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The Genetic Epidemiology of Multiple Primary Breast and Ovarian Cancer

by
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The Genetic Epidemiology of Multiple Primary Breast and Ovarian Cancer

Breast and ovarian cancers are among the most common tumours affecting Canadian women. A proportion of these tumours was thought to be due to family history and the breast cancer susceptibility gene and are more likely to occur before the age of 50. It is hypothesized that women who have both primary tumours of the breast and ovary are more likely to have a mutation in this gene. The main objective of this study is to examine the role of family history in those women with breast cancer that subsequently develop ovarian cancer. The role of chemotherapy and radiotherapy in the treatment of breast cancer, as a risk factor for future development of ovarian cancer, was also assessed.

This was a case-control study. The cases studied were women with multiple primary breast and ovarian cancers and were identified from the Quebec Tumour Registry and a database at Sunnybrook Hospital in Toronto. Interviews were administered over the telephone and included questions on family history, reproductive history and treatment received for breast cancer (cases only). The total number of cases interviewed was 65. Controls consisted of women with breast cancer only, matched within two years of the year of birth and one year of the year of diagnosis. Controls, for the most part, were identified through the Epidemiology Research Unit at the Hôtel-Dieu de Montréal. Were possible, two controls per case were interviewed. We found that the incidence of breast cancer in first-and second-degree relatives of cases who had breast cancer below the age of 50 was 35 per 100 woman-years, compared to an incidence of 20 per 100 woman-years in those women with breast cancer after the age of 50 (p=0.0065). Usual weight (OR=0.9, 95%CI 0.8-1.0), duration of radiotherapy (OR=0.9, 95%CI 0.8-1.0) and number of sisters (OR=0.5, 95%CI 0.3-0.9) significantly reduced the risk of developing ovarian cancer after breast cancer, while chemotherapy increased the risk (OR=52.7, 95%CI 1.7-1651). Family history was found to increase the risk of ovarian cancer, although not significantly (OR=1.3, 95%CI 0.6-2.9). There were some limitations discussed with this model.

To conclude, we found that the incidence of breast cancer is higher among relatives of the case if diagnosed at less than 50 years of age. Family history of breast and ovarian cancer, as well as treatment for breast cancer is not strongly related to the risk of subsequent ovarian cancer. This study indicated that for those women diagnosed with breast cancer, their physician should consider taking a complete family history of cancer and increase screening regimens (such as ultrasound or CA 125) for those who are at further risk of ovarian cancer.

L'épidémiologie génétique des cancers primaires multiples du sein de l'ovaire

Les cancers du sein et de l'ovaire sont au rang des tumeurs les plus fréquentes qui frappent les Canadiennes. Nous croyons qu'une certaine proportion de ces tumeurs sont attribuables aux antécédents familiaux et à la présence du gène qui rend ces femmes susceptibles au cancer du sein. Ce gene serait plus frequemment le siege de mutations chez les femmes atteites de tumeurs primaires du sein et de l'ovaire. Le role de la chimiotherapie et de la radiotherapie, comme facteur de risque pour l'apparition subsequente d'un cancer de l'ovaire, a egalement ete evalue dans cette etude.

Tirés du Fichier des tumeurs du Québec et d'une base de données du *Sunnybrook Hospital* à Toronto, les cas étudiés étaient des femmes atteintes de cancers du sein et de l'ovaire primaires multiples. Nous avons réalisé des interviews téléphoniques en leur posant des questions sur leurs histoire familiale de cancer et de chirurgie abdominale, ainsi que sur la prise de contraceptifs oraux. Nous avons interviewé 65 femmes et avons trouvé une incidence de 35 % de cancers du sein chez les apparentées du premier et du deuxième degré des femmes atteintes de cancers du sein avant l'âge de 50 ans, comparativement à une incidence de 20 % chez les apparentées des femmes atteintes après l'âge de 50 ans (p=0,0065). Notre modèle final de régression logistique a démontré que la chimiothérapie (OR=0.9, 95%CI 0.8-1.0), le poids habituel (OR=1.3, 95%CI 0.6-2.9), la durée de la radiothérapie (OR=0.9, 95%CI 0.8-1.0) et le nombre de soeurs (OR=0.5, 95%CI 0.3-0.9) étaient au nombre des facteurs contribuant à augmenter légèrement le risque qu'une femme serait atteinte d'un cancer de l'ovaire après avoir contribuant a augmenter legerement le risque de developpement d'un cancer de l'ovaire chez une femme deja atteinte subsequente d'un cancer de l'ovaire. Nous avons discuté des quelques restrictions que présentait l'usage d'un tel modèle.

En conclusion, nous avons trouvé que l'incidence d'un cancer du sein est plus élevée chez ses apparentées lorsqu'une femme est diagnostiquée avec ce même cancer avant l'âge de 50 ans, et que le traitement d'un cancer du sein ne semble pas etre étroitement lié au risque d'atteinte subséquente d'un cancer de l'ovaire. L'étude indique toutefois que si une femme est atteinte d'un cancer du sein ou de l'ovaire, son médecin devrait se renseigner sur les antécédents familiaux de cancer, modifier le protocole de traitement et tâcher d'affermir les schémas de dépistage de cancers subséquents.

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Thank you all and I hope I get similar support when I start the next one...groan!

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Introduction

It has been known for some time that some cancers seem to be more common in certain families. Breast cancer is one such cancer that may be disproportionately more common in relatives. Some of these families also have ovarian cancer occurring more than would be expected from the population as a whole. These two cancers share risk factors and it is no surprise that some women diagnosed with breast cancer later develop primary cancers of the ovary. In a registry study in England, Prior and Waterhouse (1981) found that in those with breast cancer there was a slight increased risk of ovarian cancer (Standardized Incidence Ratio (SIR) 1.20, $p>0.05$). However in those with breast cancer diagnosed before age 45, the SIR was 4.4 ($p<0.001$). Of those women diagnosed with both breast or ovarian cancer, 77% of the time the breast cancer occurs before the ovarian (Shah, 1993). The purpose of this report is to document the risk factors leading to the subsequent development of primary ovarian cancer in women who had a primary breast cancer.

We know that women with relatives with either breast or ovarian cancer are at a greater risk of developing a cancer themselves. The more relatives a woman has that are affected with cancer and the younger the relatives are diagnosed, the more likely she will develop one of these tumours. What we do not know is precisely why some women in a family will remain cancer-free and some will develop a cancer. If a woman is diagnosed with breast cancer, whether she will be diagnosed with ovarian cancer remains unknown. It is thought that some of these

causes are genetic and some could be related to lifestyle factors alone. There is also some thought that treatment for breast cancer itself increases the risk of ovarian cancer.

The main objective of this report is to identify the factors contributing to women with breast cancer later developing ovarian cancer. We would like to quantify the proportion of subsequent ovarian tumours resulting from a family history of breast or ovarian cancer and those resulting from lifestyle and treatment factors. The main reason for identifying those factors leading to ovarian cancer is to help predict which women with breast cancer are at a further risk of ovarian cancer.

Once those factors above are known, prevention efforts can begin. If a woman appears to be at risk for a ovarian cancer, then the course of treatment can be altered, behaviour changed or screening efforts can be intensified in both frequency and aggressiveness.

Literature Review

Breast cancer is one of the most common diseases affecting Canadian women. In Canada, breast cancer has the highest incidence rate of all cancers in females (108 new cases per 100 000 women per year) (NCIC, 1998). Ovarian cancer ranks sixth in terms of incidence rates, with 14 new cases per 100 000 women per year in Canada. Annual female mortality rate from breast cancer is 28 deaths per 100 000 women per year, the second highest after lung cancer (NCIC,

1998). For ovarian cancer mortality, the rate is 8 deaths per 100 000 women, which is identical to pancreatic cancer. According to 1998 estimates there are going to be 19 300 new cases of breast cancer and 2 500 new cases of ovarian cancer in Canada (NCIC, 1998). It is estimated there will be 5 300 deaths attributable to breast cancer and 1 400 due to ovarian cancer. Both incidence and mortality rates for the province of Quebec are generally similar to the Canadian rates (NCIC, 1998). A crude measure of survival, the case fatality rate, is 27% for breast and 56% for ovarian cancer (NCIC, 1998). From the data shown above, one can see the large impact that breast and ovarian cancers have on Canadian women. The incidence rate for breast cancer has risen an average of about 1 percent per year from 1969 to 1993. Fortunately the mortality rate for breast cancer in Canada has remained steady during the same time period (Quebec has had an average decrease of 0.5% per year). The annual incidence rate for ovarian cancer has decreased slightly over time (0.2% in Canada) but has increased slightly in Quebec (an average increase of 0.7%)(NCIC, 1998). The mortality rates for ovarian cancer decrease in both Canada and Quebec at an average of 0.8% and 0.7% annually (NCIC, 1998).

Epidemiology of Breast Cancer

Breast cancer has been studied extensively and there are many literature reviews on this subject (For specific reviews see Schottenfeld and Fraumeni, 1996;

Higginson, Muir and Munoz, 1992). A brief explanation of some of the risk factors follows.

Breast Cancer and Age

In a key article (Moolgavkar, 1979) about the effect of age on breast cancer incidence, the author examined data from Japan, Connecticut, Denmark and Iceland. It was found that the incidence rate of breast cancer increases with age until 50 years when the curve levels out. This was termed the point of inflection and coincides with the onset of menopause.

Using data from the Surveillance, Epidemiology and End Results program of the National Cancer Institute in the US, the incidence rate of breast cancer in women aged 20-39 was compared with older age groups. Only about 7% of breast cancers occur in the younger group. The trend for the younger age group has remained stable from 1973-1989, whereas for the older age groups the rates have increased in recent years. (Hankey et al.,1994).

Table 1: Risk Factors for Breast Cancer According to Menopausal Status

Risk Factor	Relative Risk in Younger Women*	Relative Risk in Older Women*
Black Race	+	-
Early age at menarche	+	+
Late age at menopause	+	+
Late age at first birth	++	+
Low Parity	+	-
History of lactation	-	?
Induced abortion	?	?
Alcohol exposure	+	+
Smoking exposure	0	0
High Dietary fat	?	?
Oral Contraceptive use (early or long)	+	0
Family history	++	+
Proliferative Breast Disease		
Without atypia	+	+
With atypical hyperplasia	+++	++
Large body size	-	+

* Note that younger women are defined as those under the age of 50 and older women are those age 50 and over.

+ = estimated relative risk (RR) of 1.1-1.9; - = estimated RR of 0.5-0.9; ++ = estimated RR of 2.0-4.0; ? = evidence insufficient; 0 = estimated RR of 1.0; +++ = estimated RR of >4.0.
Adapted from Velentgas and Daling (1994).

Table 1 shows that for some risk factors (race, parity and large body size) the effects are the opposite, depending on menopausal status. Other risk factors (late age at first birth, family history and atypical hyperplasia) have had differing magnitudes of risk depending on menopause status. For example, for age of first birth, the relative risk is 1-1.9 in post-menopausal women and 2-4 in pre-menopausal women. Women with a history of lactation and oral contraceptive use have inconclusive or no effect in post-menopausal women, only women exposed before menopause (perhaps from longer duration) have been shown to be able to alter their risk of breast cancer. As seen in Table 1, many risk factors for breast cancer are modified depending on whether the woman is pre-menopausal or post-

menopausal. The age of 50 is commonly used as a cut-off since this is the average age at which menopause occurs (Greendale, Lee and Arrida, 1999). Therefore it seems prudent to divide the cases in this manner when examining the risk factors for breast cancer.

Reproductive Risk Factors for Breast Cancer

After the effects of age, reproductive factors are most extensively studied risk factors for breast cancer. Early menarche, late menopause, low parity and late age of first birth have all been shown to increase a woman's risk of breast cancer (Kvale, 1992). The relationship between menstrual factors and the risk of breast cancer was studied by Brinton et al. (1988) using 2908 cases and 3180 controls. The relative risk of breast cancer in women who's age of menarche was 15 or more compared to women with age of menarche under 12 was 0.77 (test for trend $p<0.01$). This effect was similar in those women with breast cancer diagnosed under age 45 and those 45 and over. The same study also looked at the age of menopause and risk of breast cancer. The age-adjusted relative risk of being menopausal at the time of diagnosis of breast cancer was 1.3 (95%CI 1.1-1.5) compared with menopausal women. The higher risk in pre-menopausal women was consistent across all age groups under age 55.

