but did not ever drink any of them on a weekly basis were considered "infrequent" drinkers. Non-drinkers and infrequent

drinkers were not asked any subsequent alcohol-related questions. Subjects who had ever drank any of the three beverages on a weekly basis were then asked when they began to drink each of the beverages, whether they continued to drink them until the time of interview, and, when appropriate, the age they stopped drinking. They were also asked to indicate the average number of alcohol drinks (defined as 4 oz glasses of wine or cider, 12 oz cans or bottles of beer, 1.5 oz shots of hard liquor or spirits) consumed at the ages of 20, 30, 40 and 50 years (Appendix B). Women who ever drank any of the beverages on a weekly or daily basis are referred to here as "weekly" drinkers. Women who drank any of them on a weekly or daily basis at the time of interview are referred to here as "current" drinkers. Women who are current drinkers are included in the number of women who are weekly drinkers, whereas weekly drinkers did not necessarily drink weekly or daily at the time of interview.

Different indices of alcohol consumption for specific types and all types of alcoholic beverages combined were developed to represent lifetime drinking patterns, including indices reflecting alcohol intake at different ages (20, 30, 40 and 50), age when they first started drinking regularly, total duration of drinking, and an indicator of cumulative consumption. *Duration of total alcohol consumption* was calculated as the period of time between the age at which the subject began drinking to the age when she ceased drinking or the age at time of interview, whichever came first. *Cumulative drinking* was defined over the age interval 20-59 years, and consumption at ages 20, 30, 40 and 50 for this index was used as a estimate for each corresponding age decade. Therefore for each type of alcoholic beverage, cumulative drinking was calculated as the product of the total number of drinks in each decade and the number of years spent drinking in each decade, summed over the four decades. A total cumulative index was calculated by summing the indices for the three types of alcoholic beverages.

Potential Confounding Factors

The following accepted and suspected risk factors were considered as potential confounding factors: age, family history of breast cancer, benign breast disease, age at oophorectomy, breastfeeding, parity, age at menarche, age at menopause, age at first full-

term pregnancy, use of oral contraceptives, hormone replacement therapy use, attained level of education, body mass index, marital status, ethnicity, and smoking. Occupational exposures were not considered in this analysis, as there are no accepted risk factors.[133]

Family history of breast cancer was defined as having a first degree relative (mother or sister) who had breast cancer. Age at oophorectomy refers to the age at which both ovaries were removed. If both ovaries were removed but at separate times, the age at oophorectomy refers to the age at removal of the second ovary. Body mass index was evaluated as weight÷height^2 (in kg/m^2) two years prior to interview. We developed an ordinal variable for possible combinations of active cigarette smoking and environmental tobacco smoke exposure (ETS). A few questions detailed second hand smoke exposure (ETS) in the subjects' workplaces (occupational ETS) as well as in subject's homes before the age of 18 (domestic ETS). Age at first full-term pregnancy refers to the subject's age at first birth, where first birth is defined as the first time gestation is greater than or equal to 35 weeks, and parity was defined as the number of live or stillbirths delivered, regardless of the duration of gestation. Ethnicity was based on the highly correlated variables language spoken at home and the birthplace of the subject's parents. Only English, French, Italian and Jewish ethnicities constituted large enough groups to be classified as separate categories.

A sub-analysis was performed to investigate the association between breast cancer and alcohol consumption according to estrogen and progesterone receptor status of the case subjects. Receptor status of the cases was obtained from the pathology reports provided by the different hospitals. We used the crude differentiation of positive and negative estrogen and progesterone receptors to define the receptor status of the cases. We were unable to distinguish further because the information on the different definitions and distinct laboratory techniques of the various hospitals was unavailable to us.

Statistical Analysis

Unconditional logistic regression[134] was used to estimate odds ratios (OR) and associated 95% confidence intervals (95% CI). We made use of the Generalized Additive Models

(GAM),[135,136] as implemented in Splus,[137] in order to assess patterns of exposure-response and to provide more precise control of confounding for continuous covariates. The GAM allow the fit of continuous independent variables using non-parametric smoothing techniques, such as regression splines or locally-weighted running line smoothers (LOESS). The latter uses weighted linear regression to estimate an expected value for each data point using data points in a specified neighbourhood (span) around each index point. LOESS also allows fitting models that contain both parametric and non-parametric functions. We used LOESS because of its flexibility in specifying the amount of smoothing and its ability to model data at the end points.

We first fitted a logistic model for age, selecting the span that minimized the Akaike Information Criterion (AIC). The AIC is a penalized version of the deviance, defined as the sum of the residual deviance and the product of twice the dispersion parameter (unity for logistic models) and the residual degrees of freedom used in the model. The AIC is appropriate for comparing non-nested models, although no specific statistical test is available. The model with the lowest value of the AIC is the one that explains the most residual variation, after accounting for the number of degrees of freedom used.[136] Adjusting for age (selected span of 70%), models for each continuous variable were evaluated using LOESS functions having spans of 30% to 70% of the data and, for each separate covariate, we then selected the span that minimized the AIC.

We did not wish to lose any data because of missing values for continuous covariates and did not believe that complicated imputation techniques would be suitable. Instead, we made use of the LOESS plots to define new categorical variables by finding suitable cutpoints such that the odds of developing breast cancer was approximately constant within each category. The new variable consisted of these cutpoints plus a category for the missing data.

In developing the multivariate models, we included all variables that were known or suspected risk factors for breast cancer. Amongst related variables, we selected the one that explained the most variation in the data. For example, duration of hormone

replacement therapy was used instead of ever use of hormone replacement therapy and age at first full-term pregnancy was used instead of parity. Although history of benign breast disease is associated with an elevated risk for breast cancer, we had concerns that it may be an intermediate variable, and therefore chose to omit it from the analysis. In addition, we included a variable for proxy respondents. There were only two subjects, both cases, with missing information on the amount of education completed. For these two subjects we imputed their missing values using the mean level of education (ten years) for the total study population. In addition, we estimated first-order interactions between alcohol consumption and all relevant covariates that were included in the final models, as well as benign breast disease and age at menopause.

Results

Of the 1,662 case and control subjects eligible for this study, we conducted 609 and 668 interviews among case and control subjects, respectively. The response rates for cases was 82.3% and for controls it was 74.4%. The main reasons for non-response were from refusals of subjects to be interviewed (16.5% of all subjects) and physicians not granting permission to contact their patients (4.8%). Based on responses to the interview and the WHO criteria, we deemed that 107 (8.4%) women were ineligible because they were not postmenopausal. Among control subjects, an additional 34 women were excluded because they had cancers associated with alcohol consumption (Appendix C). Thus, the present analysis is based on 555 cases and 575 controls, including interviews with proxy respondents for 30 case and 69 control subjects. The mean age of the cases was 63.7 years and the mean age of the controls was 65.0 years. The sites of cancer most prominent in the control series were the colon (24%), endometrium (19%), rectum (8%), ovaries (8%), bladder (7%), kidney (6%) and stomach (5%). The complete distribution of the sites of cancer among the control group is found in Appendix C.

Table 4.1 shows the distribution of case and control subjects according to accepted and suspected risk factors for female breast cancer. We found associations for family history of breast cancer, history of benign breast disease, attained level of education greater than high school, early age at menarche, hormone replacement therapy, and environmental tobacco smoke (in the workplace and at home as a child). Later age at oophorectomy and longer total duration of breastfeeding were associated with a decrease in the risk of breast cancer. There was no evidence of associations with marital status, ethnicity, age at menopause, oral contraceptive use, age at first full-term pregnancy, body mass index, or parity. All of these variables, except age at menopause, were included in the multivariate model because they are suspected risk factors for breast cancer and they were included regardless of the lack of association found in our age-adjusted model. Age at menopause was not included in the multivariate model because it was unrelated to breast cancer in the age-adjusted model and, among postmenopausal women, it has been noted that increased risk of breast cancer associated with late-age menopause is generally not seen

for 10-20 years after menopause.[138] The number of years of education was consistent with a linear response and was entered in the multivariate model as a linear variable.

Table 4.2 shows odds ratios for selected indices of total consumption of alcohol, adjusted for age and for the factors listed in the footnote of Table 4.2, representing the risk factors in Table 4.1 (referred to as the fully-adjusted model). Over 57% of the controls and 48% of cases were classified as never drinkers. Twenty-three percent of the cases and 17% of the controls were drinking at the time of their interview and therefore classified as current drinkers. There were some differences in the pattern of risks between the age-adjusted and fully-adjusted estimates, with some odds ratios increasing and others decreasing in value. As compared with never drinkers, we found that women who infrequently drank alcohol and those who drank weekly were at increased risk for breast cancer (OR~1.26; all ORs quoted in the text are from the fully adjusted models). Current drinkers were also at a slightly higher excess risk (OR=1.47; 95%CI: 1.01-2.15). At age 20, we found that the odds ratios decreased with increasing frequency of consumption, with the highest odds ratio found for the lowest category of consumption (1 drink/week; OR=2.02; 95%CI: 0.95-4.30). Similar patterns were found for intake of alcohol at ages 30, 40 and 50. We note that fewer women drank in their twenties and thirties than in their forties and fifties.

Table 4.2 and Figure 4.1 show that there was no discernible pattern in the odds ratios for breast cancer according to age when first started to drink any alcoholic beverage on a weekly basis. We found a suggestion of an increase in relative risk by duration of weekly consumption, although this increase was not monotonic; substantially elevated odds ratios were found for women who drank for 11-20 years (OR=2.28; 95% CI: 1.23-4.23) and for more than 50 years (OR=2.62; 95%CI 0.93-7.42; see also Figure 4.2). There was no apparent trend in cumulative consumption, with the odds ratios fluctuating across categories (see also Figure 4.3).

Under the assumption that infrequent drinkers may have been misclassified and should have been considered as part of the lowest category (≤50 drink-years) of cumulative

exposure, a separate analysis was performed and we found similar results (data not shown). Another separate analysis was performed excluding those controls with cancer of the colon or rectum and again, similar results to those presented above were found (data not shown). Lastly, as interviews with proxy respondents were carried out for 5% of the cases and 12% of the controls, we restricted the analyses to self-respondents and found that the results were similar to the analysis that included proxy respondents (data not shown).

Table 4.3 shows separate analyses among subjects who on a weekly basis drank beer, wine, and hard liquor/spirits. Drinking at age 50 could be broken down by frequency because the numbers for each category were large enough to produce stable estimates. We were unable to do this for the other ages. In the analysis of each type of beverage, women who drank one type may also have regularly drunk other beverages, and we included a term in the model to account for this. We did not find any evidence for excess risks among women who drank beer. There was a suggestion of an association with hard liquor, with positive associations found among women who drank one drink at age 50 (OR=4.53; 95% CI: 1.51-13.57). The few number of women who drank hard liquor exclusively (n=27) was too small to allow an in-depth analysis of only hard liquor drinkers.

On the other hand, we found elevated relative risks among women who were ever drinkers of wine (OR=1.34; 95% CI: 0.98-1.82; Table 4.3). Wine intake at age 20 and 30 was not associated with an elevated risk but any wine drinking at age 40 was associated with an increased odds ratio (OR=1.38; 95% CI: 0.95-2.01). For wine intake at age 50, we found elevated risks for women who consumed one drink per week (OR=2.42; 95% CI: 1.22-4.78) and who consumed more than four drinks per week (OR=1.97; 95% CI: 0.98-3.92). Late-age (>35 years) when first started to consume wine on a weekly basis was also associated with an elevated relative risk (OR=1.55; 95% CI: 0.94-2.56) as was duration of weekly drinking over more than 26 years (OR=1.65; 95% CI: 1.04-2.63). Cumulative drinking of wine was not associated with the risk of breast cancer. We attempted to investigate the independent effects of age at first exposure and duration of

weekly drinking, by including separate terms for these variables in the statistical model, but these variables were too highly correlated to produce stable estimates (Pearson correlation coefficient=0.90).

Table 4.4 shows the results of a sub-analysis that included women who only drank wine (n=185) as compared with never drinkers (n=597). Weekly and current exclusive drinkers of wine were at an increased risk of breast cancer of about 1.6-fold. Early-age drinking (≤30 years old) was suggestive of an increased risk (OR=1.59; 95% CI: 1.00-2.52; Figure 4.4). More than fifteen years of weekly drinking of wine was also associated with an increased risk of breast cancer (OR=1.69; 95% CI: 1.01-2.84; Figure 4.5). We did not find an association with cumulative wine consumption based on Table 4.4 and Figure 4.6.

We also investigated the risks of breast cancer, for ever drinkers and for cumulative alcohol drinking, by classifying cases according to their estrogen (ER) and progesterone (PR) receptor status (Table 4.5). The majority of cases (n=309) were ER and PR positive, 64 cases had unknown receptor status, and the subgroup ER^-/PR^+ was too small (n=16) to be included in the analysis. We found that the relative risk of breast cancer was not modified by a woman's hormone receptor status. The effect of ever and cumulative exclusive wine drinking could not be analysed this way because the numbers were too small once stratified by hormone receptor status.

We assessed statistical interactions between selected risk factors for breast cancer (body mass index, duration of hormone replacement therapy, benign breast disease, tobacco smoking, education, age at menopause) and ever drinkers of total alcohol, ever drinkers of wine, cumulative consumption of total alcohol, and cumulative consumption of wine. To determine whether the model containing the interaction term fitted the data better than the adjusted model, we used the likelihood-ratio test and perused the stratum-specific odds ratios and confidence intervals. We found no meaningful statistical interactions. Statistical interactions between the risk factors mentioned above and indices of wine

consumption among exclusive wine drinkers could not be assessed because there were not enough subjects who drank only wine.