In a meta-analysis of the risk factors for breast cancer, Negri et al. (1988) pooled together 4072 cases and 4099 controls. Compared with women who

experienced menarche after age 15, those who experienced menarche at an earlier age had an increased relative risk (RR), from 1.27 to 1.32 (all $p<0.05$) depending on the parity variables controlled for. If menopause occurred under the age of 45 compared with those women over 50, the relative risk was 0.7 (95%CI 0.6-0.9). For those women with multiple births compared with those with 1 child, those with 5 children or more had a RR of breast cancer of 0.6 (95% CI 0.5-0.8). If a woman was older than 28 at the age of her first birth compared with age 22, her RR was 1.8 (95% CI 1.5-2.0). This study also controlled for family history of breast cancer in the analysis. In a review of reproductive factors and breast cancer, Kvale (1992) found five of eight studies that showed a protective effect for late menarche (after age 15). There were also five reported studies in which the effect was stronger in pre-menopausal women only, however, two studies did show a protective effect for post-menopausal women only. There have been 11 studies showing a protective effect of late menopause on the risk of breast cancer, with three additional studies showing that this effect may be strongest for older women.

Parity is closely related to age at first birth. However there have been 29 published studies that show that low parity and late age at first birth act independently to reduce the risk of breast cancer (Kvale, 1992). In a study modelling the age of any birth and breast cancer risk, Robertson and Boyle (1998) found that only the ages of the first and second births determine the odds of breast cancer.

Weiss et al. (1998) examined the risk of breast cancer in those women with

fertility problems. There was no significant risk of breast cancer in those women who reported problems getting pregnant (OR=1.1, 95%CI 0.9-1.2). However, late age at first birth and the risk of breast cancer were found to be different between women with fertility problems and those without. In women with no fertility problems, who were older than age 35 when they had their first birth (compared to those whose first birth was before age 20) the relative risk of breast cancer was 1.1 (95%CI 0.7-1.9). However, in women with fertility problems, those whose first birth was at age 35 the relative risk of breast cancer was 3.0 (95% CI 1.3-7.0). The test for trend was significant ($p<0.001$) and the interaction between fertility problems and age at first birth was also significant ($p=0.02$). Further analysis showed that these results were not confounded by family history of breast cancer (Weiss, 1998).

In a study of pre-menopausal breast cancer after induced abortion, Daling et al.(1996) conducted a case-control study of 1302 white women under the age of 45. Among those women who had ever been pregnant at least once, the RR of breast cancer in those with a prior abortion was 1.2 (95% CI 1.0-1.5) compared to women without an abortion. When examining the risk of breast cancer in nulliparous women by time of gestation, the only significant finding was in women whose abortions were in the first 8 weeks of gestation with an RR of 2.0 (95% CI 1.2-3.3). Although the logistic regression analysis enabled the authors to control for most reproductive and other risk factors, the authors remain hesitant about their results based on the potential for inaccurate reporting of abortions. A meta-analysis of 21 published studies showed that the odds ratio of breast cancer in

those who had an induced abortion compared with those that did not was 1.3 (95%CI 1.2-1.4) (Brind et al., 1996). The odds ratio was similar in women who were nulliparous (OR 1.3, 95%CI 1.0-1.6) but slightly higher in women with an abortion before a full term pregnancy (OR 1.5, 95%CI 1.2-1.8). These findings demonstrate that induced abortion is a risk factor for breast cancer regardless of a woman's eventual parity. (Brind et al., 1996)

Estrogen replacement therapy (ERT) is also thought to increase a woman's risk of breast cancer. A recent meta-analysis of women who underwent any type of menopause showed increased relative risks only after 5 years of ERT use (Schottenfeld and Fraumeni, 1996). After 15 years of use, there was a significantly increased RR of 1.30. There were however, some problems associated with those studies. First, family history of breast or ovarian cancer was not examined. Second, whether the ovaries were intact or removed was not accounted for and finally, whether the woman had a hysterectomy was not noted. The authors also note that the types of estrogen replacement therapy examined in this study are not commonly prescribed in North America (Schottenfeld and Fraumeni, 1996).

The Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC)(1997) reanalysed 90% of the research done to date on breast cancer and ERT. Using 52 705 cases and 108 411 controls they found in those women that stopped ERT use <5 years previous (compared with women who never used ERT), the relative risk of breast cancer was 1.02 (95%CI 1.01-1.04) for each year

of use. Therefore, for women with 5 years of use the relative risk of breast cancer was 1.35 (95%CI 1.21-1.49). For every 1000 women with 5 years of ERT use there would be an excess of 2 (95%CI 1-3) new cases of breast cancer. With 15 years of use there would be an estimated 12 (95%CI 5-20) new cases of breast cancer (CGHFBC, 1997). Similar estimates were not calculated on the number of excess deaths of breast cancer due to ERT use. The weight of evidence linking ERT use and increased risk of breast cancer was evaluated by Colditz (1998). It has been reported that 15 of 21 case-control studies and 4 of 4 cohort studies between 1977 and 1991 have shown that increased duration of ERT use increases the risk of breast cancer. After 1991 there have been 4 published studies that fail to discount this finding. It is proposed that the relationship between ERT use and breast cancer is causal, because the relationship is strong, has been reported consistently across many studies, has a dose response pattern and is biologically plausible (Colditz, 1998).

Breastfeeding has been hypothesised to reduce a woman's risk of breast cancer. In a case control study, Freudenheim et al. (1997) examined lifetime lactation history and the risk of breast cancer in pre- and post-menopausal women. In pre-menopausal women who have breastfed for more than 20 months (lifetime) compared with women who never breastfed, the odds ratio for breast cancer was 0.5 (95%CI 0.2-1.1). There did not seem to be an effect in post-menopausal women (OR 1.1, 95%CI 0.8-1.9). When the authors restricted by age, those women who breastfed before age 25 (compared with those who never breastfed)

had and odds ratio of 0.67 (95% 0.46-0.95) (Freudenheim et al. 1997).

Reproductive Factors and Ovarian Cancer

Specific risk factors for ovarian cancer are also linked to reproductive status. In a follow-up study on reproductive factors, Wu et al. (1988) interviewed 300 cases of epithelial ovarian cancer and 752 age-matched controls. The overall relative risk for women who were ever pregnant was 0.9 (95% CI 0.8-1.0). If a woman had her first full-term pregnancy before the age of 20, her RR dropped to 0.6 (95%CI 0.3-0.9) compared with nulliparous women. Wu et al. (1988) also found that a woman's total duration of ovulation was positively associated with ovarian cancer ($p < 0.001$ for trend). If a woman's age at menarche was greater than age 15, her RR of ovarian cancer was 0.6 (95%CI 0.4-1.0). If a woman experienced menopause after age 50, then her RR was found to be 1.4 (95%CI 0.7-2.7). In a review article by Parazzini et al. (1991) also on reproductive factors and ovarian cancer risk, similar factors were examined across different studies. If a woman was age 12 at menarche, her relative risk of ovarian cancer (as reported in 10 independent studies) ranged from 1.2-1.5, compared with women over age 15 or more (results controlled for parity). The RR of ovarian cancer (as reported in 11 studies) ranges 1.4 to 4.6 (depending on her age) in women experiencing menopause over age 55, compared to women experiencing menopause at age 40 or younger. Parazzini et al. (1991) also found that late age of pregnancy increased a woman's risk of ovarian cancer. There were also elevated RRs in women age 35 or more compared

with women age 20 or less (again results controlled for parity) with RRs ranging from 1.1 to 4.0.

In a study of French Canadian women, Godard et al. (1998) also investigated age at last childbirth and risk of ovarian cancer. The average age of last childbirth in women with ovarian cancer was 29.0 years compared with 30.9 years for the population controls suggesting a protective effect. This difference was significant (p=0.003). The authors also found that on average, cases with a family history of ovarian cancer were younger (mean of 28.2 years) than case women without a family history (mean of 29.5 years). This may suggest that the protective effect may be stronger in women with a family history of ovarian cancer than without, however this difference was not found significant (p=0.19).

Having undergone a hysterectomy (compared with women without the procedure) was found to be protective for ovarian cancer prior to 10 years from interview (RR of 0.6, p=0.05) (Parazzini et al., 1991).

Risks of Oral Contraceptive Use in Ovarian and Breast Cancer

Most of the risk factors for ovarian cancer relate to the number of ovulatory cycles a woman has had (the ovulation hypothesis). Those factors that reduce the number of cycles (including oral contraceptives) tend to reduce the risk of ovarian cancer (Wu et al., 1988). In an earlier study, oral contraceptive use more than 37

months led to a reduction in the relative risk of ovarian cancer to 0.4 (95% CI 0.2-0.7) compared with women who never used oral contraceptives (Wu et al., 1988). Schlesselman (1989) reported that oral contraceptive use in excess of three years protects against ovarian cancer. After 4 years of use there is a 50% reduction in the RR and after 7 or more years there is a 60-80% reduction in RR. In their study of the risk factors for ovarian cancer, Godard et al. (1998) found that women with ovarian cancer stopped using contraceptives at an earlier age than controls, meaning that late age of use could be protective for ovarian cancer. The average age in which a woman halted oral contraceptive use was 28.6 years compared with population controls at age 32.9 years. This difference was significant. The authors also found a non-significant protective effect of contraceptive use in women with a family history of ovarian cancer and ovarian cancer themselves (Godard et al., 1998). The Society of Obstetricians and Gynaecologists of Canada as part of their 1998 Consensus Conference state that oral contraceptives lower the risk of ovarian cancer by 54% after 8 years of use. This benefit lasts at least 15 years after use has stopped (SOGC, 1998).

Schlesselman (1989) reported that oral contraceptive use has no bearing on the risk of breast cancer. However, there may be an adverse effect from using oral contraceptives before a first, full-term pregnancy under age 45. Similarly, Newcomb et al. (1996) found only a slight increased relative risk of breast cancer RR=1.1 (95% CI 1.0-1.2) for ever users. The authors controlled for reproductive and familial factors. Duration was not related to risk. Among women aged 35-45,

recent users (within the last 2 years) had an RR of 2 (95% CI 1.1-3.9) (Newcomb et al, 1996).

Brinton et al. (1995) examined the risk of breast cancer and oral contraceptive use among women under 45 years of age. Using 1648 cases and 1505 controls the authors found that use for longer that 6 months was associated with a RR of 1.3 (95% CI 1.1-1.5). They did control for reproductive factors and the possibility of selective screening. The RR was enhanced for those cancers occurring before age 35 (RR=1.7, 1.2-2.6) and increased for those with 10 or more years of use (RR=2.2, 95% 1.2-4.1). In an examination of progesterone-only contraceptives and risk of breast cancer Skegg et al, (1996) found similar risks as with combined (estrogen + progesterone) oral contraceptive use. In women who had ever used (progesterone only) oral contraceptives the risk of breast cancer compared with women with no use was 1.1 (95%CI 0.7-1.5). However in women aged 25-34, the relative risk was 2.3 (95%CI 1.2-4.3) (Skegg et al., 1996). Furthermore, the time in which women were first taking progesterone only oral contraceptives altered their risk of breast cancer. For women who had started OC use in the last 10 years (compared with never users), their relative risk of breast cancer was 1.6 (95%CI 1.0-2.4). However in women who started OC use more that 10 years previous, their risk of breast cancer was 0.4 (95%CI 0.2-0.9) (Skegg et al. 1996). These results were controlled for age at menarche, parity, family history and other potential confounding variables.

Rosenberg et al. (1996) also examined the risk of breast cancer and oral contraceptive use. Using 3,540 cases and 4,488 controls, the relative risk of breast cancer for at least 1 year of use (compared with non-use) was 1.7 (95%CI 1.3-2.3) for women age 25-34 years; 0.9 (95%CI 0.7-1.0) for women age 35-44 years; and 1.2 (95%CI 1.0-1.4) for women age 45-59 years. For the youngest age group, the risk estimates were greatest for longer duration. The CGHFBC (1996) grouped 54 separate studies world-wide that examined oral contraceptive use and breast cancer. In those women who are current users of oral contraceptives (compared with non-users) the relative risk of breast cancer is 1.24 (95%CI 1.15-1.33). For women who stopped using oral contraceptives (compared with non-users) 1-4 years previous, their relative risk is 1.16 (95%CI 1.08-1.23). After stopping use 10 years previous, there did not appear to be a significant increased risk of breast cancer (relative risk 1.01, 95%CI 0.96-1.05).

The Society of Obstetricians and Gynaecologists of Canada as part of their 1998 Consensus Conference state that current oral contraceptive use increases the risk of breast cancer by 50% which lasts up to 10 years after use has stopped (SOGC, 1998). However women who are current users of oral contraceptives are usually younger, when the baseline incidence of breast cancer is rare.

Spicer and Pike in 1992 and 1994 showed that both ovarian and breast cancer risk are closely related to total frequency of ovulation. With a regimen of a prototype contraceptive, they estimate that with 5 years of treatment they can

reduce the RR of breast cancer by 31% and for ovary by 41%. After 15 years of treatment they estimate the risk reduction to be 70 and 84% respectively.

Non-Reproductive Risk Factors for Breast and Ovarian Cancer

There has been little research on the occupational risk factors for breast and ovarian cancer. Using 2736 cases of breast cancer and 595 ovarian cancer, Zheng et al. (1993) examined differences in occupational category (professionals, clerical, service etc.) while controlling only for age. For breast cancer, there was an increase in those women who were classified as professionals (Standardized Incidence Ratio [SIR] =158), government officials (SIR=131) and clerical workers (SIR=143). Decreased incidence rates were found in those women in the service industry (SIR=87) and craftspersons (SIR=91). All values were significant at the 5% level. Professionals also had a significant increase of ovarian cancer. The authors admit that other factors such as obesity and age at first birth could have confounded the results.

Goldberg and Labreche (1996) also reviewed 115 studies of breast cancer and occupation. They provided only limited evidence of a breast cancer risk in women working in the pharmaceutical industry. Women working as cosmetologists, beauticians and chemists were also identified as being at risk. In a prospective study of breast cancer mortality and occupation, Calle et al. (1998), followed up 563 395 women over 9 years. There were 1780 deaths due to breast cancer. After

adjusting for family history, body mass index, number of pregnancies and other potential confounders there were only two occupational groups that showed a significant increased risk of breast cancer. Women working in "administration support, including clerical positions" compared with housewives had a relative risk of breast cancer of 1.1 (95%CI 1.0-1.3). Women who were "executives" had a relative risk of breast cancer of 1.9 (95%CI 1.0-3.6). These results were unchanged when the analysis was limited to women working in their occupations for longer than 10 years (Calle et al., 1998).

A study of ovarian cancer in Washington DC by Hartge and Stewart, 1994 found that secretaries and clerks had an increased RR of 1.1 (95% CI 0.7-1.8) and teachers a RR of 1.4 (95% CI 0.8-3.4). Nurses and cleaners had a RR of 0.5 (95% CI 0.2-1.0) and 0.7 (95% CI 0.2-2.8) respectively. The authors adjusted for number of live births, oral contraceptive use, cigarette use, gynaecologic surgery, infertility and menopausal estrogen use. Small numbers were stated as a possible cause for the lack of significant results. Shen et al. (1998) reviewed 48 published studies that examined occupation and ovarian cancer. There may be an increased risk in women who are hairdressers, beauticians or employed in the printing industry but the authors hesitate about making strong conclusions. There was sufficient data on ovarian cancer risk and women who were teachers, nurses, professionals an dry cleaners but there was very little evidence shown (Shen et al. 1998).

Women who have proliferative breast disease have an increased risk of

breast cancer, the magnitude of the risk depending on the type of breast disease. Dupont and Page (1985) in a study of 3303 women (average follow-up 17 years) found that the RR of breast cancer (without atypical hyperplasia) was 1.9 (95% CI of 1.2-2.9) compared with 5.3 in women with hyperplasia (95% CI 3.1-8.8). The RR with atypia and a family history of breast cancer was 11 (95% CI 5.5-24) compared to women without either condition. The authors recommend that biopsies are warranted in women with proliferative breast disease and a family history of breast cancer.

Socio-economic status (SES) was also thought to have an effect on one's risk of ovarian cancer. A study by Tavani et al. (1993) using 194 cases and 710 controls found that the relative risk of ovarian cancer in women with 12 or more years of education was 1.6 (95% CI 1.1-3.0). Of those women in the highest social class, the RR was 1.8 (95% CI 0.7-10.5). The authors controlled for reproductive and other factors; however, the analysis was limited to women under the age of 45.

To examine body fat and risk of breast and ovarian cancer, while controlling for family history of breast cancer, Sellers et al. (1993) recorded the waist to hip ratio of 620 breast cancer cases. After 4 years of follow-up, those women in the 80^{th} percentile (compared with the remainder) had an increased RR of breast cancer of 2.1 (95% CI 1.4-3.1) but only with the presence of a family history of breast cancer (without a family history of breast cancer, RR=1.1, 95% CI 0.9-1.4). For ovarian cancer, the high waist/hip ratio and family history of breast cancer also

resulted in an increased risk (RR=4.8, 95% CI 1.6-15.1). Neither association was significant without the presence of a family history of breast cancer. Women who are taller and heavier than average at adolescence may be at increased risk of breast cancer, probably due to early puberty and thus early menarche (Kvale, 1992).

Height, Body Mass Index (BMI) and the risk of breast cancer was examined in a follow study of 25 967 women (Vatten and Kvinnsland, 1992). The relative risk of breast cancer in women in the 4th quartile of height compared to women in the lowest quartile was 1.4 (95%CI 1.2-1.7, test for trend $p<0.001$) after adjusting for age, parity and age at first birth. BMI was found to have a significant, protective effect on breast cancer risk but only in women aged 50 or less. In women of this age, those that were in the highest quartile of BMI compared to the lowest, the relative risk of breast cancer was 0.6 (95%CI 0.5-0.8). The authors hypothesize that the lower breast cancer risk could be due to a low calorie consumption during puberty which could reduce the number of total breast cells. The inverse relationship with BMI could be related to a lower rate of cell division in breast cells in obese women (Vatten and Kvinnsland, 1992).

A cohort of 92 256 women was studied by Huang et al. (1997) to examine the effects of weight and weight gain on breast cancer incidence. In post-menopausal women, the relative risk (RR) of breast cancer for women with a BMI >31 compared to women with a BMI of <20 was 1.6 (95%CI 1.1-2.3, test for trend $p>0.001$). However, higher BMI at age 18 was associated with a lower risk of breast cancer

in both pre- and post-menopausal women. The RR of breast cancer in women with a BMI of >25 compared with a BMI <18 was 0.6 (95%CI 0.5-0.8) in pre-menopausal women and 0.7 (95%CI 0.6-0.9) in post-menopausal women (Huang et al., 1997). Weight gain after the age of 18 increased the risk of breast cancer only in women who never used ERT. For women with a weight gain of 20kg the relative risk of breast cancer was 2.0 (95%CI 1.4-2.8, test for trends p<0.001) compared with women whose weight was unchanged (Huang et al., 1997). The population attributable risk (PAR) of weight gain and ERT was calculated from this population. The PAR of weight gain was found to be 16% and for ERT use alone 5%, however when the results were compared with women who never used ERT and had no weight gain the PAR was 34% (95%CI 14%-50% (Huang et al., 1997). Tavani et al. (1998) examined the effect of height on breast cancer risk using 5984 cases and 5504 controls. There was no significant increase in breast cancer found in the tallest quintile of women (height >167cm) compared to the shortest (height <156 cm) with an odds ratio of 1.0 (95%CI 0.9-1.1).

To ascertain the risk of using talc and subsequent ovarian cancer, Whittemore et al (1988) examined 188 cases of ovarian cancer and found a relative risk of 1.4, p=0.06, with no dose response. In other studies, an SMR of 5 was found, however this is disputed because there have been no animal models duplicating this effect and it was based on occupational exposure (Schottenfeld and Fraumeni, 1996). Varying exposures of talc in 313 cases and 422 controls were studied by Cook, Lamb and Weiss (1997). For those who had "ever used" talcum

powder, the RR of ovarian cancer was 1.5 (95% CI 1.1-2.0). After age adjustment, those women who had a history of perineal dusting had an increased RR of ovarian cancer of 1.6 (95% CI 1.1-2.3) and those who used genital deodorant spray had an increased RR of 1.9 (95% CI 1.1-3.1) compared with women with no use. Occupational exposure to talc was examined by Hartge and Stewart (1994). A protective effect was noted, even after ten or more years of exposure; however, there was no dose that had a significantly decreased risk. Talc exposure and risk of ovarian cancer was reviewed by Shen et al. (1998). Of the 9 studies that examined non-occupational talc exposure, only 5 found an significant increased risk of ovarian cancer with odds ratios ranging from 1.5 to 4.8.

Increased physical activity has been postulated to reduce the risk of breast cancer by lowering levels estrogen that may play are role in tumour promotion or possibly initiation (Dorgan, 1998). In a recent prospective study, increased physical activity, regardless of the intensity, was not shown to significantly reduce the risk of breast cancer (Rockhill et al. 1998). The relative risk of breast cancer women who reported strenuous activity in late adolescence compared to women with sedentary activity was 1.1 (95%CI 0.8-1.6). Recent physical activity (>7 hours per week compared with <1 hour per week) was also not shown to increase the relative risk of breast cancer (RR=1.1, 95%CI 0.8-1.5). Mezzetti et al. (1998) examined the population attributable risks for breast cancer. Low levels of occupational physical activity were found to account for 11.6% of the risk (95%CI -0.1% - 23.3) albeit not significantly. In post-menopausal women, low occupational

physical activity accounted for 14% of the risk of breast cancer (95%CI 1.5-27.3). The authors also found that high alcohol intake, low B-carotene intake and low physical activity interact to account for 33% (95%CI 19.9-46.1) of the population attributable risk of breast cancer (Mezzetti et al. 1998).

There have been a few studies examining the effect of ionizing radiation and ovarian cancer; however, there is no definitive reported risk (Schottenfeld and Fraumeni, 1996). In the studies mentioned, the magnitude of the risk was small. There has been no report of a dose-response relationship.

Family History of Breast and Ovarian Cancer

The terms genetic, inherited and familial cancers are differentiated as follows. All cancers can be considered genetic since they involve an alteration of a cell's DNA and inhibition of the normal cell cycle. However, these alterations, for the most part, occur in somatic cells. Somatic cells are not involved in reproduction and thus genetic changes in these cells cannot be "passed on" to any future offspring. Most cancer (90-95%) occurs in these cells and thus is not considered inherited/familial (Tamarin and Leavitt, 1991). For many years, researchers have observed familial clustering of cancer. As the expertise and knowledge developed, it became apparent that these clusters could be due to other, risk factors common to family members or just by chance, given the increased incidence of the cancer. The difference between inherited and familial cancer is that in the former, the major

determinants of cancer risk are inherited, where as in the latter, they are not (King et al., 1993).

Breast and/or ovarian cancer can be considered to be genetic, inherited and familial. These cancers are genetic because changes occur in one or more cells that allow a tumour to develop or progress. They can be inherited, through mutations in a number of susceptibility genes, for example, the BRCA1 or BRCA2 genes. They can also be familial, as there are women who have an excess of relatives with breast cancer but no identifiable mutation (King et al., 1993).

The risk of breast cancer is increased in those women with relatives diagnosed with breast cancer. As well, the relative risk (RR) of contralateral breast cancer is 4-5 times higher if the woman has a family history of breast cancer (Narod et al., 1993), To date, no differences in histology have been found between familial and sporadic cancers. In women with two primary breast cancers, the histology is identical in only 60% and there can be different morphological patterns within a single tumour (Narod et al., 1993). About 2-4% of all breast cancers are considered to be due to hereditary factors. This figure increases as the age at diagnosis falls (up to 28% in women under the age of 30 [Narod et al., 1993]). The risk of breast cancer increases with the number of affected relatives. For example, a woman has an RR of 8 for breast cancer if she has both a mother and sister with breast cancer (both women are pre-menopausal and at least one of the mother or sister had bilateral cancer). By contrast, the RR for breast cancer is 3 if a woman

has a mother and an aunt or 2 sisters with breast cancer (both cancers being unilateral and the women pre-menopausal) (Narod et al., 1993). Evans and Prosser (1992) noted that the RR of breast cancer is increased 3 times if a woman has a first degree relative with breast cancer and 5-10 times if the relative had bilateral cancer.

Colditz et al. (1993) interviewed 117,988 women from the Nurses' Health Study with 1.3 million person-years of follow-up to examine the RRs of breast cancer among those with affected relatives. They found that the RR of breast cancer in women whose mother was diagnosed before the age of 40 (compared with a non-affected mother) was 2.1 (95% CI 1.6-2.8). The RR decreased as age of the mother increased to a RR of 1.5 (95% CI 1.1-2.2) for a diagnosis after age 70. Having one affected sister (compared with none) led to a RR of 2.3 (95%CI of 1.6-3.2). For women with both an affected mother and sister with breast cancer, the RR was 2.5 (95%CI 1.5-4.2) compared with women with no family history. Similar results were found by Peto et al. (1996) in a study of the relatives of 3,295 women with breast cancer identified through the UK cancer registry. For the 11,678 relatives identified, the mortality rate ratio from breast cancer was significantly increased ($p<0.001$) with an SMR of 187, (based on 248 deaths). For ovarian cancer the SMR was 130 with 58 deaths ($p=0.06$). Further analysis revealed that sisters of the case had a non-significant increased risk of breast cancer compared with the mothers (SMR=122).