Discussion

In this population-based, case-control study we found positive associations between selected indices of alcohol consumption and the risk of postmenopausal breast cancer. Specifically, we found that any consumption of alcohol among infrequent, weekly, and current drinkers marginally conferred excess risks and, among weekly drinkers, there was little evidence of monotonically increasing relative risks by frequency at different ages, duration, or cumulative consumption. In addition, we did not find evidence of an association by age when first started to drink alcohol on a weekly basis. Furthermore, the consumption of wine and hard liquor was the main contributor to the associations visible for total alcohol consumption as no associations were found with consumption of beer. When the analysis of wine drinking excluded women who drank other types of alcoholic beverages, we found clear associations for wine consumed before the age of 30 and for long-term consumption (>15 years); again we did not find monotonic increases by frequency at different ages.

Our study is consistent with other findings on alcohol consumption and postmenopausal breast cancer.[60,61,77,80,84-86,100,104,117,120] The positive association between current drinking and breast cancer risk found in our study is consistent with the meta-analysis by Longnecker, who found that daily consumption of one alcoholic beverage was associated with an increased risk of breast cancer when compared to never drinkers.[19] Among six case-control studies[80,81,84,85,91,94] in which age when first started to drink alcohol was examined in postmenopausal women, no association was found in four studies.[94 80,84,85] Our study supports these reports.

The effects of beer, wine and hard liquor separately have been investigated, and no individual beverage has been clearly implicated in the etiology of breast cancer.[19] Our study suggests that drinking wine and hard liquor may be associated with the risk of developing breast cancer. Recent wine consumption has been assessed in mixed populations of premenopausal and postmenopausal women[60-63,68,69,76,78,79,83,86,88,90,92,95,98,99,107,122] in which half of the studies found an association.[60-63,79,86,90,95,98,99] Recent wine consumption has been assessed only in five postmenopausal

populations[80,87,94,117,119] of which only one study found an association.[117] Given the few studies in which this association was reported, it is premature to assess the veracity of our observations.

Previous researchers have explored interactions between many potential risk factors for breast cancer and alcohol consumption. It has been suggested that hormone replacement therapy use,[69,120] tobacco smoking,[92,119] education,[95,120] benign breast disease,[69,117] body mass index,[69,74] and family history[120] modify the association between alcohol consumption and breast cancer risk. In this study, we found no evidence of effect modification with current or cumulative consumption of wine and total alcohol.

Although we made an attempt to isolate exclusive wine drinkers in our analyses, it is difficult to determine with certainty whether the effects suggested by our data are due to wine exclusively or to total alcohol consumption. If a specific beverage is positively associated with the risk of breast cancer, and if this beverage is consumed by the heavy drinkers in the study population then the association may simply be with alcohol and not with the specific beverage.[83] In our study population, wine is the most frequently imbibed alcoholic beverage among the heavy drinkers.

Hard liquor may also be a potential risk factor but we were unable to determine the association from these data because of the small number of women who drank hard liquor or spirits exclusively. The analysis of hard liquor among women who consumed hard liquor as well as other alcoholic beverages, indicated a positive association between hard liquor consumption and breast cancer risk (but risks did not increase monotonically with frequency). It is also possible that the results found for hard liquor may be influenced by wine intake because most women who drank hard liquor also drank wine.

There was no difference in the relative risk of breast cancer according to consumption at different ages. We did not find a monotonic increase in relative risk by indices of consumption; rather, elevated risks were seen only in the lowest category of consumption. In no studies has this type of dose-response function been observed. Other than chance,

the most plausible explanation for this finding is misclassification. Assuming that the true dose-response function is monotonic, certain misclassification scenarios, including nondifferential misclassification between adjacent categories or differential misclassification, can cause such an effect.[163] It is possible that the women in our study were aware that excessive alcohol consumption may be hazardous to their health, and they gravitated towards reporting one drink per week when in fact they drank more.

Methodological Issues

A strength of this study is that it likely contained an unbiased sample of the target population, because cases and controls were selected from all of the hospitals in the Montreal area that treat breast cancer. Our study population was restricted to postmenopausal women, this may have increased the statistical power because premenopausal and postmenopausal breast cancer may be affected by intake differently. As all subjects were confirmed histologically, we were able to eliminate misclassification of disease status. We also attempted to minimized confounding bias by eliciting detailed information on the majority of known and suspected risk factors. In order for this association to be due to another risk factor, it would have to be a risk factor strongly associated with both alcohol consumption and breast cancer, we are unaware of any other risk factor having these characteristics. Our analytic strategy, that made use of the Generalized Additive Models, also minimized residual confounding effects of the measured variables. Use of these models also provided us with the opportunity to visualize the association for these risk factors as well as the various indices of alcohol consumption.

The questionnaire provided detailed information on past drinking history, including age at first exposure to alcohol consumption and duration of alcohol use. Despite our efforts to avoid it, there may have been misclassification of levels of drinking, as subjects may have had difficulty recalling the amount of alcohol they typically consumed in a week. Recall bias is always a concern when information, such as alcohol consumption, is collected retrospectively.[139] For example, it has been found that recall or reporting of alcohol drinking is often underestimated, especially for heavy or binge drinking.[140] Moderate

current drinking however, is associated with much less error.[141] In fact, among the dietary factors often analysed in case-control studies, alcohol is one of the most correctly reported.[141] Furthermore, differential recall should be minimized because both the cases and controls have cancer and all participants should have equal concern about their disease. Nondifferential recall bias, therefore is likely to be minimal.

Exposure assessment of the intake of alcohol is also difficult, especially since the information relies on self reports. For this particular study, there are two areas of alcohol assessment that were difficult to measure. Current drinking was only assessed as Yes or No, and we had no index that measured recent drinking. The only measurement close to recent drinking was average alcohol consumption at age 50, which could be an indicator for recent drinking among the women diagnosed with breast cancer before age 55. However, for women diagnosed at a later age, for example age 70, there is a 20 year difference between the time of diagnosis and drinking at age 50. The drinking habits of these women are most likely to change in that time period. We felt that this was not a good indicator for recent alcohol intake and therefore were unable to make inferences about recent drinking. Cumulative alcohol consumption was also difficult to measure, but a reasonable estimate could be made using a weighted average of the different exposure periods. Drinking at age 20 is a surrogate for the decade between age 20 and 30 under the assumption that alcohol consumption changes minimally between age 20 and 30. The same was done for the other exposure periods.

We used drinks per week as our measurement of alcohol intake. We did not convert to the measurement of grams per day because, in Canada, standard servings of any alcoholic beverage represent the same alcohol content (14 grams).[142,143] Although there are variations in the actual serving consumed by an individual, these variations in drinking volumes were not measured in our study. In addition, the questionnaire asked for alcohol intake in the form of drinks per week. In our view, converting this data to grams per week increases the chance of greater misclassification, leading to attenuated risks and reduced statistical power.

The type of comparison group that we used, namely cancer controls, may have an important methodological impact. Current disease many have an impact on both current drinking habits and on the recall of recent and past drinking.. Cancer controls were used to minimize the potential for differential recall bias and to increase response rates over that which would be obtained using a general population sample. The use of cancer controls is justified if "subjects who are admitted to the hospital for the case disease would have been admitted to the same hospital for the control disease", and if admission does not depend on exposure.[144] Also, the cancer sites of the control group should not be associated with exposure, otherwise estimates of risk will be attenuated. The large number of sites of cancer used in this study, based on previous and current research, are not associated with alcohol consumption.[129] Colo-rectal cancer and alcohol consumption has been investigated in many studies. Although, the findings from these studies are inconsistent, the data appear to suggest that there is no association.[129] To ensure that retaining controls with cancer of the colon and rectum did not attenuate the risks, a separate analysis excluding controls with cancer of the colon and rectum was performed and the results were similar to those reported above.

Our response rates of 82% for cases and 74% for controls were reasonable, although lower than expected, especially since our control group was chosen to ensure relatively high response rates. The percentage of refusals from subjects (17%) was high, which could bias the results, if the non-participants did not participate because they were more likely heavy drinkers or non-drinkers. This is highly unlikely as the main focus of the study was on occupational exposures; alcohol consumption was one question among many.

Our study population was restricted solely to postmenopausal women, however the recruitment of subjects was limited to women 50 years old and over. We are aware that, potentially, some subjects may have been excluded from the study as some eligible women may have reached menopause before age 50. However, we feel that we captured the majority of the postmenopausal population.[145]

Nine percent of respondents were proxy respondents. We decided that proxy information, which is known to be less accurate than self responses,[146] would provide better information and produce less bias than omitting those subjects that died before the time of interview or were too sick to participate in an interview. As there were more proxies in the control series (12%) than in the case series (5%), we adjusted for proxy respondents in our multivariate analyses. In addition, an analysis of the alcohol indices restricted to self respondents, gave similar results to the analysis that included proxy respondents.

Many mechanisms have been hypothesized to explain the association between alcohol consumption and breast cancer, including alcohol's ability to decrease pineal melatonin production[147-149] as well as alcohol's effect on pituitary prolactin secretion[147,150,151] and on the metabolism and clearance of estrogen by the liver.[147,152,153] Other mechanisms are alcohol's ability to facilitate carcinogen transport to breast tissue,[147] to disrupt membrane functions,[154] to increase the production of cytotoxic protein products,[155,156] and to lead to immunocompetence due to liver disease or nutritional deficiencies.[147,155,157] The most plausible mechanisms are the following: i) alcohol's ability to induce the cytochromes P_{450} which metabolize xenobiotics,[27] including carcinogens, ii) alcohol's ability to increase hormone levels,[158-160] iii) the metabolism of carcinogens in alcoholic beverages other than ethanol,[150,161] or iv) possibly a metabolite of alcohol directly, acetaldehyde.[150] Based on our review of the literature, further studies are needed to prove a causal association.

There may be a different metabolic mechanism for wine than other alcoholic beverages. Little biological data on the potential mechanisms of separate beverages exists.[150,161] It is know that wine has anti-oxidant properties. It is possible, however, that at the low dose of one drink per week these properties may be too small to induce their protective effect. Further biological investigations need to be done to determine the exact nature of wine's involvement.

In conclusion, the data from our study suggests a weak, positive association between alcohol consumption and breast cancer. The associations found may be due to chance,

misclassification of alcohol consumption, or confounding. Misclassification of alcohol consumption is a very likely explanation, as it is known that people have difficulty responding accurately to questions about alcohol[141,162] and in some studies[116,123] only half of the eligible subjects even responded to such questions. This may explain the lack of a dose-response relationship. It seems unlikely in the present study that the excess risks found are due to known risk factors, as we accounted for all of the major variables known to be associated with the risk of breast cancer. It is always possible that some unknown risk factor could account for these findings. At present, the results of other studies are inconsistent, primarily because they vary considerably in design, conduct, analysis, and results. If these findings are eventually recognized as causal, their implications will have to be weighed in the light of other findings, such as the suggestion that moderate alcohol consumption could be protective against cardiovascular disease. In such an event, a woman should carefully assess her overall risk for both cardiovascular disease and cancer. If her individual risk of breast cancer outweighs her cardiovascular risk she should think seriously about abstaining from alcohol drinking.