The Cancer and Steroid Hormone (CASH) Study found that having a mother or a sister with breast cancer increases the risk of breast cancer (RR=2.5), however having a grandmother or aunt affected only slightly increases the risk of breast cancer (RR=1.5): women with both mother and a sister with breast cancer have a RR of 14. This study may overestimate the risk because this sample had more people with family history of breast/ ovarian cancer (Couch, 1995) than what would normally be expected. In a later, detailed analysis of the same CASH Study, the family history of breast cancer of over 4 500 women with breast cancer and the same number of controls were examined. Thompson (1994) examined the odds of affected relatives in women with breast cancer at ages 20-44 and 45-54 (Table 2). For the 25-44 age group, the odds ratio for breast cancer increased from 3.1 (95%CI 2.3-4.2) with one sister affected to 21.7 (95%CI 3.1-94.7) with 2 or more first degree relatives affected. For second degree relatives, the odds ratios for breast cancer range from 1.4 (95%CI 1.2-1.8) with an affected maternal grandmother to 2.2 (95%CI 1.4-3.4) with 2 or more affected second degree relatives. For women in the 45-54 age group the odds ratios were somewhat smaller. The odds ratios for breast cancer in a first degree relative increase from 1.9 (95%CI 1.5-2.4) with an affected mother, to 6.8 (95%CI 2.5-19.8) for 2 or more affected first degree relatives. The risk of breast cancer with a family history of other cancer was also examined. Families including women with endometrial cancer the RR of subsequent, primary breast cancer was 2.1 (95% CI 1.0-4.4).

Using logistic regression models, the authors calculated multiplicative risk

factors to estimate a woman's RR of breast cancer based on the number of affected relatives. These factors were based on the number of affected relatives and the woman's age. These factors range from a RR of 1.36 for one or more affected second degree relatives to a RR of 3.83 for breast cancer in two or more first degree relatives. The authors estimate that 14.5% of breast cancer in women 20-44 is due to family history of breast cancer compared with 13% in women 45-54 years old (Thompson, 1994). This study consisted of over 2000 cases and controlled for a number of reproductive factors.

Table 2 : Numbers and Odds Ratios for Reported History of Breast Cancer in Female Relatives of Breast Cancer Patients and Control Subjects; Cancer and Steroid Hormone Study

	Age 20-44		Age 45-54	
Occurrence of breast cancer in female relatives	Cases/Controls	Odds Ratio (95% CI)	Cases/Controls	Odds Ratio (95% CI)
No first or second degree relative reported to have been affected	1459/1665	1.00 (referent)	1865/2100	1.00 (referent)
First degree				
Mother affected	191/70	3.11 (2.33-4.17)	220/132	1.88 (1.49-2.36)
Sister affected	57/21	3.10 (1.82-5.36)	125/64	2.20 (1.60-3.07)
Mother or sister with onset < 45 yr.	93/30	3.54 (3.09-5.49)	97/39	2.80 (1.92-4.08)
2 or more affected	19/1	21.7 (3.09-94.7)	30/5	6.76 (2.49-19.8)
Second degree				
Maternal grandmother or aunt affected	235/187	1.43 (1.16-1.77)	257/186	1.56 (1.27-1.91)
Paternal grandmother or aunt affected	178/129	1.57 (1.23-2.01)	188/134	1.58 (1.25-2.00)
2 or more affected	66/34	2.22 (1.43-3.44)	69/35	2.22 (1.44-3.42)

Adapted from Thompson (1994).

The risks above give an indication of what a susceptible family looks like. A common definition of family history of breast and ovarian cancer is more than 4 female relatives with breast cancer in the first and second degree relatives, cancers occurring under the age of 50 and at least one relative with ovarian cancer at any

age (Easton et al., 1993). A woman who is a member of such a family is thought to be predisposed to breast or ovarian cancer. Further, a woman's risk increases as the age of onset in relatives decreases. The RR for a woman to develop breast cancer is 4.2 if she has a relative who was diagnosed with breast cancer at age 30 compared with a RR of 1.7 if the relative was diagnosed at age 50. A slight increased RR (not found to be significant) of subsequent breast cancer for women having a previous ovarian tumour has also been reported.

Women with breast cancer are twice as likely to develop a new primary ovarian tumour than women without breast cancer, providing limited evidence of a hereditary link between the two tumours (Gallion and Park, 1995). The risk of ovarian cancer in the general population is approximately 1.4%. If a woman has a first degree relative with breast or ovarian cancer her risk of ovarian cancer increases to 5%. If she has two relatives, the risk is 7% (Gallion and Park, 1995). The early age of onset of the tumours in relatives is not a determinant of risk of ovarian cancer as it is for familial breast cancer (Narod, 1991).

Compared to family history and breast cancer, less research has been performed on the family history of ovarian cancer. Family history of ovarian cancer was studied by Schildkraut and Thompson (1988). Using 493 cases of ovarian cancer and 2465 population controls, they found that the odds ratio for ovarian cancer in first degree relatives was 3.6 (95%CI 1.8-7.1) compared with women with no family history of ovarian cancer. In second degree relatives the odds ratio was

2.9 (1.6-5.3). The odds ratio of ovarian cancer was higher in mothers (OR 4.3, 95%CI 1.8-7.1) than sisters (OR 1.7, 95%CI 0.2-7.0) (Schildkraut and Thompson, 1988). Parrazzini et al. (1991) reviewed 9 studies that examined the risk of ovarian cancer in relatives of women with ovarian cancers. Eight of the studies identified significant excess risks, with relative risks ranging from 1.9-18.2 for first and second degree relatives. In a follow-up study of 1188 ovarian cancer cases, Easton et al. (1996) found that there was an increased risk of death from ovarian cancer in relatives of ovarian cancer cases. The standardized mortality ratio (SMR) of ovarian cancer in first degree relatives was 2.23 ($p<0.001$). If the case had 2 relatives with ovarian cancer the SMR was 24.2 (95%CI 6.6-61.9) (Easton et al., 1996). In a study of ovarian cancer risk factors among French Canadians, Godard et al. (1998) examined the cumulative incidence of cancer (by age 70) in first degree relatives of the ovarian cancer cases compared with population controls. The relative risk of breast cancer in first degree relatives was 3.7 (95%CI 2.0-6.7), however the relative risk of ovarian cancer was not significantly increased (1.3, 95%CI 0.5-3.3)(Godard et al., 1998).

Risk of Multiple Primary Cancers

In a large Swedish cohort study, the authors examined the risk of any second cancer after the first breast cancer (Adami, 1984). The cohort consisted of 11,452 women with breast cancer, followed for 13-16 years or 94,078 person

years of observation. A second cancer was reported in 738 women or 6.4%. They found a significant increase of endometrial cancer in those women 70 years or older (RR=2.4 95%CI 1.6-3.5), but not for ovarian cancer (RR=1.2, 95% CI 0.9-1.5), colon (RR=1.2, 95% CI 1.0-1.4) or rectal (RR=1.1 95% CI 0.8-1.6) cancers. The authors state that in analysing the long term survival of patients with breast cancer, one must take into account the increased risk of a second primary cancer. Their analysis of secondary primary cancers did not include other breast cancers. For all ages, endometrial cancer had an increased RR as well (1.4, 95% CI 1.1-1.8). There was also decrease in RR for cervical cancer (RR=0.5, 95% CI 0.3-0.9). For women diagnosed with breast cancer before the age of 50, the RR of subsequent ovarian cancer was 2.2 (95% CI 1.5-3.3). The authors attribute this to mis-classified metastatic disease. It was also reported that the proportion of ovarian cancers diagnosed at autopsy is higher than in the rest of the cohort. Frequent metastases to the ovary could be a source of bias as well as the fact that the high frequency of oophorectomies could have over estimated the number of women at risk, and thus the number of expected cases, leading to an underestimation of the SMR (Adami, 1984). In a study of multiple primary cancer of the breast an ovary, Prior and Waterhouse (1981) found that the risk (measured as a standardized incidence ratio) of a second primary tumour in the ovary after an initial breast tumour was 4.37 ($p<0.001$). In women with both breast and ovarian cancer the average time between the two was 4.6 years (+/- 3.9 years) (Schildkraut, 1995).

Breast Cancer Susceptibility Gene (BRCA1)

The first breast cancer gene identified, termed BRCA1 is located on the long arm (q) of chromosome 17. The frequency of this gene in the population was originally estimated to be 1 in 150 but it is presently estimated as 1 in 833 (due to other breast cancer genes and different mutations etc.) (Easton, 1994). BRCA1 acts as a tumour suppressor, meaning that mutations can cause the loss or reduction in normal cell activity. BRCA1 is currently described as being on chromosome 17q15-17 between markers D17S1321 and D17S1325, a region that is 600 kb long. Miki et al. (1994) found that the marker D17S855 was located within the BRCA1 locus. The resultant protein codes for 1863 amino acids and a possible zinc finger domain at the amino terminus. It contains 22 coding exons and is roughly 100kb of genomic DNA.

The LOD score is defined as the logarithm of the probability of linkage to a gene. A LOD of three means that the odds of the breast-ovarian cancer gene being linked to that particular region on chromosome 17q are 1000 to one. These odds are currently used as the point where one can be quite confident that the location of the gene is correctly identified (Tamarin, 1991). Linkage analysis can identify which markers are coinherited with the disease in families. Note that one can have multiple cancers in a family without it being inherited and one could inherit the gene mutation and not get cancer because the disease is not completely penetrant.

Futreal et al. (1994) states that if BRCA1 is the correct gene for breast cancer susceptibility then if a gene was deleted in loss of heterozygosity cases, the other allele would contain inactivating mutations in BRCA1. They found mutations in examining four families with breast cancer. One mutation resulted in a stop codon and the other three involved missense mutations. All four represent susceptibility alleles. Two of the four families had positive family histories of breast cancer. The mutation in an African-American woman with bilateral cancer (Met1775Arg) has been found in other African-American families. The notation is read as "the Methionine amino acid in position 1775 is replaced by an Arginine". The authors admit that their screening procedure (looking for loss of heterozygosity) can miss some of the mutations.

Hall et al. (1990) first reported that familial breast cancer was linked to a particular chromosomal region. They identified a region on chromosome 17q, section 21 (q designating the long arm), that had LOD score of 5.98 for linkage to the marker D17S74. One should note that this "name" identifies the closest marker to the gene. Negative LOD scores were calculated in women with late onset, meaning that late onset breast cancer was not related to a gene in this area. For 23 families analyzed as a group, linkage to D17S74 was significant at $p < 0.01$. When the families were tested one at a time, only 40% (9 families) linked to the marker. Multi-point analysis (more that one marker) was also tested using markers D17S78-D17S41-D17S74-D17S40. This yielded likelihood ratios of 2000:1 to 1.4×10^6:1 which is considered to be indicative of a high probability of linkage and

a probable location of the susceptibility gene.

Soon after, Narod et al. (1991) confirmed the results of linkage to 17q12-23 near the D17S74 locus. This was also the first study to extend the linkage to familial ovarian cancer. Every family studied had at least 3 women with breast cancer and 2 with ovarian cancer. Half the breast cancer cases were diagnosed before the age of 40. The median age for ovarian cancer was 47. However, the authors did not find a difference in LOD scores by age.

Subsequent research narrowed down the region on chromosome 17 until the gene itself was isolated. Simard et al. (1993) examined the candidate genes RARA (retinoic acid receptor alpha) and EDH17B2 (involved in the regulation of estrogen) near 17q12-21. Both were excluded as the potential BRCA1 gene. They did find BRCA1 to be relative to a position centromeric to THRA1 and telomeric to D17S579. The telomere is the end of a chromosome and the centromere is the middle. Their results placed BRCA1 between RARA and D17S78. The next study, which involved testing 214 families, of which, 57 families had members with breast and ovarian cancer and 31 families with two cases of breast and ovarian cancer, examined 6 markers near the hypothesised region (Easton, 1993). The strongest markers were for D176S588, with a LOD score of 21.68 and D17S579 with a LOD score of 12.02. They found that the gene lies between markers D17S588 and D17S250, and has a length of 8.3 cM (cent-Morgan, a unit of distance for chromosomes) in males and 18.0 cM in females. The cumulative risk of either

breast or ovarian cancer (identified from families with both cancers) was calculated to be 67% by age 50 (95% CI 44%-80%) and 76% by age 70 (95% CI 52%-88%). The cumulative risk of either cancer in women identified from families with breast cancer only was 49% by age 50 and 90% by age 70; these proportions did not differ significantly. There was no difference in those families with one or many ovarian cancer cases in the age-specific penetrance (cumulative risk or breast or ovarian cancer) of the gene. The proportion of families linked to BRCA1 in this study was estimated to be 62%. Although young cases are more likely to be linked.