TABLE 4.1: Distributions of Accepted and Suspected Risk Factors for Postmenopausal Breast Cancer and Associated Odds Ratios (OR) and 95% Confidence Intervals (CI)

	Number of Cases	Number of Controls	Age-adjusted OR*	95% CI
Mother or sister with breast cancer				
No†	277	352	1.0	
Yes	122	67	2.36	1.68-3.31
Missing	156	156	1.29	0.98-1.69
History of benign breast disease				
No†	301	462	1.0	
Yes	252	113	3.31	2.54-4.32
Missing	2	0		
Age at oophorectomy (years)				
Never had an ovary removed†	397	275	1.0	
Only one ovary removed	44	42	0.69	0.44-1.08
<40	18	22	0.57	0.30-1.08
40-49	52	41	0.90	0.58-1.40
50-59	30	71	0.28	0.17-0.44
≥60	11	105	0.08	0.04-0.14
Missing	3	19	0.11	0.03-0.36
Level of education (years)				
≤ 7†	147	210	1.0	
8-10	120	136	1.27	0.92-1.76
11-12	129	107	1.68	1.20-2.34
13-14	65	52	1.74	1.14-2.65
15-17	66	51	1.73	1.13-2.65
≥18	26	19	1.82	0.96-3.43
Missing	2	0		
Marital status				
Married/common law†	300	288	1.0	
Single after marriage	183	227	0.83	0.64-1.08
Never been married	72	60	1.16	0.79-1.70

Table 4.1 (continued)

	Number of Cases	Number of Controls	Age-adjusted OR*	95% CI
Ethnicity				
French†	365	339	1.0	
English	43	54	0.80	0.52-1.23
Jewish	27	40	0.65	0.39-1.08
Italian	36	55	0.61	0.39-0.95
Other	84	87	0.89	0.64-1.25
Age at menarche (years)				
≥16†	37	61	1.0	
15	45	49	1.49	0.84-2.65
14	91	98	1.52	0.92-2.50
13	154	141	1.79	1.12-2.87
12	110	129	1.37	0.85-2.22
11	77	56	2.12	1.24-3.63
≤10	34	31	1.69	0.89-3.20
Missing	7	10	1.10	0.38-3.17
Age at menopause (years)				
≤40†	86	89	1.0	
41-43	46	39	1.30	0.77-2.20
44-47	82	90	1.00	0.65-1.52
48-49	65	56	1.25	0.79-2.00
50	81	86	1.03	0.67-1.58
51-52	83	76	1.15	0.75-1.78
53-55	76	90	0.91	0.60-1.40
>55	35	41	0.87	0.51-1.49
Missing	1	8	0.15	0.03-0.87
HRT use				
Never†	243	308	1.0	
Ever	310	261	1.44	1.13-1.83
Missing	2	6	0.41	0.08-1.97

Table 4.1 (continued)

	Number of Cases	Number of Controls	Age-adjusted OR*	95% CI
Duration of HRT (months)				
0†	243	308	1.0	
1-19	70	81	1.08	0.75-1.56
20-44	45	41	1.35	0.85-2.14
45-74	45	23	2.29	1.34-3.90
75-124	53	43	1.41	0.91-2.21
125-219	44	37	1.40	0.88-2.25
≥220	48	30	2.03	1.25-3.31
Missing	7	12	0.76	0.29-1.96
Oral contraception use				
Never†	348	404	1.0	
<12 months	57	36	1.67	1.06-2.63
≥12 months	147	131	1.16	0.86-1.57
Missing	3	4	0.81	0.18-3.65
Cumulative period of breastfeeding (weeks)				
0†	437	435	1.0	
>0-30	50	52	0.95	0.63-1.43
31-80	41	40	1.07	0.68-1.69
>80	27	47	0.60	0.37-0.98
Missing	0	1	0.05	0.00-21.58
Tobacco exposure				
None†	60	78	1.0	
Occupational ETS only	41	43	1.18	0.68-2.04
Domestic ETS only	92	98	1.17	0.75-1.82
Active only	24	35	0.86	0.46-1.59
Occupational and domestic ETS	108	80	1.60	1.02-2.50
Occupational ETS and active	28	26	1.32	0.70-2.50
Active and domestic ETS	78	95	1.01	0.64-1.59
Occupational ETS, domestic ETS and active	122	115	1.24	0.80-1.90
Missing	2	5	0.47	0.09-2.48

Table 4.1 (continued)

	Number of Cases	Number of Controls	Age-adjusted OR	95% CI
Age at first full-term pregnancy (years)				
Never pregnant†	111	108	1.0	
<21	77	83	0.90	0.60-1.36
21-23	82	100	0.77	0.52-1.15
>23-24.5	59	58	1.00	0.64-1.57
>24.5-26	52	67	0.75	0.48-1.18
>26-28	54	56	0.97	0.61-1.53
>28-30	33	31	1.07	0.61-1.87
>30	66	47	1.40	0.89-2.23
Pregnant but never for full-term	21	25	0.80	0.42-1.52
Body mass index (kg/m^2)				
≤21†	70	68	1.0	
>21-22	40	51	0.78	0.46-1.34
>22-23.5	63	86	0.72	0.45-1.15
>23.5-25	100	84	1.15	0.74-1.79
>25-27	95	77	1.21	0.77-1.90
>27-29	65	69	0.94	0.58-1.51
>29-32	67	66	1.03	0.64-1.67
>32	54	74	0.72	0.44-1.17
Missing	1	0		
Parity				
No live or still births†	126	123	1.0	
1	61	56	1.06	0.68-1.65
2	148	141	1.00	0.71-1.41
3	93	107	0.84	0.58-1.23
4-5	88	101	0.88	0.60-1.29
6-7	31	24	1.36	0.75-2.46
≥8	8	23	0.38	0.16-0.86

ETS, environmental tobacco smoke.
HRT, hormone replacement therapy
*Odds ratios (OR) and associated 95% confidence intervals (CI) of all variables adjusted for age.
†Reference group

TABLE 4.2: Associations between Postmenopausal Breast Cancer and Total Alcohol Consumption, by Selected Indices of Alcohol Intake

	Number of Cases	Number of Controls	Age-adjusted OR	Age-adjusted 95% CI	Fully-adjusted* OR	Fully-adjusted* 95% CI
Never drinkers†	267	330	1.0		1.0	
Any drinkers‡	288	245	1.37	1.08-1.74	1.26	0.94-1.69
Infrequent drinkers§	93	73	1.51	1.06-2.14	1.26	0.83-1.89
Weekly drinkers	193	171	1.31	1.00-1.71	1.26	0.91-1.74
Current drinkers	126	98	1.50	1.10-2.04	1.47	1.01-2.15
Alcohol intake at age 20						
1 drink/week	28	14	2.32	1.20-4.50	2.02	0.95-4.30
>1-4 drinks/week	44	32	1.60	0.98-2.59	1.44	0.81-2.55
>4 drinks/week	21	29	0.80	0.44-1.44	0.79	0.40-1.57
Drank at other ages‖	91	82	1.28	0.91-1.80	1.30	0.87-1.95
Alcohol intake at age 30						
1 drink/week	36	22	1.90	1.09-3.32	2.11	1.09-4.06
>1-4 drinks/week	52	54	1.13	0.74-1.71	0.88	0.54-1.43
>4 drinks/week	40	33	1.35	0.82-2.22	1.50	0.83-2.72
Drank at other ages	55	48	1.33	0.87-2.03	1.40	0.86-2.27
Alcohol intake at age 40						
1 drink/week	33	25	1.51	0.87-2.60	1.90	0.99-3.65
>1-4 drinks/week	74	62	1.40	0.96-2.05	1.15	0.74-1.80
>4 drinks/week	54	46	1.33	0.86-2.04	1.34	0.80-2.24
Drank at other ages	23	24	1.10	0.61-2.00	1.15	0.59-2.25
Alcohol intake at age 50						
1 drink/week	26	20	1.52	0.83-2.79	2.11	1.03-4.30
>1-4 drinks/week	73	61	1.38	0.95-2.02	1.18	0.75-1.85
>4 drinks/week	60	51	1.36	0.90-2.04	1.30	0.80-2.12
Drank at other ages	24	22	1.23	0.67-2.25	1.17	0.59-2.32

Table 4.2 (continued)

	Number of Cases	Number of Controls	Age-adjusted OR	Age-adjusted 95% CI	Fully-adjusted OR*	Fully-adjusted 95% CI
Age when first started to drink alcohol weekly (years)						
<20	59	47	1.46	0.96-2.22	1.40	0.86-2.30
20-25	29	25	1.31	0.75-2.30	1.05	0.55-2.02
26-30	35	36	1.12	0.68-1.84	1.16	0.65-2.07
31-40	32	25	1.48	0.86-2.57	1.51	0.81-2.82
41-50	23	22	1.20	0.65-2.21	1.06	0.53-2.12
>50	15	17	1.10	0.54-2.24	1.21	0.54-2.71
Duration of weekly alcohol intake (years)						
≤10	30	31	1.10	0.65-1.87	0.94	0.51-1.72
11-20	40	22	2.03	1.17-3.52	2.28	1.23-4.23
21-30	30	40	0.82	0.49-1.36	0.78	0.43-1.43
31-40	46	44	1.18	0.75-1.84	1.06	0.63-1.80
41-50	32	27	1.43	0.83-2.45	1.38	0.73-2.60
>50	15	8	2.70	1.12-6.48	2.62	0.93-7.42
Cumulative intake of weekly alcohol consumption (drink-years)						
≤50	66	57	1.32	0.89-1.96	1.31	0.83-2.06
51-100	56	35	1.87	1.18-2.94	1.79	1.06-3.01
101-150	23	26	1.04	0.58-1.87	1.03	0.53-2.03
151-300	18	23	0.90	0.47-1.70	0.72	0.34-1.51
>300	18	14	1.46	0.71-3.00	1.49	0.64-3.46

*Odds ratios (OR) and associated 95% confidence intervals (CI) adjusted for age, family history, age at oophorectomy, education, marital status, ethnicity, age at menarche, duration of hormone replacement therapy use, total duration of breastfeeding, smoking status, body mass index, age at first full-term pregnancy, and proxy respondents.

† Reference group for all categories of alcohol consumption.

‡ Some women stopped drinking before age 20 or started drinking after age 60. The sum of the strata does not add up to the total (n=1130) due to missing values (<1%) and women with the aforementioned drinking pattern (<2%).

§ Women who reported ever drinking at least one type of alcohol for at least once a month but did not ever drink any alcohol beverage on a weekly basis.

|| Women who are non-drinkers at the specified age but drank at some other age.

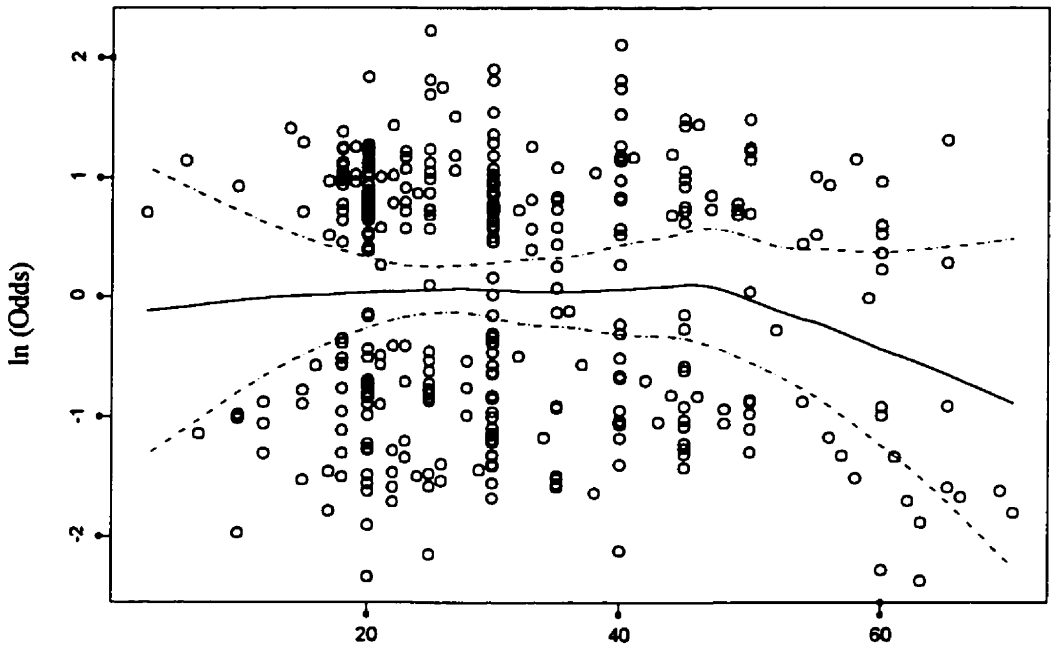

FIGURE 4.1: The log odds of breast cancer risk (solid line) and 95% confidence intervals (dashed lines) according to age (in years) at first exposure to alcohol. The circles above and below the line represent the residuals of the cases (above) and the controls (below). This graph is produced using the non-parametric smoothing technique of locally-weighted running line smoothers (LOESS) to fit the data, using a span of 70%. The odds ratios are adjusted for all of the factors listed in the footnote of Table 4.2.

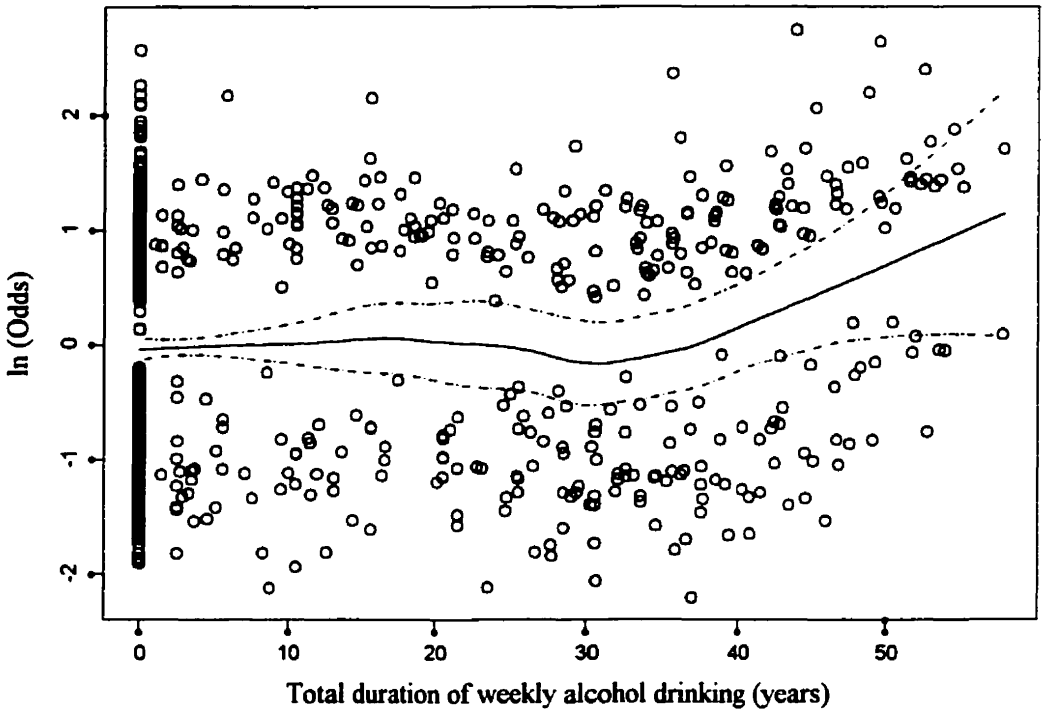

FIGURE 4.2: The log odds of breast cancer risk (solid line) and 95% confidence intervals (dashed lines) according to total duration (in years) of weekly alcohol drinking. The circles above and below the line represent the residuals of the cases (above) and the controls (below). This graph is produced using the non-parametric smoothing technique of locally-weighted running line smoothers (LOESS) to fit the data, using a span of 70%. The odds ratios are adjusted for all of the factors listed in the footnote of Table 4.2.

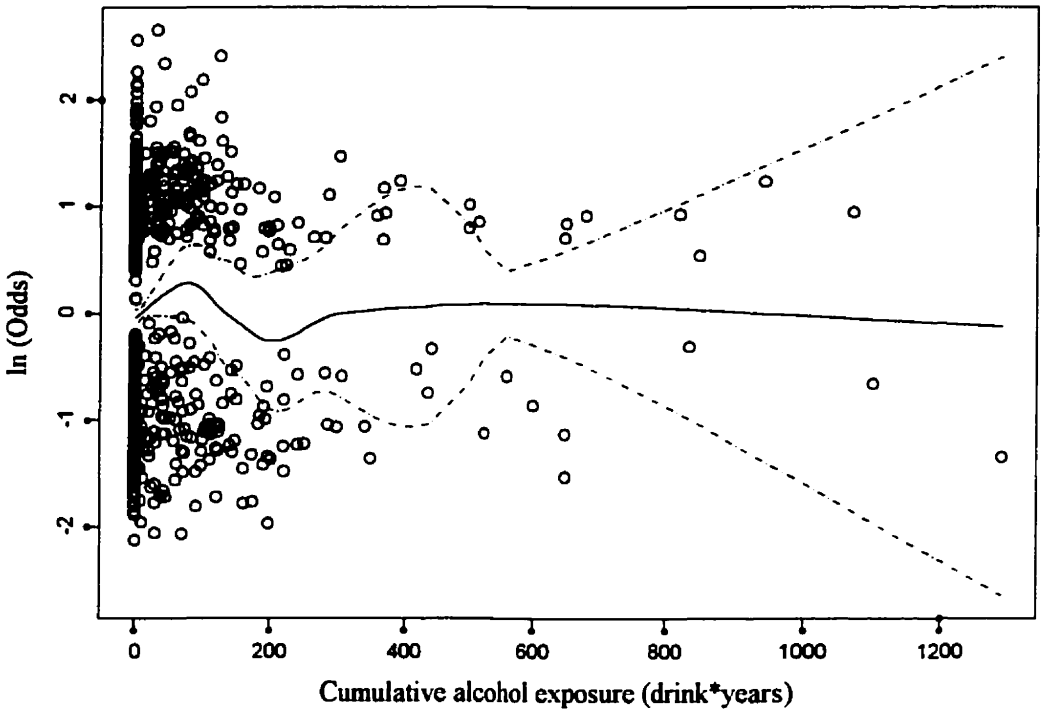

FIGURE 4.3: The log odds of breast cancer risk (solid line) and 95% confidence intervals (dashed lines) according to cumulative alcohol exposure (product of number of drinks and years). The circles above and below the line represent the residuals of the cases (above) and the controls (below). This graph is produced using the non-parametric smoothing technique of locally-weighted running line smoothers (LOESS) to fit the data, using a span of 70%. The odds ratios are adjusted for all of the factors listed in the footnote of Table 4.2.

TABLE 4.3: Associations between Postmenopausal Breast Cancer and Selected Indices of Consumption of Specific Alcoholic Beverages

	Beer Drinkers			Wine Drinkers			Hard Liquor Drinkers		
	Number of Cases	OR*	95% CI	Number of Cases	OR*	95% CI	Number of Cases	OR*	95% CI
Never drinkers†	267	1.0		267	1.0		267	1.0	
Ever drinkers	109	1.13	0.77-1.64	247	1.34	0.98-1.82	123	1.24	0.85-1.81
Weekly drinkers	55	0.93	0.58-1.47	155	1.40	0.99-2.00	79	1.28	0.82-1.99
Current drinkers	27	0.99	0.52-1.89	107	1.64	1.09-2.48	33	1.72	0.89-3.31
Drinkers at age 20	26	1.21	0.63-2.35	61	1.19	0.73-1.92	35	1.27	0.67-2.39
Drinkers at age 30	30	1.00	0.55-1.84	98	1.36	0.90-2.06	53	1.51	0.88-2.61
Drinkers at age 40	37	1.03	0.60-1.79	128	1.38	0.95-2.01	57	1.59	0.94-2.69
Drinkers at age 50	33	0.87	0.50-1.53	131	1.49	1.02-2.17	55	1.52	0.90-2.57
1 drink/week	9	0.98	0.35-2.77	31	2.42	1.22-4.78	18	4.53	1.51-13.57
1-4 drinks/week	10	0.55	0.24-1.29	67	1.08	0.68-1.72	23	1.10	0.54-2.24
>4 drinks/week	14	1.47	0.56-3.85	33	1.97	0.98-3.92	14	1.18	0.48-2.89
Age when first started to drink alcohol weekly (years)									
≤20	15	0.86	0.39-1.90	36	1.59	0.86-2.92	20	1.61	0.72-3.62
21-35	18	0.88	0.41-1.87	64	1.19	0.73-1.94	35	1.12	0.61-2.08
>35	21	0.99	0.50-1.95	55	1.55	0.94-2.56	24	1.28	0.65-2.51

Table 4.3 (continued)

	Beer Drinkers			Wine Drinkers			Hard Liquor Drinkers		
	Number of Cases	OR*	95% CI	Number of Cases	OR*	95% CI	Number of Cases	OR*	95% CI
Duration of weekly intake (years)									
≤12	20	1.18	0.56-2.50	33	1.40	0.75-2.62	22	1.10	0.54-2.22
13-26	14	1.33	0.58-3.06	39	0.97	0.55-1.73	27	1.46	0.72-2.97
>26	17	0.74	0.35-1.55	74	1.65	1.04-2.63	28	1.52	0.75-3.10
Cumulative intake of weekly alcohol consumption (drink-years)									
≤30	17	0.93	0.43-2.02	37	1.29	0.72-2.33	34	1.94	0.96-3.89
31-90	13	0.89	0.39-2.06	73	1.42	0.90-2.24	22	1.05	0.52-2.11
>90	19	1.35	0.62-2.93	34	1.34	0.71-2.51	19	1.31	0.57-2.97

*Odds ratios (OR) and 95% confidence intervals (CI) adjusted for age, family history, age at oophorectomy, education, marital status, ethnicity, age at menarche, duration of hormone replacement therapy use, total duration of breastfeeding, smoking status, body mass index, age at first full-term pregnancy, proxy respondents and intake of other types of alcohol.
† Reference group for all categories of alcohol consumption.

TABLE 4.4: Associations between Postmenopausal Breast Cancer and Levels of Wine Consumption for Subjects who Only Drank Wine

	Number of Cases	Number of Controls	Age-adjusted OR	Age-adjusted 95% CI	Fully-adjusted* OR	Fully-adjusted* 95% CI
Never drinkers†	267	330	1.0		1.0	
Exclusive wine drinkers	103	82	1.43	1.02-2.00	1.40	0.94-2.08
Weekly drinkers	82	63	1.50	1.04-2.18	1.59	1.03-2.46
Current drinkers	72	52	1.59	1.07-2.36	1.62	1.01-2.60
Wine drinkers at 20	39	31	1.45	0.88-2.40	1.34	0.75-2.38
Wine drinkers at 30	57	51	1.28	0.84-1.94	1.30	0.80-2.12
Wine intake at 40	81	65	1.42	0.98-2.06	1.41	0.91-2.18
Wine drinkers at 50	82	63	1.49	1.03-2.16	1.51	0.97-2.34
1 drink/week	22	18	1.44	0.76-2.75	1.98	0.92-4.27
1-4 drinks/week	42	30	1.58	0.96-2.61	1.26	0.71-2.26
>4 drinks/week	18	15	1.36	0.67-2.75	1.41	0.61-3.29
Age when first started to drink wine weekly (years)						
≤30	49	36	1.59	1.00-2.52	1.59	1.00-2.52
>30	33	27	1.39	0.81-2.38	1.39	0.81-2.38
Duration of weekly wine intake (years)						
≤15	25	20	1.40	0.75-2.59	1.14	0.57-2.26
>15	53	43	1.44	0.93-2.23	1.69	1.01-2.84
Cumulative intake of weekly wine consumption (drink-years)						
≤50	46	36	1.46	0.92-2.34	1.51	0.87-2.61
51-90	18	16	1.29	0.65-2.60	1.30	0.60-2.81
>90	14	14	1.16	0.54-2.49	1.17	0.49-2.80

*Odds ratios (OR) and 95% confidence intervals (CI) adjusted for age, family history, age at oophorectomy, education, marital status, ethnicity, age at menarche, duration of hormone replacement therapy use, total duration of breastfeeding, smoking status, body mass index, age at first full-term pregnancy, and proxy respondents.
† Reference group for all categories of wine consumption.

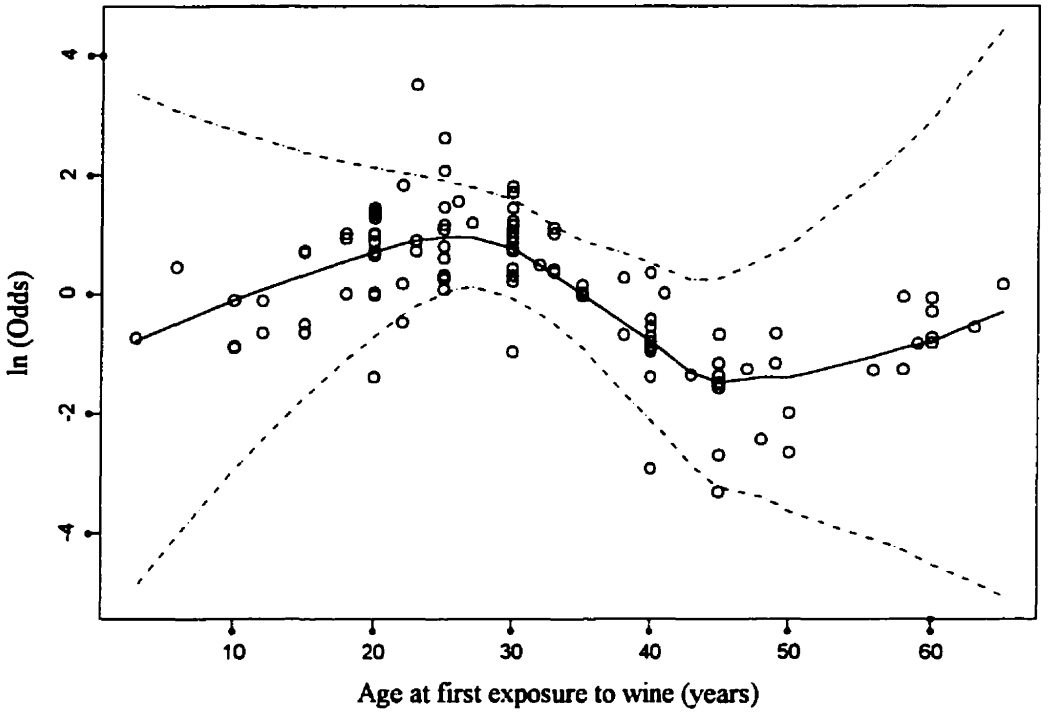

FIGURE 4.4: The log odds of breast cancer risk (solid line) and 95% confidence intervals (dashed lines) according to age (in years) at first exposure to wine for those women who drank wine exclusively. The circles above and below the line represent the residuals of the cases (above) and the controls (below). This graph is produced using the non-parametric smoothing technique of locally-weighted running line smoothers (LOESS) to fit the data, using a span of 70%. The odds ratios are adjusted for all of the factors listed in the footnote of Table 4.2.