To further, narrow down the gene Smith et al. (1993) tested 31 breast cancer only with 12 breast-ovarian cancer families, for a total of 229 individuals. Based on recombination methods the authors indicate that the gene lies between markers D17S588 and D17S250. Under their model, 100% of breast-ovarian families and 45% of breast only families would link to mutations in this region. Only a proportion of the families with breast cancer (and no ovarian cancer cases) result from mutations on the locus on 17q, which may indicate another susceptibility gene for breast cancer.

Miki et al. (1994) was the first to propose a location for the actual BRCA1 gene. Predisposing mutations were detected in five of eight families that segregated (passed on to offspring) the susceptibility gene. For those families (four in total) with early onset breast or ovarian cancer, including at least 3 affected family members the LOD score was 9.49 (odds that this was linked to the correct

region was $10^{9.49}$ to one). The mutations identified included a deletion, insertion, nonsense, missense and a regulatory mutation. Deletion, frame-shift and nonsense mutations lead to the early termination of the protein. The authors note that there was at least one woman in each of 4 families that had a mutation and did not develop breast cancer by age 80. The authors also state that it is important to identify other factors that alter the effects of these mutations.

To estimate the proportion of breast-ovarian cancer families that are linked to BRCA1, Tonin et al. (1995) performed linkage analysis on 26 families with hereditary breast or ovarian cancer. They found that 94% of families (15 of 16 total) that had at least one ovarian cancer were linked to BRCA1. None of the breast cancer only families were estimated to be linked to BRCA1, but this analysis involved only 10 families. The proportion of families linked to BRCA1 is estimated in other reports (Smith et al., 1993 above) to be closer to 45% in those families with breast cancer only. Those hereditary breast cancer families with at least one member with ovarian cancer are considered to be linked to BRCA1 88% of the time.

Similar to the previous studies, Simard et al. (1994) found 12 mutations in 30 tested families. There were four 5382insC (read as an extra cytosene at position 5382), four 185delAG and the remainder were unique. All of the mutations resulted in frameshifts that led to premature stop codons as one would predict from a tumour suppressor model. From 372 unrelated patients with breast or ovarian cancer chosen from high risk families, 38 distinct mutations were identified by

Shattuck-Eidens et al. (1995). A total of 54 (86%) mutations resulted in a truncated protein product.

Further research has found that certain mutations in the BRCA1 (and BRCA2) gene are more common in different ethnic populations. Tonin et al. (1998) studied BRCA1 and BRCA2 mutations in French Canadian families with breast and ovarian cancer. Of the 97 families studied, 41 families had a known mutation and there were two mutations that were found in 28 of the families. In the BRCA1 gene, 17 families had the C446T mutation and in the BRCA2 gene, 11 families had the 8765delAG mutation. The authors indicate that these mutations maybe more common in French Canadian families because of immigration patterns in the 17th century (Tonin et al., 1998). Mutations in Ashkenazi (European decent) Jewish women were studied by Gotlieb et al. (1998). In 59 women with epithelial ovarian cancer 19 carried mutations that have been found to be common in Ashkenazi women. Eleven women had the 185delAG mutation in the BRCA1 gene, and two women had the 6124delT mutation in BRCA2 (Gotlieb et al, 1998).

There is one other breast cancer gene, BRCA2, but it is not strongly predispose to ovarian cancer and is likely related to male breast cancer (Wooster et al., 1994). BRCA2 is also characterized as less likely to have an earlier age of onset of breast cancer compared with those with BRCA1. Krainer et al. (1997) compared the contributions of BRCA1 and BRCA2 to early onset breast cancer. Among the 73 women with breast cancer studied, two women (2.7%, 95%CI 0.4%-

9.6%) were found to have mutations in BRCA2. Nine women (12%, 95%CI 5.8%-22%) had mutations in the BRCA1 gene. This difference was found to be significant (p=0.03) (Krainer et al, 1997). BRCA2 mutations are not as common in women with ovarian cancer (compared with BRCA1 mutations), regardless of family history (Takahashi et al., 1996).

Risks Due to the Breast Cancer Susceptibility Gene

In a review of the current knowledge, members of the Breast Cancer Linkage Consortium reviewed the genetic epidemiology of BRCA1. They state that over 80% of families with multiple cases of early onset breast cancer as well as ovarian cancer, or if the family has only ovarian cancer cases, all will have a mutation in the BRCA1 gene (Easton, 1994). Based on statistics from this consortium, the relative risk (RR) of breast cancer with a mutation is estimated to be 51% by age 50 and 85% by age 70. The RR of ovarian cancer is 23% by age 50 and 63% by age 70 (Easton, 1994). Women in families with a mutation and who have breast cancer are at a higher risk of bilateral breast cancer and ovarian cancer (Easton, 1994). The BRCA1 mutations explain probably only 1% to 5% of breast or ovarian cases (Easton, 1994). Claus (1994) estimates that mothers and sisters of breast cancer cases diagnosed by the age of 50 have a RR of 0.7% and 4.8% respectively of getting breast cancer before 50 compared with 1.5% and 5.2% if the case was diagnosed after 50. The RR of breast cancer in women aged 40 and 50 with a sister with bilateral breast cancer (diagnosed by age 40) is 7.7% and 23.5%

respectively, compared with 4.9% and 50% when the sister was diagnosed between 41-50.

The relationship with those with hereditary breast-ovarian cancer and oral contraceptive use (OC) has not been established. Schlesselman (1989) reviewed all the studies to date on risk of breast cancer and OC use in women with a family history of breast cancer. There were 4 studies showing a "positive" effect and 5 showing a "negative" or no effect. The largest and best designed of these studies appeared to show that women with a family history of breast cancer that use OCs are not an increased risk of breast cancer (Schlesselman, 1989). Oral contraceptive use and the risk of ovarian cancer in women with hereditary ovarian cancer was examined by Narod et al. (1998). There were 207 cases of hereditary ovarian cancer and 161 sisters as controls that all had mutations in BRCA1 or BRCA2. The odds ratio for ovarian cancer and OC use compared with non-use was 0.5 (95%CI 0.3-0.8) adjusted for year of birth, parity, age at first birth and study area. The risk of ovarian cancer increased with longer duration of use (test for trend $p<0.001$). For those with a BRCA1 mutation the OR=0.5 (95%CI 0.3-0.9) and for BRCA2 the OR=0.4 (95%CI 0.2-1.1) (Narod, 1998).

The effect of smoking on the risk of breast cancer in women with a mutation in either the BRCA1 or BRCA2 gene was studied by Brunet et al. (1998). After adjusting for reproductive variables, there was a reduced risk of breast cancer among women either mutation who smoked. For those women with mutations in the

BRCA1 gene who smoked more than 4 pack years, compared with non-smokers, the odds ratio for breast cancer was 0.5 (95%CI 0.3-0.9). In women with mutations in the BRCA2 gene, the odds ratio for smoking and breast cancer was 0.4, however it was not significant (95%CI 0.1-1.5), possibly due to smaller numbers with this mutation (Brunet et al., 1998). The protective effect of smoking on risk of breast cancer remained when the cut-off point for smoking was raised or lowered. The authors mention the anti-estrogenic properties of smoking as potential explanation of their findings.

Schildkraut et al. (1995) studied mutations in women with both breast and ovarian cancer. In 22 women studied, 15 (68%) had breast cancer before ovarian, and the remaining 7 (32%) had ovarian cancer first. Eight of the 21 women tested (38%) had a loss of heterozygosity in the markers on 17q11-21; 6 of the 13 women with breast cancer first and 2 of 6 women with ovarian cancer first. Because the survival rate of the two cancers is different (70% for breast and 30% for ovarian) there are more women with breast cancer at risk for ovarian than vice versa (Schildkraut et al., 1995).

Preventing the Risk of a Second Cancer or Relapse

Ford et al. (1994) found that the RR of ovarian cancer following breast cancer (before age 70) is 29% by age 50 and 44% by age 70, thus showing the relationship between the two tumours. The authors did not examine the effect of

treatment or of any other possible risk factors discussed previously. One study gives frequencies of the direction of multiple primary breast ovarian cancer (Shah, 1993). However this study did not attempt to examine the risk factors associated with those cancers. In women with a BRCA1 mutation, the risk of breast cancer is influenced by reproductive history (increased risk with early menarche and nulliparity). For ovarian cancer, the risk decreased with increased age at last child birth as expected, but the risk increased with increasing parity which was the reverse of what has been found in cases of sporadic breast cancer (Narod, 1995). Therefore fertility related factors can alter the penetrance of the BRCA1 gene.

Tamoxifen and Other Prophylactic Agents

Tamoxifen is a medication often used prophylactically to prevent the re-occurrence of breast cancer. Tamoxifen can also reduce the risk of heart disease and osteoporosis (Love, 1992; Morrow and Jordan, 1993). However most of the clinical trials have tested only post-menopausal women. Recent trials have not been able to equivocally show that Tamoxifen reduces the incidence of breast cancer. Recently there have been 4 large studies examining Tamoxifen and breast cancer, 2 showed no reduction in risk while the other 2 showed significant reductions. Powels (1998) in a cohort of 2471 women with a mean follow-up of 70 months found no difference in breast cancer incidence in women taking Tamoxifen and women taking a placebo (relative risk 1.1;95%CI 0.7-1.7). Veronesi et al., (1998) in a randomized control trial of 5408 followed up for an average of 46

months between women taking Tamoxifen (22 cases of breast cancer) versus those on a placebo (19 cases). There was no difference between the two groups ($p=0.64$). The Early Breast Cancer Trialists' Collaborative Group (EBCTC)(1998) pooled information from 55 trials of adjuvant Tamoxifen and breast cancer in women with estrogen receptor negative tumours. For women who were taking Tamoxifen for 1, 2, and 5 years the proportional reduction in recurrence after 10 years of follow-up was 21%(Standard Deviation (SD) of 3), 29% (SD 2) and 47%(SD 3) respectively. Similarly the reduction in mortality for users of 1, 2, and 5 years was 12% (SD 3), 17% (SD 3), and 26%(SD 4) respectively (EBCTC, 1998). The preventative effects of Tamoxifen were also examined as part of the National Surgical Adjuvant Breast and Bowel Project. Fisher et al. (1998) found that Tamoxifen reduced the risk of breast cancer in women by 49% ($p<0.00001$) compared with other women on a placebo who were also at high risk of breast cancer. The cumulative incidence of breast cancer after 69 months of follow-up was 43.4 per 1000 women in the Tamoxifen group compared with 22.0 in the placebo group. The risk of breast cancer was decreased in all age groups (Fisher et al. 1998).

Baum et al. (1992) followed-up over 2,000 women in a clinical trial comparing long-term Tamoxifen and cyclophosphamide use over 10 years. At the end of the ten years there was no benefit for the cyclophosphamide, but a significant improvement in the disease-free survival of the Tamoxifen group. Fisher et al. (1997) compared the disease-free and overall survival at 5 years in women

with estrogen-receptor positive breast cancer according to different treatments. In women prescribed Tamoxifen alone, their disease-free survival was 84% and overall survival 94%. The disease-free survival in women prescribed Tamoxifen, cyclophosphamide, methotrexate and 5-florouracil was 90% and an overall survival of 97% (compared with the Tamoxifen only group). These differences were significant $p<0.01$) (Fisher et al., 1997).

In a study examining ovarian tumours in postmenopausal women, Cohen et al. (1996) examined 175 women treated with tamoxifen over 5 years. Of these women, 9.1% underwent a total hysterectomy and 62.5% of those had either uni- or bi-lateral ovarian tumours, an overall incidence rate of 5.7%. This rate is 4-5 times higher than the rate reported for general screening. The authors state two possibilities: one, that these women were prone to develop these tumours (possibly due to genetic factors) regardless of Tamoxifen status, or two, that Tamoxifen may stimulate existing tumours or may even cause them. It is not known if the use of Tamoxifen increases the risk of ovarian cancer. A study conducted in New York (Schneider, 1995) found that of women who had breast and ovarian cancer, those using Tamoxifen had a decreased interval (23 months compared to 120 months) between the breast and subsequent ovarian cancer compared with those who were not on a Tamoxifen regimen. The authors controlled for fertility factors but did not examine any family history of breast or ovarian cancer (and thus any relation to genetic predisposition). Therefore the role of Tamoxifen and the risk of subsequent ovarian cancer is still unknown.