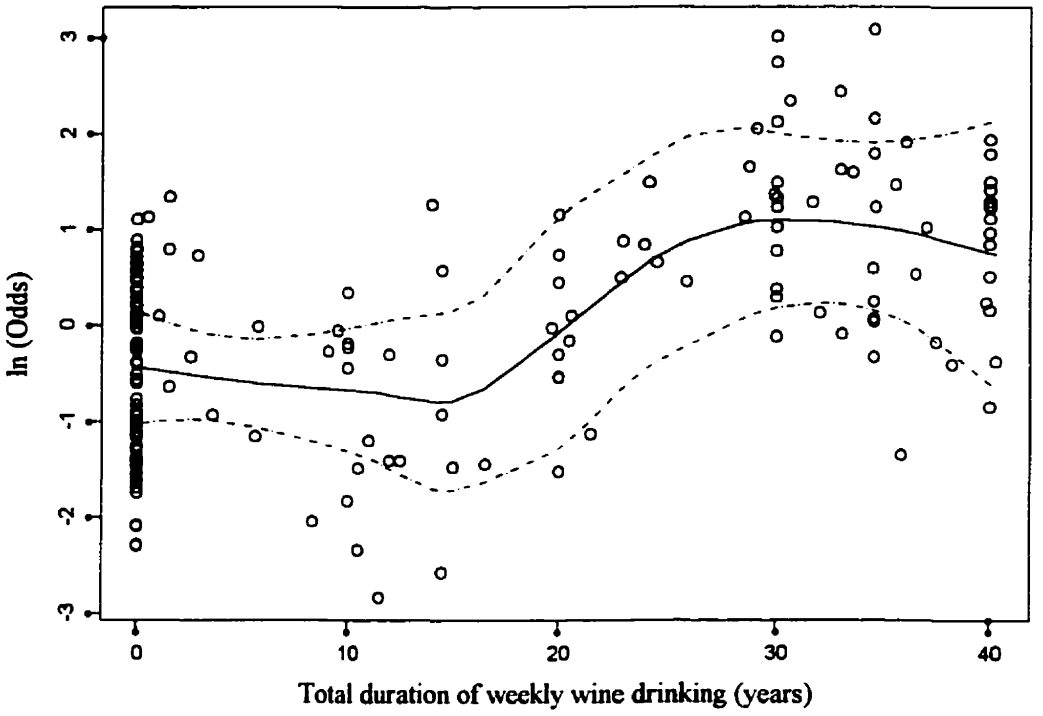

FIGURE 4.5: The log odds of breast cancer risk (solid line) and 95% confidence intervals (dashed lines) according to total duration (in years) of weekly wine drinking for those women who drank wine exclusively. The circles above and below the line represent the residuals of the cases (above) and the controls (below). This graph is produced using the non-parametric smoothing technique of locally-weighted running line smoothers (LOESS) to fit the data, using a span of 70%. The odds ratios are adjusted for all of the factors listed in the footnote of Table 4.2.

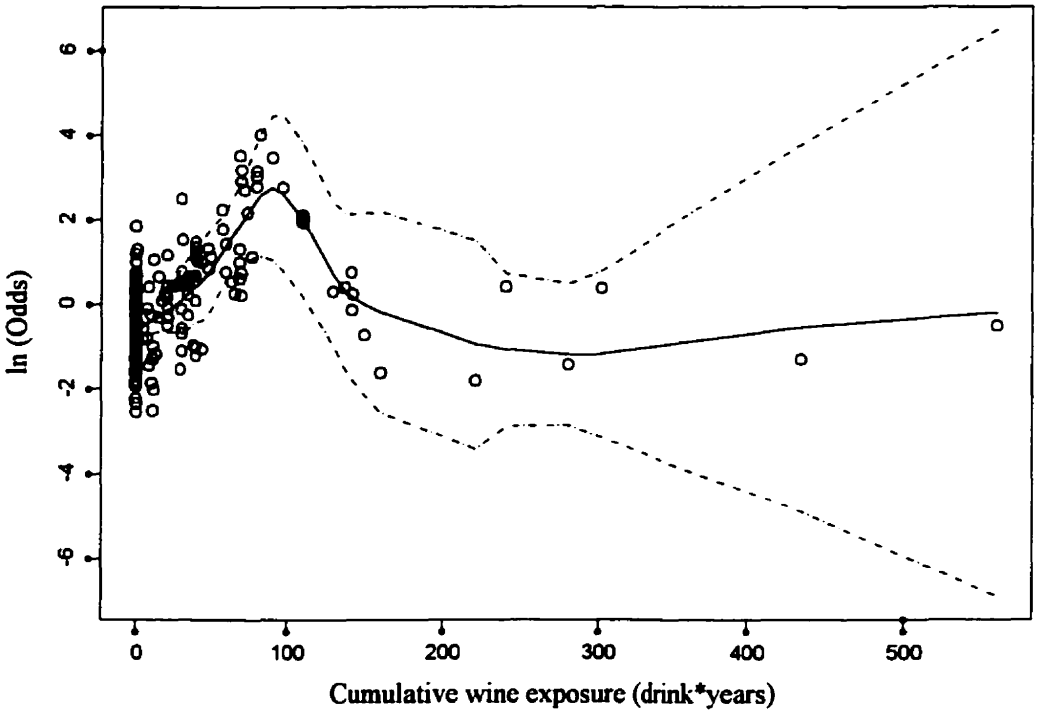

FIGURE 4.6: The log odds of breast cancer risk (solid line) and 95% confidence intervals (dashed lines) according to cumulative wine exposure (product of number of drinks and years) for those women who drank wine exclusively. The circles above and below the line represent the residuals of the cases (above) and the controls (below). This graph is produced using the non-parametric smoothing technique of locally-weighted running line smoothers (LOESS) to fit the data, using a span of 70%. The odds ratios are adjusted for all of the factors listed in the footnote of Table 4.2.

TABLE 4.5: Associations between Postmenopausal Breast Cancer and Cumulative Total Alcohol Consumption according to Estrogen Receptor (ER) and Progesterone Receptor (PR) Status

		ER^+/PR^+ (Number of cases=309)		ER^-/PR^- (Number of cases=84)		ER^+/PR^- (Number of cases=82)		$ER_{missing}/PR_{missing}$ (Number of cases=64)	
	Number of Controls	OR*	95% CI	OR*	95% CI	OR*	95% CI	OR*	95% CI
Never drinkers†	330	1.0		1.0		1.0		1.0	
Ever drinkers‡	245	1.06	0.75-1.51	0.93	0.52-1.67	1.14	0.61-2.11	1.47	0.60-3.60
Infrequent drinkers§	73	0.87	0.51-1.46	1.05	0.47-2.34	1.94	0.90-4.19	1.53	0.63-3.72
Cumulative intake of weekly alcohol consumption (drink-years)									
≤80	82	1.34	0.84-2.15	0.82	0.35-1.90	0.70	0.28-1.76	1.92	0.76-4.83
>80	73	1.11	0.67-1.87	1.01	0.44-2.31	0.52	0.18-1.53	1.67	0.63-4.43

* Odds ratios (OR) and 95% confidence intervals (CI) adjusted for age, family history, age at oophorectomy, education, marital status, ethnicity, age at menarche, duration of hormone replacement therapy use, total duration of breastfeeding, smoking status, body mass index, age at first full-term pregnancy and proxy respondents.

† Reference group for all categories of alcohol consumption.

‡ Some women stopped drinking before age 20 or started drinking after age 60. The sum of the strata does not add up to the total (n=1130) due to missing values (<1%) and women with the aforementioned drinking pattern (<2%).

§ Women who reported ever drinking at least one type of alcohol for at least once a month but did not ever drink any alcohol beverage on a weekly basis.

CHAPTER 5: SUMMARY AND CONCLUSIONS

The objective of this thesis was to determine the association between alcohol consumption and the risk of breast cancer. In order to gain knowledge on the topic, I carried out an extensive literature review. In analysing the literature, I found that, although there were numerous studies on the topic, they varied considerably in design, conduct, analysis, and results. In summary, the results of these studies are inconsistent. The cohort studies, meant to be the pinnacle of epidemiological studies, had many fundamental flaws. Limitations in the design of these cohort studies include low response rates, high percentage of missing information, and improper statistical analyses. Therefore the number of cohort studies that were "well-designed"[77,117,119] (n=3) were too small in number to provide enough information on the association between alcohol consumption and the risk of breast cancer. Although, there were more case-control studies than cohort studies, the number of "well-designed" case-control studies was also small. Among the nine "well-designed" case-control studies,[60,61,76,79,85,86,88,93-95] an association between recent alcohol consumption and the risk of breast cancer was suggested in four studies.[60,61,79,85,86] No association was seen in the other five studies.[76,88,93-95] Clearly, this is an indication that the relationship between alcohol consumption and the risk of breast cancer is still unresolved, as half of the studies suggest an association and the other half do not.

There were few researchers that investigated measurements of alcohol consumption other than current, recent or usual drinking. In only two of the "well-designed" case-control studies[79,85] was past intake levels investigated. Positive results for average lifetime consumption was found in one study.[85] No association was found for early-age drinking or duration of alcohol consumption although both were investigated. Only one "well-designed" cohort study assessed past alcohol history. This study found an association for both early-age alcohol consumption and long duration of alcohol intake.[77] Based on these studies, it is hard to know if the risk of breast cancer is associated with past alcohol intake. Due to the small number of studies, it is difficult to make inferences and none should be made until more studies have been completed. More "well-designed" studies should be undertaken, giving special consideration to alcohol assessment during different age periods.

The questionnaire for this study, of which the analysis for this present thesis is based on, had information on alcohol intake at different age periods. We were able to investigate drinking at ages 20, 30, 40, 50 as well as age at first exposure to alcohol, duration in years of total alcohol consumption, and cumulative consumption of alcohol. We were able to assess these different indices for total alcohol consumption, beer, wine, hard liquor and exclusive wine drinking. Our findings suggest a positive association between any alcohol consumption and the risk of postmenopausal breast cancer. Specifically, we found that any consumption of alcohol among infrequent, weekly, and current drinkers marginally conferred excess risks and, among weekly drinkers, there was little evidence of monotonically increasing relative risks by frequency at different ages, duration, or cumulative consumption. In addition, we found no association between the age at first exposure to any alcoholic beverage and breast cancer. Our findings also indicate an association between the risk of breast cancer and wine drinking. From our data, it is suggestive that exclusive wine drinking is a risk factor for breast cancer if wine is consumed at 1) an early-age (before age 30) or 2) for a duration of 15 years or greater.

Our study had many strengths and limitations. First, the study was population-based and involved all the hospitals in the Montreal area, thus capturing most of the cancer cases that occurred in the one year period, spanning the years 1996-1997. The questionnaire provided detailed information on past drinking history, including age at first exposure to alcohol consumption and duration of alcohol use. The questionnaire also provided excellent information on the majority of known and suspected risk factors, which enabled us to adjust for these risk factors in our analyses to eliminate potential confounding bias. Histological confirmation was obtained for 100% of the breast cancer cases and the controls, removing any concern about misclassification of disease status. Our study population was also restricted to postmenopausal women. This reduced the chance of missing the true association between breast cancer and alcohol consumption because premenopausal and postmenopausal breast cancer may be effected by alcohol intake differently.

Limitations of this study include those common to case-control studies, including the chance of errors in recall and misclassification of alcohol consumption. However, we believe that our study design minimized the chances of both of these biases, although the lack of finding a monotonic increase in risk by increasing levels of consumption may be due to errors in recall of drinking.

In summary, our findings suggest alcohol intake, more specifically wine, increases the risk of breast cancer. Future investigations should try and decipher further the aspects of alcohol intake that influence this increased risk. The discovery of a biological mechanism would also help elucidate the true association. The main purpose of these studies is to determine the risk factors of breast cancer. This, in turn, allows us to better educate women about the causes of the disease. Hopefully, in time we will have the ability to produce better preventative methods to battle breast cancer.

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APPENDIX A: LETTER OF INTRODUCTION AND ETHICS APPROVAL

APPENDIX B: QUESTIONNAIRES

Occupational and Environmental Health Unit
Montreal Public Health Department

Epidemiology and Biostatistics Unit
Institut Armand-Frappier

Department of Occupational Medicine
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Department of Epidemiology and Biostatistics
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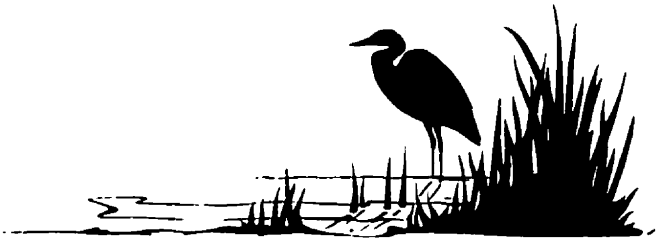


Women's Health and the Environment

This questionnaire concerns:

Is the address listed above correct?

❍ Yes ❍ No ➔ **The correct address is :**

_____

_____

_____

Telephone number: _____

Date of birth: _____
day month year

Place of birth: _____

If you were not born in Canada, in what year did you settle in Canada? 19___

❑ **Si vous préférez répondre en français, veuillez cocher la case et retourner le questionnaire dans l'enveloppe timbrée ci-jointe.**

A. Please list below all of the jobs you have had in your life. Start with the most recent. Include all major job changes within any company.

Job No.	Dates	Company or Organization, and description of main activities
1	From 19___ To 19___	Name: Address: Production or activity:
2	From 19___ To 19___	Name: Address: Production or activity:
3	From 19___ To 19___	Name: Address: Production or activity:
4	From 19___ To 19___	Name: Address: Production or activity:
5	From 19___ To 19___	Name: Address: Production or activity:
6	From 19___ To 19___	Name: Address: Production or activity:
7	From 19___ To 19___	Name: Address: Production or activity:
8	From 19___ To 19___	Name: Address: Production or

activity:

Please indicate your job title or job description and an outline of the tasks

Job Title:
Specific Tasks:

Job Title:
Specific Tasks:

Job Title:
Specific Tasks:

Job Title:
Specific Tasks:

Job Title:
Specific Tasks:

Job Title:
Specific Tasks:

Job Title:
Specific Tasks:

Job Title:
Specific Tasks:

B. Substances checklist

You will find below a list of substances that are often found **in workplaces**. We would like to know whether you have ever used or worked near them. **If Yes,** just tick the box beside the name of the substance in the column marked "**Yes**". Please indicate in which jobs this occurred (see previous page for job numbers). If you **never** worked with or were near any of the substances listed below, please tick this box: ❑.

Yes	Substances		In which job(s)?
❑	Engine exhausts	→	_____
❑	Burning or heating of materials	→	_____
❑	Welding or soldering	→	_____
❑	Solvents or degreasing agents	→	_____
❑	Paints, varnishes or woodstains	→	_____
❑	Gasoline or other fuels	→	_____
❑	Cutting fluids	→	_____
❑	Lube oils or greases	→	_____
❑	Acids	→	_____
❑	Alkalis (caustic)	→	_____
❑	Glues or adhesives	→	_____
❑	Inks or dyes	→	_____
❑	Insecticides	→	_____
❑	Herbicides	→	_____
❑	Asbestos	→	_____
❑	Other insulation material	→	_____
❑	Asphalt or tar products	→	_____
❑	Sand or concrete	→	_____
❑	Wood preservatives	→	_____

❑ Other dusts, liquids, fumes, smoke (specify) → _____

_____

C. Present and past dwellings

1. When did you move into your present home? Date: ___/___
   Month Year

2. Where did you live before moving to your present home? Please list each of the places you lived in, starting with **your most recent address**. If you have difficulty remembering the exact address where you lived, try using your previous tax records. If you do not have these handy and you cannot remember the exact street number, please indicate the street you lived on and the nearest cross-street.

Dates (month, year) From To	**Address (number and street or closest cross-street)**	**City/town/municipality**	**Province/Country**

3. Thinking back to places where you have lived during your lifetime (from birth to the present) were any of these residences within **2 kilometers (1.2 miles)** of the following?

Have you ever lived within 2 kilometers (1.2 miles) of the following:	**No**	**Don't know**	**Yes**	**Dates (years) From**	**To**
Electric power lines (only large high tension lines)	☐	☐	☐ ⇒	____	____
Major highway (at least 4 lanes)	☐	☐	☐ ⇒	____	____
Chemical plant (specify type)	☐	☐	☐ ⇒	____	____
_____					
Electrical power plant	☐	☐	☐ ⇒	____	____
Foundry (plant where ore and metals are melted)	☐	☐	☐ ⇒	____	____
(specify type)_____					
Pulp mill	☐	☐	☐ ⇒	____	____
Underground mine or quarry (specify type)	☐	☐	☐ ⇒	____	____
_____					
Oil refinery	☐	☐	☐ ⇒	____	____
Sanitary landfill site	☐	☐	☐ ⇒	____	____
Hazardous waste site	☐	☐	☐ ⇒	____	____
Other source(s) of pollution (please specify)	☐		☐ ⇒	____	____
_____					

D. Diet assessment

The following pages include questions on the foods you eat.

1. For each food listed, check (_) the box indicating how often, **on average**, you have used the amount specified **one year ago**.

   Example: The example below shows consumption of:
   - 1 glass of milk (6 oz.) per day
   - no table or whipping cream
   - ½ cup of ice cream, 3 to 6 times a week
   - 1 tomato per day in season (end of Summer and beginning of Fall)
   - less than 1 tomato per month, not in season

EXAMPLE	Average use last year					
	Never or less than 1 per month	1-3 per month	1-2 per week	3-6 per week	1 per day	More than 1 per day
Milk (8 oz. glass)					_ (6 oz.)	
Cream e.g. table, whipping (¼ cup/65 ml)	_					
Ice cream or ice milk (½ cup/125 ml)				_		
Tomato, in season (1)					_	
Tomato, rest of the year (1)	_					

For each food listed, check (_) the box indicating how often, **on average**, you have used the amount specified **one year ago.**

Abbreviations: oz.: ounce ml: milliliter cm: centimeter

Foods and amounts	**Average use last year**					
	Never or less than 1 per month	1-3 per month	1-2 per week	3-6 per week	1 per day	More than 1 per day
Dairy products						
Milk (8 oz. glass)						
Cream e.g. table, whipping (¼ cup / 65 ml)						
Ice cream or ice milk (½ cup / 125 ml)						
Sour cream (¼ cup / 65 ml)						
Hard cheese (1 ½ oz., 1 inch cube)						
Other cheese, plain or as part of a dish: (1 slice or 1 oz. serving)						
Yoghurt (¾ cup / 175 ml)						
Milk-based sauce, soup or dessert						
Fats						
Butter (pat) added to food or bread: exclude use in cooking						
Margarine (pat), added to food or bread: exclude use in cooking						
Fruits and vegetables						
Orange (1), grapefruit (½), tangerine (1), clementines (2)						
Orange, grapefruit, pineapple or tangerine juice (small glass)						
Apple (1)						
Apple and other fruit juice (small glass)						

Foods and amounts	Average use last year					
	Never or less than 1 per month	1-3 per month	1-2 per week	3-6 per week	1 per day	More than 1 per day
Peach or nectarine (fresh or canned)						
Fruits and vegetables						
Apricot (1 fresh, or ½ cup canned)						
Apricot or peach, dried (1-2)						
Fruit salad (½ cup / 125 ml)						
Berries, in season (½ cup) : blueberries, strawberries, raspberries, etc.						
Berries, the rest of the year (½ cup) : blueberries, strawberries, raspberries, etc.						
Cantaloup, in season (¼ melon)						
Watermelon, in season (1 slice, 20 x 2 cm)						
Manguo or papaya (1)						
Pumpkin, in pies or other preparations (½ cup)						
Carrots, raw or cooked (1 or ½ cup)						
Peas and carrots (½ cup)						
Peas, canned or frozen (¼ cup)						
Mixed vegetables or macedoine (¼ cup)						
Broccoli (½ cup)						
Tomato, in season (1)						
Tomato, rest of the year (1)						
Tomato/vegetable juice (small glass)						
Tomato sauce e.g. spaghetti sauce (½ cup)						
String beans, green or yellow (½ cup)						
Turnip (1 cup)						
Potato, boiled or baked (1)						
Potatoes, mashed or scallopped (½ cup)						
Cauliflower (½ cup)						
Red pepper, mild (½)						

Foods and amounts	Average use last year					
	Never or less than 1 per month	1-3 per month	1-2 per week	3-6 per week	1 per day	More than 1 per day
Asparagus (8 or 1 cup)						
Brussels sprouts (½ cup)						
Fruits and vegetables						
Cabbage or coleslaw (½ cup)						
Romaine or other dark green lettuce (1 helping)						
Beets greens (½ cup)						
Endive or leek (½ cup)						
Avocado (1/ 8-9 cm)						
Mushrooms, cooked or raw (½ cup)						
Sweet potato or yam (1/13x5cm or ½ cup)						
Swiss chard or kale (½ cup)						
Yellow or winter squash (½ cup)						
Eggs, meat, fish and substitutes						
Egg (1), omelet or quiche						
Chicken, turkey or other poultry (4-6 oz.)						
Beef (4-6 oz.)						
Pork or ham (4-6 oz.)						
Processed meat: bacon, bologna, salami, ...						
Fish or seafood, fresh (3-6 oz.)						
Fish or seafood, canned (3-6 oz.)						
Liver (beef, pork, chicken, veal) (3-4 oz.)						
Kidneys, beef (3-4 oz.)						
Nuts and seeds (¼ cup)						
Grain products						
Bread, white, whole wheat, rolls, bagels, etc. (1 slice or portion)						

Foods and amounts	Average use last year					
	Never or less than 1 per month	1-3 per month	1-2 per week	3-6 per week	1 per day	More than 1 per day
Breakfast cereals (1 cup)						
Egg noodles and pasta (macaroni, spaghetti, etc.) (¾ cup)						

2. Do/did you ever take vitamin supplements?

☐ YES ⇒ **IF YES, please fill in the following table**
☐ NO ⇒ **IF NO, the questionnaire ends here**

Vitamin type	Average number of months per year	For how many years
Multiple vitamins	_____	_____
Vitamin A	_____	_____
Vitamin C	_____	_____
Vitamin E	_____	_____

Thank you for having completed this questionnaire.
Your collaboration is extremely important to the success of the study!

Please send back this questionnaire to us

in the pre-addressed stamped envelope.

If you have any questions, comments, or suggestions,
please feel free to call us at 686-5609 or 337-8675, extension 4613,
or you can write down your comments on the following page.

Comments, suggestions, etc.

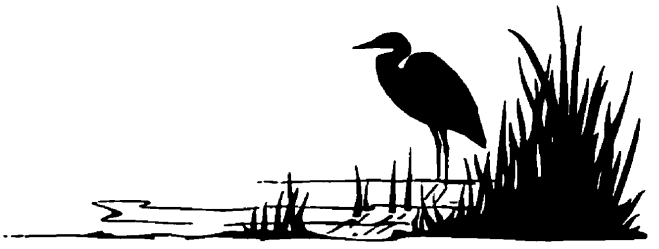
Thank you again!

Occupational and Environmental Health Unit
Montreal Public Health Department

Epidemiology and Biostatistics Unit
Institut Armand-Frappier

Department of Occupational Medicine
Université de Montréal

Department of Epidemiology and Biostatistics
Department of Occupational Health
McGill University



Women's Health and the Environment

Main Questionnaire

This is the main questionnaire mentioned in our letter. We have included it for your information. It is not necessary to fill it out now, as we will ask you these questions over the telephone. Please feel free to read it at your leisure.

Women's health and the environment

Date: ____ / ____ / ____ *ID #:*_____

Day Month Year

A. GENERAL INFORMATION

We would like to start by asking you some general questions about yourself.

1. *What is your date of birth:* ____ / ____ / ____
   Day Month Year

2. *How tall are you?*

   ____ *meters* ____ *centimeters* **OR** ____ *feet* ____ *inches*

3. *How much did you weigh 2 years ago?*

   ____ *kilograms* **OR** ____ *pounds*

4. *What was your approximate weight when you were 20-21 years old?*

   ____ *kilograms* **OR** ____ *pounds*

5. *What is the most you have ever weighed? (Exclude pregnancy)*

   ____ *kilograms* **OR** ____ *pounds*

6. *What is your present marital status? (Check all that apply.)*

- ☐ *Married*
- ☐ *Common law*
- ☐ *Widowed*
- ☐ *Other* ☐ *Please specify* _____
- ☐ *Divorced*
- ☐ *Separated*
- ☐ *Single (never married)*

7. *What language do you usually speak at home? (If you speak more than one, select the one you speak most often.)*

- ☐ *French*
- ☐ *English*
- ☐ *Italian*
- ☐ *Spanish*
- ☐ *Greek*
- ☐ *Arab*
- ☐ *Chinese*
- ☐ *Portuguese*
- ☐ *Vietnamese*
- ☐ *Creole*
- ☐ *Other* ☐ *Please specify:* _____

_____

8. *To which ethnic or cultural group(s) did your parents belong? (Check as many items as apply.)*

- ☐ *French (from France)*
- ☐ *French (Quebec or Canada)*
- ☐ *English (from United Kingdom)*
- ☐ *English (Quebec or Canada)*
- ☐ *Italian*
- ☐ *Jewish*
- ☐ *African (Please specify:* _____ *)*
- ☐ *Greek*
- ☐ *Chinese*
- ☐ *Portuguese*
- ☐ *Lebanese*
- ☐ *European (other) (Please specify:* _____
- ☐ *Native American*
- ☐ *Haitian*
- ☐ *Carribean Islands (other) (Please specify:* _____
- ☐ *South-American (Please specify:* _____
- ☐ *Asian, other than Chinese (Please specify:* _____
- ☐ *Other (Please specify:* _____

9. *Were you born in Canada?*

- ☐ *YES*
- ☐ *NO* ☐ *In what country were you born?* _____

10. *Into which religious group were you born?*

☐ *Catholic* ☐ *Jewish*

☐ *Protestant* ☐ *None*

☐ *Orthodox* ☐ *Other (Specify: _____)*

11. *How many years of elementary school or high school have you completed?*

_____ *Years* ☐ *Never attended school*

12. *How many years of post-secondary school (e.g. trade school, CEGEP, university) have you completed?*

_____ *Years* ☐ *None*

B. MENSTRUAL AND REPRODUCTIVE HISTORY

We would like to now ask you some questions about your reproductive history.

13. *As nearly as you can recall, how old were you when you had your **first** menstrual period?*

____ *years old*

14. *Did your periods occur **regularly** (predictably once a month) within a year after you began menstruating?*

☐ *YES* ☐ ***IF YES, GO TO QUESTION 15***

☐ *NO* ☐ a. ***IF NO**, have they **ever** occurred regularly?*

☐ *YES, at what age? ____ years old*

☐ *NO* ☐ ***IF NO, GO TO QUESTION 15***

b. *Did anything cause your periods to become regular? (For example, pregnancy, hormones)*

☐ *YES*_____
(Please specify)

☐ *NO*

15. *Have you ever been pregnant? (Mark "YES" even if your pregnancy did not result in a living child)*

☐ *YES*
☐ *NO* ☐ ***IF NO, GO TO QUESTION 18***

a. *How many* ***pregnancies****, in all, have you had?* _____ *(number)*

b. *For each pregnancy you have had, no matter how the pregnancy ended (i.e. livebirth, stillbirth, abortion, miscarriage), please give the date of birth or termination of pregnancy, the outcome, and the duration of pregnancy.*

Pregnancy number	***Date of birth or termination (month/year)***	***Outcome (livebirth and number of children, stillbirth, miscarriage, etc.)***	***Duration of pregnancy (weeks)***
1	_____	_____	_____
2	_____	_____	_____
3	_____	_____	_____
4	_____	_____	_____
5	_____	_____	_____
6	_____	_____	_____
7	_____	_____	_____
Last	_____	_____	_____

16. *Did you ever try to breastfeed?*

☐ *YES*
☐ *NO* ☐ ***IF NO, GO TO QUESTION 18***

17. *Were you successful in breastfeeding?*

☐ *YES* ☐ ***IF YES, GO TO QUESTION 17a***
☐ *NO* ☐ ***IF YOU WERE NOT SUCCESSFUL,*** *what do you think was the reason?*
- ☐ *Insufficient milk*
- ☐ *Nipple problems (soreness, bleeding, etc.)*
- ☐ *Other reason (specify):* _____

a. At what age did you breastfeed for the first time?
_____ *years old*

b. How long did you breastfeed each of your children?