Many chemotherapeutic agents have shown to be toxic to the ovary and many of them are regularly used in the treatment of breast cancer (Taylor, 1993). Toxic, defined here as any impaired function of the ovary, such as amenorrhea. The most toxic of these is cyclophosphamide, an alkylating agent, which is used in the chemotherapy of breast cancer. Other agents associated with breast cancer treatment and toxic to the ovary are cis-platinum and melphan. In a study of 1081 women comparing radio and chemotherapy and subsequent second malignancies, Lavey et al. (1990) found that neither impacted negatively on patient's overall risk for a second malignancy. The median follow-up in this study was only 5.2 years (although they do report some follow-up extending to 16 years) so perhaps a longer follow-up is necessary to ascertain the risk of a second malignancy.

Oral contraceptive use may counteract the effects of chemotherapy on hormone levels by bringing the menstrual cycle back to normal (Taylor, 1993, Reichman and Green, 1994, Shapiro and Recht, 1994). One study by Arriagada and Rutquist (1991) involving 1113 women followed for ten years found a total of 3 ovarian cancers. The relative risk for any cancer was 0.22, p=0.0003. Bonadonna (1993) also showed no increase in cancer in 15 years of follow-up.

Risk of a Subsequent Cancer After Prophylactic Surgery

Some women decide to have prophylactic oophorectomies to lessen the chance of developing ovarian cancer. Unfortunately, this is not a perfect solution

(Struewing et al. 1995). Intra-abdominal carcinomatosis, which is histologically similar to ovarian cancer, can still occur. In their study of 16 breast-ovarian cancer families, 28 women had oophorectomies, and 3 cases (11%) later developed carcinomatosis. For those women in a high risk family (compared to those in a low risk family), and who do not have an oophorectomy there was an increased RR of ovarian cancer of 24 (95%CI 10-47). For those women with an oophorectomy, the RR was 13 (95%CI 1.0-47) and was not statistically significantly different from women without an oophorectomy (Struewing et al. 1995).

Objectives

The main objective of this study is to examine the role of family history of breast and ovarian cancer in women with breast cancer who subsequently develop primary ovarian cancer. We know the risks of cancer in relatives of women with breast or ovarian cancer but not both. It is believed that these cancers in women with both primary cancers are more likely to be familial, i.e. due to the BRCA1 gene. A past history of breast cancer has been reported in 4.6% of ovarian cancers vs. 26.3% of those with familial cancer. For family history of ovarian cancer, the relative risk of ovarian cancer is 3.6 if one has a first degree relative with the disease and 2.9 with a second degree relative (Narod, 1993). Women with double primaries should be studied to further estimate cancer risks as well as to see if these risks are altered by family history of breast or ovarian cancer.

The secondary objectives of this study are to examine how other factors influence the risk of ovarian cancer in women with previous breast tumours. Reproductive factors such as age of menarche and menopause and the use of hormone replacement therapy have been shown to alter the risk of ovarian and breast cancer (Negri et al., 1998; Wu et al., 1988) but no study has revealed how they affect the risk of ovarian cancer after breast. The same can be said for treatment factors, chemotherapy and Tamoxifen use (Taylor et al., 1993; Cohen et al., 1996, and Fisher et al., 1998). The benefits in treating and preventing breast cancer are clear, but what if the risk of ovarian cancer is heightened as a result.

If a significant association is found between those factors and the development of a second primary cancer, the course of treatment of the breast cancer may be altered in order to help reduce the risk of an ovarian tumour. This knowledge may also be used to increase the frequency of screening visits for specific detection of ovarian tumours, which otherwise would be missed.

Materials and Methods

This project is a case control study. The cases were women with multiple primary breast and ovarian cancer and the controls were women with single primary breast cancer. Using Quebec Tumour Registry data, women were identified that were diagnosed with both breast and ovarian cancer, and who were treated in one of the hospitals in the city of Montreal from 1980 to 1991. Controls were gathered from a breast cancer research pool set-up at the Epidemiology Research Unit, Hôpital Hôtel Dieu de Montréal as well as from the Montreal General Hospital. The controls were matched within two years of the year of birth and within one year of diagnosis. Medical records for each subject were examined to ensure accuracy of the information and were compared with responses from a telephone questionnaire given to both cases and controls.

This questionnaire was developed to learn about the risk factors experienced by the cases and controls. Information was collected on family history (first and second degree relatives only) of all cancer including breast and ovarian tumours. Information on fertility, treatment for cancers, OC use and other possible confounders was also collected. The information was analyzed by conditional logistic regression to obtain the odds ratio while maintaining the matched design as part of the analysis. Analysis of women who developed ovarian cancer before breast cancer was not considered because of the rarity of finding suitable cases

and controls.

The results of this study will be used to determine the effect of family history on the development of primary ovarian tumours in women with previous breast cancer as well as identifying the effect of reproductive factors and treatment. Multiple primaries in the same individual could result from genetic predisposition, treatment of the first malignancy, environment or chance.

Selection of Cases

Cases were women who had been diagnosed with both cancers of the breast and ovary (ICD9 codes 174 and 183 respectively) and who had been identified through the Quebec Tumour Registry from 1980-1991. The registry data is current up to 1992 because of delays in entering cases and limitations in getting accurate incidence data. The registry file contains the name, birth date, hospital, file number, last date seen and death date (if applicable). French speaking cases were followed up by Chantal Perret from the Epidemiology Research Unit, Hôpital Hôtel Dieu de Montréal. From the information from the registry file, Ms. Perret and I were able to locate the medical record. Any woman who was treated at a Montreal hospital was eligible for the study so that results can be compared. For this study, analysis of women who developed ovarian cancer before breast cancer was not considered because of the rarity of finding suitable cases and controls. Case selection was halted on December 31, 1995. Thirteen patients from Sunnybrook Hospital in

Toronto from a previous study were also included in this study. This study received ethics approval for boards at the Montréal General Hospital, Sunnybrook Hospital and the Hôpital Hôtel Dieu de Montréal.

After each woman was identified, her medical record was examined to find the dates of diagnoses of the cancers and treatments received (to compare with responses obtained in the questionnaire), name of primary physicians and the address and phone number of the patient. Only patients with ovarian carcinoma were selected; others such as women with Brenner's tumour for example, were not included. The patient's physician was contacted so that Ms. Perret or I could obtain more up-to-date information on the patient as well as permission to contact her. If the case was deceased, we also asked permission to contact the next of kin. After getting permission, we wrote a letter to the cases informing them that they would be contacted in 2 weeks.

Selection of Controls

Controls were women who were diagnosed with breast cancer within 2 years of the year of the diagnosis for the case of breast cancer and did not subsequently develop ovarian cancer. Since the controls were matched on year of diagnosis, and any control with ovarian cancer was excluded (and would then have been a case) I also allowed for the length of follow-up between the two cancers. In other words, if there was a gap of, for instance, 6 years between the two cancers in the case,

then the control would have been contacted at least 6 years after the breast cancer and to be eligible would have been free of ovarian cancer. Two controls for each case were used to improve power. The majority of controls were from a breast cancer research pool collected for a number of studies at the Epidemiology Research Unit, Hôpital Hôtel Dieu de Montréal. As women are diagnosed with breast cancer they are asked if they want to participate in any future research projects. If so, they are placed in this research pool. The subjects were women who were treated in one of the hospitals in the City of Montréal and were thus comparable with the cases. These subjects were asked if they wished to be involved in any type of breast cancer research and if they agreed, their name was put into a database. Other controls were taken from the Montréal and Jewish General Hospitals as well as Toronto's Sunnybrook hospital, matching on geographic region. Year of diagnosis was used to ensure comparability of treatments over time as well as the practicality of finding age-matched controls (since those who carry mutations in BRCA1 are more likely have a younger age of onset). Therefore, controls were comparable to the cases and would have the possibility of becoming cases themselves. Controls that were seen at French hospitals were followed up by Chantal Perret and those that were followed up at the English hospitals were followed up by myself.

Questionnaire

To assess the effect of treatment on subsequent ovarian cancer and to

control for the various confounders and effect modifiers, a questionnaire suitable for telephone interview was developed. The questionnaire was originally developed in English and was later translated in to French because both Francophones and Anglophones were part of the sample. It was also back-translated to ensure comparability between the French and English versions. This translation and re-translation was performed at from the Epidemiology Research Unit, Hôpital Hôtel Dieu de Montréal. The questionnaire took on average 20 minutes to complete. Information was obtained on demographics (ethnic group, religion, place of birth, parental ancestry), height and weight (current, usual and previous), fertility (including breastfeeding and menopause), exposure to talc and tobacco, and occupational history. The main exposure, family history of breast and ovarian cancer, was also obtained for first and second degree relatives. The diagnoses of these cancers were not confirmed. Treatment received for breast cancer was also asked in the questionnaire because it could potentially affect the onset of ovarian cancer. Information on Hormone Replacement Therapy as well as oral contraceptive use was also requested because of the potential relationship with subsequent ovarian cancer. A copy of the questionnaire is in the Appendix.

Ascertainment of Exposure

This study is a case-control study with cross-sectional "exposure" ascertainment. The "exposure" is genetic and one that is present before the disease occurs unlike other studies where latency can be a problem, we're allowing for

latency of disease development. All cases of multiple primary breast and ovarian cancer agreeing to have a blood sample taken were analyzed for the presence of the BRCA1 gene. Controls were not tested. Analysis of the blood samples is secondary to the main study. Testing for the BRCA1 gene is ongoing and will be discussed at a later date. Since about 38% of ovarian metastases are from a breast cancer (Gagnon and Tetu, 1989), the medical records were examined to make sure each case was in fact a double primary. Blood samples were not taken from controls based on the rarity of the mutation in the general population. From the genetic analysis, one should be able to increase surveillance of the two cancers in those who are gene carriers and possibly look for mutations in the gene that are unique for multiple primary cancers. The relative risk of cancer in relatives was also estimated from the family history of breast and ovarian cancer. Once an case subject had agreed to participate and the questionnaire had been administered, the cases were asked if they wished to contribute a blood sample. Twenty-nine women agreed to donate a blood sample for an overall response rate (based on all 65 cases) of 45%. Since there were only 41 women who were eligible to give a blood sample (i.e. non-proxy), a more accurate response rate would be 71%. The blood samples were tested for mutations in the breast cancer susceptibility gene.

Statistical Analysis

The risk of cancer in first and second degree relatives (not affected at the time) was calculated using the total number of cancers observed by the number of

person years at risk. This was performed using the LIFETEST procedure (the procedure used to create life-tables) in SAS. Results were analysed by the age the proband (the main person under study, or the case) was diagnosed with breast cancer (before and equal to age 50 and after age 50) and between cases and controls.

To examine the effect of family history of breast and ovarian cancer, reproductive and treatment factors on the risk of ovarian cancer, hypothesized risk factors were evaluated by conditional logistic regression models using the EGRET program. The regression estimates were matched for year of birth and year of diagnosis. The main effect to be examined was the number of relatives with breast or ovarian cancer and was entered into every model. Possible confounders (such as pregnancy, age of menarche, hormone replacement therapy and oral contraceptive use) were also added to the model if they were found to contribute significantly. For model selection purposes this level was set at 0.2. Radio- and chemotherapy exposure (among other variables that could be classified as yes or no) were dichotomous (y/n) and were based on the format, "Did you receive...". Other treatment variables such as Tamoxifen use were evaluated as a secondary hypothesis. Certain continuous variables such as weight, age at menarche and menopause, duration of treatment and family history (number of relatives with breast or ovarian cancer) were examined in models as categorical variables in order to determine whether there was a dose response effect. The analysis was not separated into proxy and non proxy because of the small numbers in this study;

however, proxy status was entered into the regression model. The mean difference in duration between the two cancers (for the Tamoxifen analysis) was examined by using an unpaired, unequal variance t-test.

Results

A total of 216 double primary cases, women with both breast and ovarian cancer, were identified from the Quebec Tumour Registry from January 1990 to December 1994. There were also 15 cases from Sunnybrook Hospital in Toronto giving us 231 potential cases. Case accrual stopped in December of 1995. Cases who were deceased longer than five years were excluded because information from the proxy respondent would be suspect. This resulted in 95 of the cases being declared ineligible, leaving 136 cases. Of these, 5 had no medical record available and 2 were found to be duplicates in the tumour registry database and were also declared ineligible. There were a further 4 cases deemed ineligible for having ovarian cysts and not primary ovarian cancer. One physician refused us permission to contact their patient. There were 54 cases that could not be contacted with no next of kin or family friend available for interview. Five cases refused to participate. A total of 65 cases were interviewed. Based on the 216 identified from the tumour registry, the overall response rate among cases was 30%.

There were 41 interviews conducted with the case themselves (63%) and proxy respondents (husband, sister or daughter) were used for the remaining 24 cases. There were 33 interviews conducted among the French speaking hospitals and 32 among the English speaking hospitals.