Child	***Month and year of birth (month/year)***	***Duration of breastfeeding***		
		weeks	***OR***	***months***
1	_____	_____	***OR***	_____
2	_____	_____	***OR***	_____
3	_____	_____	***OR***	_____
4	_____	_____	***OR***	_____
5	_____	_____	***OR***	_____
6	_____	_____	***OR***	_____
7	_____	_____	***OR***	_____
Others	☐ *Add up duration of breast feeding and indicate total here* ☐	_____	***OR***	_____

18. *Have you ever had a hysterectomy (removal of uterus)?*

☐ *YES*

☐ *NO* ☐ ***IF NO, GO TO QUESTION 18b***

***IF YES**, for what reason was it done?*

☐ *Cancer* ☐ *Dysplasia*

☐ *Polyps* ☐ *Other reason (specify):*_____

☐ *Excessive bleeding*

a. *At what age did you have this done?* ____ *years old.*

b. *Have either or both of your ovaries ever been removed?*

☐ *YES*

☐ *NO* ☐ ***IF NO, GO TO QUESTION 19***

☐ *DO NOT KNOW* ☐ ***IF DO NOT KNOW, GO TO QUESTION 19***

What was the reason?

☐ *cancer*

☐ *cysts*

☐ *other* _____

(please specify)

c. *How many of your ovaries were removed?*

☐ *1* ☐ *2* ☐ *Do not know*

d. *At what age(s) did you have this done?*

___ *years old* ___ *years old*

(first or both ovaries) *(second ovary)*

19. *Are you still menstruating?*

☐ *YES*

☐ *NO* ☐ ***IF NO,** how old were you at the time of your **last** menstrual period?* _

__ *years old*

20. *Have you started to experience or experienced symptoms of menopause? (E.g. hot flashes, night sweats, irregular menstrual periods, changes in the number of days or amount of bleeding, etc.)*

☐ *YES*

☐ *NO* ☐ ***IF NO, GO TO SECTION C***

21. *At what age did you start having the first symptoms of menopause (e.g. hot flashes, night sweats, irregular menstrual periods, changes in the number of days or amount of bleeding, etc.)*

___ *years old*

C. MEDICAL HISTORY

22. *Have you ever had any surgical operations on your breasts before this year?*

☐ *YES*
☐ *NO* ☐ ***IF NO, GO TO QUESTION 23***

If YES, please specify the nature or the reason of the surgery (Check all that apply).

☐ *Benign disease*
☐ *Breast cancer*
☐ *Breast implant*
☐ *Breast reduction*
☐ *Other reason or surgery (specify):*_____

23. *Breast diseases*

a. *Have you ever had any benign diseases or conditions of your breasts? (For example: cyst, lump, mastitis or other inflammation)*

☐ *YES*
☐ *NO* ☐ ***IF NO, GO TO QUESTION 24***

b. *What type of benign disease did you have, when was it first diagnosed, and how was it treated (check all that apply)?*

	Cyst	***Lump/mass***	***Mastitis or inflammation***	***Other:***
When was it first diagnosed?	*19___*	*19___*	*19___*	*19___*
How was this treated?				
- no treatment				
- surgery or biopsy				
- drugs				
- radiation				
- other (specify) _____				

24. *Has a doctor ever told you that you had any of the following diseases or conditions?*

		No	Yes	If yes, please specify what type:	Age at diagnosis
a.	Diabetes	☐	☐	_____	_____
b.	Heart trouble	☐	☐	_____	_____
c.	Circulatory disease	☐	☐	_____	_____
d.	Stroke	☐	☐	_____	_____
e.	Liver disease	☐	☐	_____	_____
f.	Kidney disease	☐	☐	_____	_____
g.	Anemia/other blood disorders	☐	☐	_____	_____
h.	Arthritis	☐	☐	_____	_____
i.	Tuberculosis	☐	☐	_____	_____
j.	Thyroid disease ☐		☐	_____	_____
k.	Cancer ☐		☐	_____	_____

l. *If you have or have had any other significant health condition(s) not listed above, please describe them here:*

Other significant health condition(s):	Age at diagnosis
1) _____	_____
2) _____	_____
3) _____	_____
4) _____	_____

25. *Radiation exposure*

Have you ever had any diagnostic or therapeutic radiographs (x-rays) of your upper body (abdomen and above)? Do not take dental exams into account.*

* *Including:*
- *mammograms*
- *lung X-ray*
- *spinal X-ray (e.g. scoliosis)*
- *treatment for certain diseases (mastitis, tuberculosis)*

☐ *YES* ☐ ***IF YES,*** *please list below all procedures that you had since you were 10 years old.*

☐ *NO* ☐ ***IF NO, GO TO SECTION D***

	Age when X-rays taken	***Number of X-rays***	***Area of the body X-rayed (e.g. chest, breast, etc.)***	***Reason for X-ray (e.g. tuberculosis)***
1	*From To*			
2	*From To*			
3	*From To*			
4	*From To*			
5	*From To*			
6	*From To*			
7	*From To*			
8	*From To*			
9	*From To*			
10	*From To*			

D. FAMILY HISTORY

26. *Did your biological mother or grand-mothers have breast cancer?*

	Did she ever have breast cancer?	**At what age was it detected?**	**Was she pre- or post-menopausal?**
Mother	☐ *Yes* ☐ *No* ☐ *Do not know*	_____ *Years old* ☐ *Do not know*	☐ *Pre-menopausal* ☐ *Post-menopausal* ☐ *Do not know*
Maternal Grand-mother	☐ *Yes* ☐ *No* ☐ *Do not know*	_____*Years old* ☐ *Do not know*	☐ *Pre-menopausal* ☐ *Post-menopausal* ☐ *Do not know*
Paternal Grand-mother	☐ *Yes* ☐ *No* ☐ *Do not know*	_____*Years old* ☐ *Do not know*	☐ *Pre-menopausal* ☐ *Post-menopausal* ☐ *Do not know*

27. a. *Do you have any sisters or half sisters?*

☐ *YES*
☐ *NO* ☐ ***IF NO, GO TO SECTION E***

b. *If you do, how many? (Include deceased)*
_____ *sisters or half-sisters*

c. *Have any of your sisters or half sisters ever had breast cancer?*

☐ *YES*
☐ *NO* ☐ ***IF NO, GO TO SECTION E***
☐ *DO NOT KNOW* ☐ ***IF DO NOT KNOW, GO TO SECTION E***

Please give the following information for your sister(s) who have been diagnosed with breast cancer.

Sister's initials	***Birth year***	***Relationship (half, full)***	***Age at diagnosis of breast cancer***	***Was she pre- or post menopausal?***
			_____ Years old ☐ Do not know	☐ Pre-menopausal ☐ Post-menopausal ☐ Do not know
			_____ Years old ☐ Do not know	☐ Pre-menopausal ☐ Post-menopausal ☐ Do not know
			_____ Years old ☐ Do not know	☐ Pre-menopausal ☐ Post-menopausal ☐ Do not know
			_____ Years old ☐ Do not know	☐ Pre-menopausal ☐ Post-menopausal ☐ Do not know
			_____ Years old ☐ Do not know	☐ Pre-menopausal ☐ Post-menopausal ☐ Do not know

E. HORMONES

28. Oral contraceptives

a. *Have you ever taken oral contraceptives (birth control pills)?*
- ☐ *YES*
- ☐ *NO* ☐ ***IF NO, GO TO QUESTION 29***
- ☐ *DO NOT KNOW* ☐ ***DO NOT KNOW, GO TO QUESTION 29***

b. *Did you take oral contraceptives for at least 12 consecutive months?*
- ☐ *YES*
- ☐ *NO* ☐ ***IF NO, GO TO QUESTION 29***
- ☐ *DO NOT KNOW* ☐ ***DO NOT KNOW, GO TO QUESTION 29***

c. *How old were you when you took these oral contraceptives?*

From _____ *to* _____ *years old*

From _____ *to* _____ *years old*

From _____ *to* _____ *years old*

From _____ *to* _____ *years old*

29. *Female replacement hormones*

Doctors give female replacement hormones (estrogens and/or progesterone) as pills, shots, patches or creams to women for a variety of reasons.

a. *Have you **ever** taken any female replacement hormones?*

☐ *YES*

☐ *NO* ☐ ***IF NO, GO TO SECTION F***

☐ *DO NOT KNOW* ☐ ***DO NOT KNOW, GO TO SECTION F***

b. *Please check the reason(s) you received these hormones and provide the age begun, the number of months/years taken and the type or brand name of medication.*

Reason		**Age begun**	**Duration**			**Type or brand name of medication**
			Years		**Months**	
a.	*alleviate acne*	_____	_____	**OR**	_____	_____
b.	*regulate periods*	_____	_____	**OR**	_____	_____
c.	*eliminate painful periods*	_____	_____	**OR**	_____	_____
d.	*test for pregnancy*	_____	_____	**OR**	_____	_____
e.	*prevent miscarriage*	_____	_____	**OR**	_____	_____
f.	*treat infertility*	_____	_____	**OR**	_____	_____
g.	*reduce discomfort during intercourse (vaginal dryness)*	_____	_____	**OR**	_____	_____
h.	*replace hormones after ovaries removed*	_____	_____	**OR**	_____	_____
i.	*alleviate menopausal symptoms (hot flashes, sweating)*	_____	_____	**OR**	_____	_____
j.	*prevent osteoporosis*	_____	_____	**OR**	_____	_____
k.	*other* _____ *(please specify)*	_____	_____	**OR**	_____	_____

c. *Are you still taking female replacement hormones?*

☐ *YES*

☐ *NO* ☐ *At what age did you stop?* _____ *Years old*

F. PERSONAL HABITS

30. *Which hand do you usually write with?*

☐ *Left* ☐ *Right* ☐ *Right (obliged)* ☐ *Both hands*

31. *Physical activity*

How many hours per week, on average, did you spend doing the following physical activities, when you were a teenager, a young adult, and more recently?

	From 12 to 19 years old			From 20 to 39 years old			From age 40		
	Never	Hours/ week	Do not know	Never	Hours/ week	Do not know	Never	Hours/ week	Do not know
Walking									
Jogging									
Running									
Bicycling									
Swimming									
Skating									
Gardening									
Golf									
Ski									
Dancing									
Ballet									
Aerobic exercises									
Gymnastics									
Competitive sport: _____									
*Other:*_____									

32. *Smoking history*

a. *Have you ever smoked 100 cigarettes in your life?*

☐ *YES*
☐ *NO* ☐ ***IF NO, GO TO QUESTION 33***
☐ *DO NOT KNOW* ☐ ***IF DO NOT KNOW, GO TO QUESTION 33***

b. *At what age did you start to smoke?*

_____ *years old*

c. *Were there ever any periods when you gave up smoking and then took it up again?*

☐ *YES* ☐

Periods when you stopped smoking
from age ___ to age ___
from age ___ to age ___

☐ *NO*

☐ *DO NOT KNOW*

d. *Do you still smoke regularly?*

☐ *YES* ☐ ***IF YES, GO TO QUESTION 32f***
☐ *NO*

e. *If NO, at what age did you stop?*

_____ *years old*

f. *On average, how many did/do you smoke a day?*

_____ *cigarettes*

g. *Did/do you generally smoke filter or non-filter cigarettes?*

☐ *mainly filter*
☐ *mainly non-filter*

☐ *both types*
☐ *Do not know* ☐ ***IF DO NOT KNOW, GO TO QUESTION 33***

h. *What is the largest number of cigarettes a day you have smoked regularly?*
_____ *cigarettes per day*

i. *For how long did you smoke this amount?*
_____ *years*

33. *Passive smoking*

When you were a child or an adolescent (less than18 years old) living at home, were there any persons who smoked cigarettes, cigars, or pipes indoors?

☐ *YES* ☐ ***IF YES,*** *for each person who smoked indoors, please answer the questions below.*

☐ *NO* ☐ ***IF NO, GO TO QUESTION 34***

	Specify who smoked (father, mother, uncle, etc.)	***How old were you when you started to be exposed to their smoke?***	***How old were you when they stopped smoking?****	***Specify what he/she smoked: Cigarette (Ct) Cigar (Cr) Pipe (P)***	***Approximate number smoked per day***
1					
2					
3					
4					
5					
6					
7					
8					

**If they continued to smoke after you left home, put your age when you left home.*

34. Alcohol consumption

We have a few questions about consumption of alcoholic beverages. We realise that consumption of alcoholic beverages can vary over time. ***Please try to indicate average amounts consumed.***

	Beer	***Wine/cider***	***Liquors/spirits***
a. *Has there ever been a period when you drank beer, wine, cider, or liquor* ***at least once a month?***	☐ *YES* ☐ *NO* ☐ *DO NOT KNOW*	☐ *YES* ☐ *NO* ☐ *DO NOT KNOW*	☐ *YES* ☐ *NO* ☐ *DO NOT KNOW*
	IF YOU ANSWERED NO TO ALL 3 CATEGORIES, GO TO SECTION G.		
b. *Has there ever been a period when you drank beer, wine, cider, or liquor* ***at least once a week?***	☐ *YES* ☐ *NO* ☐ *DO NOT KNOW*	☐ *YES* ☐ *NO* ☐ *DO NOT KNOW*	☐ *YES* ☐ *NO* ☐ *DO NOT KNOW*
	IF YOU ANSWERED NO OR DO NOT KNOW TO ALL 3 CATEGORIES, GO TO SECTION G.		
c. *If YES, at what age did you start to drink alcohol* ***at least once a week****?*	____ *Age (years)*	____ *Age (years)*	____ *Age (years)*
d. *Do you still drink at least once a week?* *If NO, at what age did you stop?*	☐ *YES* ☐ *NO* ☐ *DO NOT KNOW* ____ *Age (years)*	☐ *YES* ☐ *NO* ☐ *DO NOT KNOW* ____ *Age (years)*	☐ *YES* ☐ *NO* ☐ *DO NOT KNOW* ____ *Age (years)*
e. *On average, how many cans/bottles, glasses or shots did you consume per week when you were:*	*Small bottle or can = 12 oz.*	*Glass= 4 oz.* *5-6 glasses/750ml bottle*	*Shot= 1.5 oz.* *17 small glasses/ 26 oz.*
20 years old	_____ *small bottles or cans*	_____ *glasses or bottles*	_____ *shots*
30 years old	_____ *small bottles or cans*	_____ *glasses or bottles*	_____ *shots*
40 years old	_____ *small bottles or cans*	_____ *glasses or bottles*	_____ *shots*
	_____ *small bottles or*	_____ *glasses or*	

	Beer	Wine/cider	Liquors/spirits
a. *Has there ever been a period when you drank beer, wine, cider, or liquor* ***at least once a month?***	☐ *YES* ☐ *NO* ☐ *DO NOT KNOW*	☐ *YES* ☐ *NO* ☐ *DO NOT KNOW*	☐ *YES* ☐ *NO* ☐ *DO NOT KNOW*
50 years old	*cans*	*bottles*	____ *shots*

_ ***PLEASE GO TO THE GENERAL WORK HISTORY***

G. ELECTRIC APPLIANCES USE

We would like to ask you some questions about usage of appliances, electric heating, and air conditioning in your home.

35. Electric heating

During the past 10 years, could you please indicate whether you used electric heating and what type (baseboard, portable electric heater). Please specify this for each residence that you lived in over those 10 years.

	Years used	**Type of heater (baseboard, portable electric heater, etc.)**
1		
2		
3		
4		
5		
6		
7		

36. Appliance history

Now we would like to ask you some questions about a variety of electrical appliances that you may have had in your home in the past 10 years. We are only interested in ***residential appliance use****. Do not include appliances that you may have used as part of a job.*

a. *During the past 10 years, did you ever have a digital electric clock or clock radio in your bedroom, i.e. an electric clock that gives the time with large lighted numbers (most often red or green)?*

□ *YES* □ ***IF YES,*** *1- how many years did you use it? ____ years*

2- how far away from the clock did you sleep?

____ feet OR ____ meters

□ *NO*

□ *DO NOT KNOW*

b. *During the past 10 years, did you ever have a* ***non****-digital electric clock or clock radio in your bedroom, i.e. a clock without lighted numbers?*

□ *YES* □ ***IF YES,*** *1- how many years did you use it? ____ years*

2- how far away from the clock did you sleep?

____ feet OR ____ meters

□ *NO*

□ *DO NOT KNOW*

c. *Here is a list of electrical appliances often used at home. Please indicate whether in the past 10 years you used each of these, for how many years you used them, and the amount of time used.*

During the past 10 years, did you ever have a:	***In the past 10 years, how many years did you use it?***	***During that time, how much time (per day, week or month) did you spend using the appliance?***
Hair dryer? ☐ *Yes* ☐ *No* ☐ *Do not know*	_____ *years*	_____ *minutes* *Circle one:* *per day / week / month / year*
Curling iron? ☐ *Yes* ☐ *No* ☐ *Do not know*	_____ *years*	_____ *minutes* *Circle one:* *per day / week / month / year*
Electric massage unit? ☐ *Yes* ☐ *No* ☐ *Do not know*	_____ *years*	_____ *minutes* *Circle one:* *per day / week / month / year*
Sewing machine? ☐ *Yes* ☐ *No* ☐ *Do not know*	_____ *years*	_____ *minutes* *Circle one:* *per day / week / month / year*
Vacuum cleaner, either canister or upright ☐ *Yes* ☐ *No* ☐ *Do not know*	_____ *years*	_____ *minutes* *Circle one:* *per day / week / month / year*
Pop-up toaster? ☐ *Yes* ☐ *No* ☐ *Do not know*	_____ *years*	_____ *minutes* *Circle one:* *per day / week / month / year*
Mixer or blender? ☐ *Yes* ☐ *No* ☐ *Do not know*	_____ *years*	_____ *minutes* *Circle one:* *per day / week / month / year*

Microwave oven? ☐ *Yes* ☐ *No* ☐ *Do not know*	_____ *years*	_____ *minutes* *Circle one:* *per day / week / month / year*
Fluorescent table or desk lamp? ☐ *Yes* ☐ *No* ☐ *Do not know*	_____ *years*	_____ *minutes* *Circle one:* *per day / week / month / year*
Colour television? ☐ *Yes* ☐ *No* ☐ *Do not know*	_____ *years*	_____ *minutes* *Circle one:* *per day / week / month / year*
Black and white television? ☐ *Yes* ☐ *No* ☐ *Do not know*	_____ *years*	_____ *minutes* *Circle one:* *per day / week / month / year*
Personal computer? ☐ *Yes* ☐ *No* ☐ *Do not know*	_____ *years*	_____ *minutes* *Circle one:* *per day / week / month / year*

d. *Here are some commonly used devices. Please indicate which ones you have used in the past 10 years and the amount of time used.*

	Electric blanket	***Electric mattress pad/ Heating La-Z-Boy***	***Electric water bed heater***
In the last 10 years, which of the following, if any, did you use at your residence?	☐ *Yes* ☐ *No* ☐ *Do not know*	☐ *Yes* ☐ *No* ☐ *Do not know*	☐ *Yes* ☐ *No* ☐ *Do not know*
During the last 10 years, for how many years did you use it?	_____ *years*	_____ *years*	_____ *years*
On average, how many months of the year did you use it?	_____ *months*	_____ *months*	_____ *months*
Did you usually keep the unit on all the time you used it or did you put it off before using it?	☐ *Sleep with unit on* ☐ *To warm bed only* ☐ *Do not know*	☐ *Used with unit on* ☐ *Used with unit off* ☐ *Do not know*	☐ *Sleep with unit on* ☐ *To warm bed only* ☐ *Do not know*
How many hours at a time did you usually use it?	_____*hours/night*	_____ *hours/day* *or* *night*	_____ *hours/night*
What temperature did you usually have it on?	☐ *High* ☐ *Medium* ☐ *Low* ☐ *Do not know*	☐ *High* ☐ *Medium* ☐ *Low* ☐ *Do not know*	☐ *High* ☐ *Medium* ☐ *Low* ☐ *Do not know* *Temperature:*____

37. *Air conditioning and electric fans*

Please indicate whether, in the past 10 years, you used air conditioners and electric fans in your bedroom, and the amount of time used.

	Air conditioner	***Electric fan***
In the last 10 years, which of the following, if any, did you use in your bedroom, while you slept?	☐ *Yes* ☐ *No* ☐ *Do not know*	☐ *Yes* ☐ *No* ☐ *Do not know*
During the last 10 years, for how many years did you use it?	_____ *years*	_____ *years*
On average, how many months of the year did you use it?	_____ *months*	_____ *months*

H. HOBBIES AND LEISURE

Now we would like to ask some questions about your hobbies and leisure activities.

38. *Since you were a teenager (age 15), did you have a regular hobby or a leisure activity that you would do at least 10 times a year, for 2 years or more? If yes, how often did you do it per year, how many hours at a time, during how many years, and how old were you when you started?*

	Number of times per year	**Number of hours per session**	**Total number of years**	**At what age did you start?**
☐ *Cabinet making or wood working*	_____	_____	_____	_____ *Years*
☐ *Paint stripping (furniture or other)*		_____	_____	_____ *Years*
☐ *Painting, artistic*	_____	_____	_____	_____ *Years*
☐ *Painting, other (furniture, walls, cars)*		_____	_____	_____ *Years*
☐ *Metal working*	_____	_____	_____	_____ *Years*
☐ *Soldering (soldering iron)*		_____	_____	_____ *Years*
☐ *Welding (electric arc or acetylene)*	_____	_____	_____	_____ *Years*
☐ *Pottery*		_____	_____	_____ *Years*
☐ *Weaving or other textile work*	_____	_____	_____	_____ *Years*
☐ *Wine or beer making*		_____	_____	_____ *Years*
☐ *Fur or leather processing*	_____	_____	_____	_____ *Years*
☐ *Animal stuffing*		_____	_____	_____ *Years*
☐ *Printing/publishing*	_____	_____	_____	_____ *Years*
☐ *Photograph developing*		_____	_____	_____ *Years*
☐ *Spraying of trees, weeds or grass*	_____	_____	_____	_____ *Years*
☐ *Other handicrafts*		_____	_____	_____ *Years*
☐ *please specify:* _____	_____			
☐ *Other activities (please specify):*				
a) _____	_____	_____	_____	_____ *Years*
b) _____		_____	_____	_____ *Years*
c) _____	_____	_____	_____	_____ *Years*

d) _____	_____ _____ _____ _____ _____ _____ _____ _____ _____	_____	_____	_____ Years

39. *Since you were 15 years old, in your activities at home, did you use any of the following products at least 10 times a year, for 2 years or more:*

	Number of times per year	Number of hours per session	Total number of years	At what age did you start?
☐ *Air fresheners*	_____	_____	_____	_____ Years
☐ *Herbicides*	_____	_____	_____	_____ Years
☐ *Fungicides*	_____	_____	_____	_____ Years
☐ *Insecticides*	_____	_____	_____	_____ Years
☐ *Other pesticides* ☐ *please specify:* _____ _____	_____	_____	_____	_____ Years
☐ __	_____	_____	_____	_____ Years
☐ *Chemical solvents (e.g. turpentine, paint remover, white spirit)*	_____	_____	_____	_____ Years
☐ *Oil-based paints, lacquers, stains or varnishes*	_____	_____	_____	_____ Years
☐ *Latex paints*	_____	_____	_____	_____ Years
☐ *Film developing fluids*	_____	_____	_____	_____ Years
☐ *Wood glue*	_____	_____	_____	_____ Years
☐ *Epoxy & plastic glues/resins*	_____	_____	_____	_____ Years
☐ *Gasoline, oils, fuels*	_____	_____	_____	_____ Years
☐ *Metal cleaners/degreasers/ oven cleaners*	_____	_____	_____	_____ Years
☐ *Nail polish remover*	_____	_____	_____	_____ Years
☐ *Hair sprays*	_____	_____	_____	_____ Years
☐ *Hair dyes*	_____	_____	_____	_____ Years
Floor waxes				

Thank you for your time!

APPENDIX C: Distribution of Sites of Cancer Among the Control Subjects

Site of Cancer	ICD-9 Code	Number of Subjects	Percent of Controls
Included in the Analysis			
Stomach	151	27	4.7%
Small intestine	152	3	0.5%
Colon	153	138	24.0%
Rectum	154	46	8.0%
Gallbladder and extra-hepatic bile ducts	156	1	0.2%
Peritoneum	158	9	1.6%
Nasal cavity	160	2	0.3%
Bone	170	2	0.3%
Connective tissue	171	5	0.9%
Skin melanomas	172	22	3.8%
Uterus	179	3	0.5%
Cervix uteri	180	15	2.6%
Endometrium	182	111	19.3%
Ovaries	183	45	7.8%
Other female genital organs	184	8	1.4%
Bladder	188	39	6.8%
Kidney	189	33	5.7%
Eye	190	2	0.3%
Thyroid	193	22	3.8%
Lymph nodes	196	29	5.0%
Lymphosarcomas and reticulosarcomas	200	2	0.3%
Other malignant neoplasms of lymphoid and histiocytic tissue	202	6	1.0%
Multiple myeloma and immunoproliferative neoplasms	203	5	0.9%

Appendix C (continued)

Site of Cancer	ICD-9 Code	Number of Subjects
Excluded from the Present Study		
Tongue	141	6
Major salivary glands	142	4
Gums	143	2
Mouth	144-145	4
Oropharynx	146	3
Nasopharynx	147	1
Other sites of oral cancer	149	1
Esophagus	150	2
Larynx	161	11
Excluded from Original Study		
Liver, intrahepatic bile duct	155	
Pancreas	157	
Lung, bronchus, trachea	162	
Non-melanoma skin cancer (other malignant neoplasms of skin)	173	
Breast	174	1
Brain and nervous system	191-192	
Malignant neoplasm of other and ill-defined sites	195	
Leukemias	204-208	