Information was collected for only 87 controls, out of a possible 130 controls (67%) - two for every case. There were 5 cases (requiring 10 controls) that a match could not be found for because of their age and age of diagnosis of breast cancer. For 33 controls, there was not enough information found for contacting the woman or her next of kin. To match by proxy status we tried to obtain 48 proxy controls. This proved difficult and it was decided to use live controls when a match was not possible. A proxy control for a proxy case was identified and interviewed for 27 of 48 (56%); however, not all deceased cases were matched with one live and one deceased control. Also, two matched controls were not found for all cases. For only seven proxy cases were two controls found. For eight cases only one proxy control could be found. In one instance a proxy control was interviewed for matched live case. The lack of controls was due to the rarity of their year of birth and the year in which they were diagnosed with breast cancer.

Of the 41 live cases, 29 donated a blood sample and 12 refused. One of the samples was donated by a sister of the case who had been diagnosed with pre-menopausal breast cancer. The remainder were proxy respondents.

The number of cases and controls, mean value, standard deviation and t-test between the means of cases and controls was calculated for the appropriate variables. The results are shown in Table 3. Since the cases and controls were matched on age, the average age of cases and controls were almost identical (67 years). Cases and controls were similar for most of the variables shown in Table

3. There were a few variables that differed between cases and controls. The age a case started fertility drugs was 41 compared with a control of 23. However there was only one case and one control that were prescribed fertility medication. Age at menopause was shown to be significantly different ($p=0.05$) even though the values were only 2 years apart (46 years versus 48.1 years). Number of miscarriages (6 in cases and 20 in controls) was significantly different as well ($p=0.02$). The average number of sisters also differed (1.7 in cases and 2.3 in controls) significantly ($p=0.04$). Mastectomy surgery over lumpectomy and ever prescribed chemotherapy differed between cases and controls ($p=0.002$ and $p=0.04$, respectively). If one examines the duration of menopause medication use (drug stopped-drug started) cases were using medications for 2 years compared with 7 years for the controls ($p=0.004$). The remaining variables were not found to be significantly different between cases and controls.

Table 3: Distribution of Selected Variables Among Cases and Controls

	CASES			CONTROLS			
	N*	Mean	Std Dev	N*	Mean	Std Dev	P Value
Potential Confounding Variables							
Age	65	67.7	13.3	87	67.0	12.6	0.77
Age of breast cancer	65	55.9	13.2	86	58.0	12.5	0.32
Age at menarche	47	13.0	1.6	73	13.1	1.4	0.85
Age of ovarian cancer	65	55.5	13.7	0	0	0	
Age at 1st child	50	25.4	5.1	67	26.2	5.1	0.75
Age at menopause	57	46.0	6.1	71	48.1	6.1	0.05
Age started fertility drug	1	41.0	.	1	23.0	.	
Breastfeeding duration	40	1.7	3.6	52	1.3	2.4	0.84
Number of abortions	65	0.2	0.6	87	0.2	0.7	0.85
Number of live births	65	1.8	1.4	87	1.7	1.5	0.76
Number of miscarriages	65	0.1	0.4	87	0.3	0.6	0.02
Number of pregnancies	65	2.1	1.4	87	2.2	1.8	0.57
Number of still born	65	0.0	0.1	87	0.0	0.2	0.44
Oral contraceptives start	21	28.3	7.4	31	29.8	8.9	0.53
Oral contraceptives stop	21	31.7	8.0	31	34.4	10.1	0.29
Relatives with cancer	62	1.8	1.9	86	1.3	1.2	0.22
Relatives with breast or ovarian cancer	62	0.7	1.0	86	0.6	1.0	0.36
Demographic Variables							
1st diploma duration	24	3.2	1.9	36	2.5	1.7	0.13
2nd diploma duration	2	3.0	0.0	2	2.5	0.7	0.18
Age started smoking	29	23.7	8.5	37	20.8	5.5	0.78
Age stopped smoking	16	49.3	17.6	30	45.2	16.8	0.45
Average # packs smoked	28	7.0	5.5	37	5.4	3.9	0.94
Current Weight	62	63.5	14.4	85	65.8	14.8	0.35
Brothers	63	2.4	1.9	85	2.3	2.3	0.84
Height	63	160.8	6.8	85	161.8	6.3	0.80
Sisters	63	1.7	1.5	85	2.3	2.1	0.04
Usual weight	60	63.1	12.3	85	64.3	12.4	0.56
Weight at age 20	56	54.2	8.0	82	56.3	10.6	0.21
Weight at age 30	56	56.8	7.7	82	57.4	8.7	0.69
Weight at age 40	58	60.1	10.1	84	60.5	9.1	0.82
Years in Canada	16	37.3	9.7	20	37.3	12.9	0.63
Years of School	60	10.3	2.5	83	10.3	2.8	0.86
Treatment Variables							
Age had Tamoxifen	30	58.5	12.5	44	62.4	13.0	0.20
Chemotherapy 1 duration	34	8.3	5.3	29	8.3	7.5	0.74
Chemotherapy 2 duration	14	6.9	5.7	5	5.0	1.4	0.27
Menopause drug started	9	45.8	11.0	19	48.2	4.1	0.55
Menopause drug stopped	9	47.8	11.9	19	55.6	6.2	0.13
Number of breasts w/cancer	63	1.2	0.4	86	1.1	0.3	0.44
Radiotherapy duration	33	25.6	8.6	61	25.7	4.9	0.16
Tamoxifen duration	27	36.8	31.3	42	44.5	36.6	0.33

* Number of respondents

Figures 1 through 16 show the frequency distributions for selected variables. From these figures one can more accurately see the differences between cases and controls. Figure 1 shows the age distribution by age group, the largest group being 65-69. Most age groups were similar in frequency between cases and controls, based on the matching criteria (within two years of the year of birth) and any discrepancy was probably because the matching occurred across strata. The last year of school completed is found in Figure 2. Most cases (25 or 38%) and controls (29 or 33%) finished at least Grade 12, and there were 7 cases and 9 controls (10% each) finishing Grade 13. Figures 3 and 4 show the distributions of weight at age 20 and current weight. For both cases and controls, most women weighed between 50-59 kilograms. The proportion of women in this weight group was much higher for weight at age 20 than for current weight (over 50% of cases and controls for weight at age 20 compared with approximately 35% for current weight).

Figure 5 shows the length of time between menarche and menopause or the total years of menstruation. Most women experienced 35-39 years, corresponding to menarche at age 15 and menopause at 50. There are more cases with 25-29 and 30-34 years of menstruation and more controls with 40-44. Figure 6 shows the distribution of the age of a woman when she had her first child, if applicable. The most common ages were between 20-24 and 25-30. Figure 7 shows the distribution of the number of children for cases and controls. Most women (approximately 25% for both cases and controls) had no children, followed by women who had 1 to 3 children. Figure 8 illustrates the ages when a woman first started to use oral

contraceptives. The peak ages were 20-24 and 25-29.

For those women who used oral contraceptives (Figure 9), most used oral contraceptives for only one or two years, and almost all less than 5. A few women used oral contraceptives for over 10 years. From Figure 10, the age when a woman was prescribed Tamoxifen is shown. The distribution peaks at ages 60-64. There appears to be an increased number of cases at ages 40-44 and controls at ages 75-79 who were prescribed the drug. The duration of Tamoxifen use (Figure 11) shows that most of the users take the drug for less than 5 years and almost all for less than 10. Figure 12 illustrates the average age of menopause. The most frequent age group was between 50 and 54. It appears that a greater proportion of cases experienced menopause before age 50 (from Table 3, cases 46 years on average compared with controls an average of 48.1 years). The younger age of menopause was due to either chemotherapy treatments or hysterectomy.

Figures 13 and 14 show the number of relatives with cancer and the number of relatives with breast and/or ovarian cancer. Twenty cases (30%) and 26 controls (30%) did not have any relatives with cancer. In addition, 29 cases (45%) and 52 controls (60%) did not have a relative with breast or ovarian cancer. The distribution of the age at diagnosis for breast cancer is in Figure 15. This distribution appears bimodal, with peaks at 45-49 and 60-64. Figure 16 shows the duration of chemotherapy treatment. The vast majority of women were given treatment for less than 6 months.

Frequency Analysis

As mentioned previously there were 65 cases and 87 controls interviewed. In terms of family ancestry, 26 cases (40%) reported their mother being French, followed by 13 women (20%) whose mothers were English. As expected, this was very similar to paternal ancestry where 25 women (38%) reported their father as French and 15 (17%) as English. The majority of the controls came from French backgrounds as well. Forty-five controls (52%) had mothers that were of French background and 11 (13%) had an English maternal background. The results were identical for paternal ancestry.

For those women who had a diploma or degree, 9 (29%) were secretarial or commercial in nature. Forty-five of the controls (52%) did not receive any post-secondary education. Of those that did, the most common career field was secretarial or commercial as stated by 11 controls (13%). This was followed by 7 controls with post-graduate training in nursing and 3 in teaching. There was no common degree or diploma in cases or controls.

There was also no difference in the occupations that women (or their proxies) stated, the majority of occupations were in clerical or teaching positions. Eight cases (13%) were not in paid employ at any time. A total of 78 (90%) of the controls had been employed. The most common occupation was secretary or office worker by 19 controls (22%). This was followed by nursing with 7 controls (8%).

The most common religion of the cases was Catholic with 38 women (59%) reported being a member, followed by 6 women (9%) that were Jewish. Six case women stated that they did not have a religion. The most common religion among controls was Roman Catholic, with 54 controls (62%) reporting this religious affiliation. The second most common religion was Judaism reported by 10 controls (12%), however having no religion at all, also showed a similar frequency.

Of all the cases, 29 women (44%) had been regular smokers once in their lives. Of these women who smoked, 14 (48%) still smoked or were smoking when they died. Of the controls, 39 women (45%) were classified as regular smokers. Of those who were regular smokers, 12 (31%) were still smoking or had smoked up until death.

All cases had gone through menopause whether natural or otherwise. Thirty-one (48%) of the cases had had a natural menopause, while for 21 (32%), the menopause was due to surgery (hysterectomy). Seven cases (11%) reported that their menopause was due to chemotherapy. One was due to radiotherapy and another from both chemo- and radiotherapy. All of the controls had been through menopause, although 10 controls (12%) were unable to determine the reason. For controls, the most common reason for menopause was naturally occurring; this occurred in 51 controls (59%). This was followed by surgical menopause in 15 (17%) controls. Menopause by chemotherapy or radiation each occurred in 10 controls (12%).

Nine cases (14%) received medications to control menopause. The most common medication used was Premarin (4 women) followed by Provera (2 women). Three cases could not remember the name of the medication prescribed. Twenty-two percent of the controls (19 controls) had taken medication to control the symptoms of menopause. The most popular drug was Premarin, used by 12 controls (64% of those who used medications). Estrogen was used by two controls (2%). The remaining controls could not recall the name of the medication prescribed.

Fifty-one (79%) of the cases had become pregnant and 48 (74%) had had children at some point. Sixty-nine controls (79%) had become pregnant at least once. Of those controls that were pregnant, 72% had had live births. The frequencies of the number of live births are found in Figure 7. Six case women had miscarriages and one case that had a still born child. There were 20 control women (23%) that had miscarriages. Three control women (3%) had delivered still born children.

Most of the cases (44 women or 68%) had a first or second degree relative with any cancer type. Twenty-six out of 62 cases that could recall (42%) had at least one relative with breast or ovarian cancer as well (the vast majority were breast). Nine women (14%) had two relatives with breast or ovarian cancer and four women had 3 or more relatives. Most of the controls, 58 women (67%), had at least one relative with any cancer. Twenty-eight controls (33%) had one relative

with cancer and 6 controls had at least 4 relatives with cancer. Thirty-one percent of the controls (36%) had at least one relative with breast cancer. Nine controls (11%) had at least two relatives and 2 women had at least 4 relatives with breast cancer. Eleven case women (18%) and eleven of the controls had bilateral breast cancer (13%).

Of all the cases, 21 (36%) had used oral contraceptives at least once and there were 2 women who had used them more than 3 time periods (stopped then started again). Of all the controls, 31 (36%) had used oral contraceptives at least once. Duration of oral contraceptive use is found in Figure 9.

Almost half of the cases had used Tamoxifen. Thirty-two women or 49% reported some use. Seven cases (11%) could not recall. Forty-five of the controls (52%) reported Tamoxifen use. There were 4 controls (5%) unable to respond.

When asked about the use of talc, there were 26 cases (40%) stated they had used it regularly; the most common application was "all over" with 8 women reporting (12%). Only 7 (11%) women reported use in the perineal area. Thirty-one controls (36%) were regular users of talcum powder, and only 5 women (6%) used it near the perineum.

Of the breast cancers among cases, 32 had had lumpectomies (49%) and 30 had had mastectomies (46%). One woman had had multiple surgical procedures

and the rest were unknown. There were 12 case women (18%) who had surgery on both breasts. Of these 12, five women had had mastectomies, five women had lumpectomies and the remainder were not able to recall which proceedure. All cases had had at least one breast surgery for their cancer. Of the controls, 63 women or 72% had previous lumpectomies and 22 women (25%) had received mastectomies. Two controls could not recall. There were 17 (20%) women who had surgery on both breasts. Of these surgeries 12 (14%) were lumpectomies and 5 (6%) were mastectomies. In all, there was only one control who did not have at least one surgery for breast cancer.

The majority of the cases received chemotherapy for either of their cancers. For treatment of breast cancer 28 (43%) women received chemotherapy and 11 (17%) received it only for ovarian cancer. Note that this was based on recall during the telephone interview. The most common agent used for breast cancer was 5-fluorouracil, which was used by 8 women (21%). This was followed by cis-platinum with 7 (18%) of women. Half the cases did not remember what the medication was. For treatment of breast cancer, 36 (41%) controls had received chemotherapy. Two controls did not know whether they had received chemotherapy. The type of chemotherapy was known in only 10 women (11%). Four women had received a combination of cyclophosphamide, methotrexate and 5-fluorouracil and 4 women had just received cyclophosphamide. Duration of chemotherapy use is found in Figure 16.

Radiotherapy was used in 38 cases (58%). There were 5 cases whose treatment was unknown. There were 14 cases (22%) who had radiotherapy for other diseases. The most common was for ovarian cancer, which occurred in eight women. There were two women who had radiotherapy to bone marrow. Sixty-six controls (77%) had received radiation for breast cancer. Nine of the controls (10%) had received radiotherapy for diseases other than breast cancer. The majority of these, six (7%), were for treatments to the bone or spine, which were likely due to metastases.

The majority of cases (35 women or 54%) reported having reproductive organ surgery. Three cases did not remember. Of those who underwent surgery, 24 (69%) had had a hysterectomy, followed by tubal ligation (7 women or 20%) and removal of uterine cysts (5 cases or 14%). The controls' history of reproductive surgery was also asked. Almost half of the controls, 41 women or 47% had indicated reproductive surgery. The most common procedure was tubal ligation in 16 controls (42% of all surgeries) followed by 13 women who received hysterectomies.

Cases were asked if they had ever suffered from any other illnesses apart from the two primary cancers. A wide number of responses was revealed, the most common being hypertension (occurring in 5 of the cases), tonsillitis (4 cases) and arthritis (3 cases). The controls were also asked if they suffered from any other illnesses apart from breast cancer. There were no patterns of illness in the

controls; many diseases were mentioned but there was not discernable pattern.

Women were also asked about previous surgery. The most common operation was appendectomy with 16 cases (25%) followed by cholecystectomy with 8 (12%). Over half of the cases had not received any abdominal surgery (35 women or 54%). The most common procedure in controls was for removal of a biliary tumour occurring in 14 women (16%). This was followed by appendectomies in 11 controls (13%). Forty-nine of the controls (57%) had not had any abdominal surgery.

Some of the cases had ovarian problems apart from cancer. Four women had ovarian cysts and two cases were diagnosed with fibromas. Most women (53 of 56 that knew) had had the whole ovary removed. In 10 cases only one ovary was removed. In those women that had both ovaries removed, 87% of the time, the whole ovary was removed rather that a subsection . All but 2 cases (97%) had surgery to remove the tumour(s). Some controls experienced reproductive problems apart from cancer. Twenty controls (22%) had had problems with at least one ovary. Ten controls (11%) reported problems with both ovaries. The most common surgery was a hysterectomy which occurred in 7 controls (8%). There were 2 controls with cysts. There were 17 controls that had one ovary removed (20%) and of these 17, five controls had only part of the ovary removed. There were 12 (14%) women with both ovaries removed and 11 (13%) of them had had the whole ovary removed.

Cumulative Incidence of Breast Cancer in Relatives

To examine the risk of breast cancer in first and second degree relatives of a woman diagnosed with cancer, Kaplan-Meier survival curves were plotted to age 75. The cases were divided into two groups, one where the case was diagnosed with breast cancer at age 50 or less and the second group where the case had been diagnosed after age 50. The age of 50 was chosen as the cut off point because this is the average age of menopause. The analysis was also split into first and second degree relatives and first degree relatives only. Figure 17 shows the cumulative incidence of breast cancer in first and second degree relatives before the age of 75. Age 75 was used as the cut-off to be consistent with other studies. Figure 18 is similar to the previous but for first degree relatives only.

There were a total of 42 cases of breast cancer in first and second degree relatives (20 where the case was diagnosed less than or at 50 years of age and 22 where they were older than 50) out of a total of 257 identified relatives (84 where the case $\leq$ 50 and 173 >50). At the age of 75, there was a cumulative risk of 35% for relatives of the cases $\leq$ 50, and 20% for relatives of cases > 50. These two cumulative incidence curves were statistically different with p=0.0065. The analysis was repeated for first degree relatives only, because some of the proxy information was suspect.

There were 19 cases of breast cancer in first degree relatives (8 for cases

under 50 and 11 for cases over 50) out of a total of 164 first degree relatives (51 for cases $\leq$ 50 and 113 >50). By the age of 75, the cumulative incidence of cancer was 26% for relatives of cases $\leq$ 50 compared with 15% of cases older than 50. In this case the two curves were not statistically significant with a p-value of 0.1201. In Figures 17 and 18 the breast cancers tend to occur at earlier ages when the case was $\leq$ 50 and at later ages when the case was > 50 years old.

The cumulative incidence was also compared for cases and controls using the Kaplan-Meier method. For both first and second degree relatives there were a total of 597 relatives, 257 related to the cases and 340 related to controls. There were a total of 96 breast cancers reported in relatives for both cases and controls. There were 42 cancers among the relatives of the cases and 54 in the relatives of the controls. Figure 19 shows the cumulative incidence of breast cancer in cases and controls for all relatives. By the age of 75 the cumulative incidence of breast cancer in relatives of the cases was 25% and 27% for relatives of the controls. This was not found to be significant (p=0.9056). The cumulative incidence rate is higher in cases than controls until the age of 65, then the curves intersect. The gap between the two rates seems largest at age 50. Figure 20 shows similar results but for first degree relatives only. There were 441 relatives identified, 164 for the cases and 277 for the controls. Among these relatives, there were 45 breast cancers, 19 among the relatives of the cases and 26 among relatives of the controls. By the age of 75 the cumulative incidence of breast cancers in the relatives of cases was 19%, compared with 17% among relatives of the controls. This was not found to be

significant (p=0.3821). The relatives of the cases had the higher cumulative incidence rate of breast cancer; this time, however, incidence among controls did not surpass that of the cases. Again the largest gap between cases and controls occurred at age 50.

To examine the risk of breast cancer in relatives of the cases, the age of the proband with the age of the relative was compared. There were 39 relatives where both the relative and the proband were less than 50 years old. This resulted in a odds ratio of 1.8 (95% CI 1.0-3.0). In other words, if a woman was diagnosed with breast cancer under the age of 50 the relative risk of breast cancer in her relatives was 1.8 times higher, than if the woman was diagnosed with breast cancer over the age of 50.

Conditional Logistic Regression Analysis

Twenty-six cases (and their respective controls) had to be excluded from the logistic regression analysis since their diagnosis of ovarian cancer occurred before the breast cancer. Another 6 pairs were removed from the analysis due to missing information. This left 33 matched pairs available for analysis.

Table 4 (Tables start on page 76) contains the univariate analysis of all the dichotomous (usually yes/no) variables. For this step, matching by age and age of breast cancer was not performed. Only one variable was significant at the 5% level

although radiotherapy was borderline. Breast surgery (mastectomy or lumpectomy) had an odds ratio of 0.37 (95% CI, 0.19-0.75), meaning that having a mastectomy was protective against ovarian cancer. Radiotherapy was also found to be protective with an odds ratio of 0.48 (95% CI, 0.23-1.01). There were elevated risks for bilateral cancer, chemotherapy, use of fertility drugs, proxy respondent and any reproductive surgery; however, the confidence intervals were wide and included the null value.

Each variable then was entered separately into the model to find an estimate of risk while matching for age and year of diagnosis. The results are presented in Table 5. When the cases and controls were matched and entered into the logistic model, five variables were significant. The variables for number of still born children and years between the cancers were not resolved by the EGRET program and could not be analyzed. With the number of missing values, the matrix could not be inverted or was unable to converge with any precision. Family history of breast or ovarian cancer has a slightly increased risk of ovarian cancer (OR=1.14, 95%CI 0.72-1.81) but was not significant. Breast surgery (mastectomy over lumpectomy) was found to show a significant increased odds of cancer (OR=2.64, 95%CI 1.20-5.81). Current weight (OR=0.96, 95%CI 0.93-1.00), number of sisters (OR=0.59, 95%CI 0.37-0.92), radiotherapy treatment (OR=0.30, 95%CI 0.11-0.81) and usual weight (OR=0.96, 95%CI 0.92-1.00) all showed significant protective effects. Breast surgery was the only variable that significantly increased the risk of subsequent ovarian cancer.

The effect of Tamoxifen on the development of subsequent ovarian cancer was then examined. Tamoxifen use compared with women who had never used the drug, there was an association with an odds ratio of 1.00 (95%CI 0.81-1.24). For duration of Tamoxifen use the odds ratio was 1.01 (95%CI 0.99-1.02). Neither of the variables were predictors of ovarian cancer. Tamoxifen use was not entered into any further models.

The difference in the duration between the breast and ovarian cancer cases for those using Tamoxifen and those who had not, was also examined. The average time between the breast and ovarian cancer for those taking Tamoxifen was 6.2 years and those not taking Tamoxifen the duration was 6.07 years. The p-value for this difference was 0.95.

In the next step of the analysis, all the variables in the model were examined to determine their mutually adjusted effects. Family history of cancer as well as breast and ovarian cancer were added to all models. Variables with a p-value of less than 0.2 were entered, as were duration variables (treatment or drug) and those variables with prior evidence of altering the risk of ovarian cancer were included. The results are shown in Table 6. All of the variables collected were added to the model, however, the matrix could not be inverted. There were no variables that were significant at the 5% level. There were some variables that had extreme odds ratios and corresponding confidence intervals. The odds ratio for relatives with breast or ovarian cancer was 4014 (95%CI 0.00-1.2e^{10}) when

controlled for the other selected variables. Having a mastectomy compared with a lumpectomy was associated with an odds ratio 127,700 (95%CI 0.00- $2.1e^{14}$). The limits are wide due to the reduced sample size. Chemotherapy (OR=0.43, 95% CI 0.04-4.69) and radiotherapy (OR=0.00, 95% CI 0-$2.16e^{6}$) were found to be protective, however duration of chemotherapy and radiotherapy were found to have increased OR. For duration of chemotherapy the odds ratio was 3.63 (95%CI 0.42-31.27) and for duration of ratiotherapy the odds ratio was 1.49 (95%CI 0.74-2.97). The variable number of sisters also showed a strong protective effect (OR of 0.02, 95% CI 0.00 –12.76). Usual weight, number of pregnancies and age at menopause showed an increased risk with borderline significance. Next, a stepwise procedure was done in order to find the most parsimonious set of variables that had an independent explanatory value for the risk of subsequent cancer. A stepwise procedure is an automated method of model selection that enters and removes each variable based on their contribution to the overall model until all the variables contribute to a final model. The in and out criteria in this instance was based on a significance level of 0.05. The results of this procedure are shown in Table 7A. Since the number of relatives with breast or ovarian cancer did not make it into the model, they were forced in and a new model was created (Table 7B). The addition of this family history variable did not change the significance of any of the variables in Table 7A with the exception of the number of sisters. The upper limit of the 95% CI decreased from 1.03 to 0.91. Therefore the discussion will be based on the results from Table 7B. Duration of radiotherapy was entered in the model to determine if it effected the estimate for radiotherapy, it did not effect the estimate

and was therefore not included. The odds ratio for women with relatives with breast or ovarian cancer was 2.43 (95% CI 0.76-7.80). Having a mastectomy rather than a lumpectomy was associated with a large increased odds (OR=15.1, 95% CI 13.9-164.5) and was the only variable with a significantly increased odds of ovarian cancer. Chemotherapy was also shown to increase the odds ratio, although not significantly (OR=1.3 95% CI 0.4-3.6) and duration of chemotherapy had a similar, non-significant increased odds ratio of 1.4 (95% CI 0.9-2.1). There were three variables that had significant odds ratios under one. Usual weight had an odds ratio of 0.8 (95%CI 0.7-1.0), none of the other variables dealing with weight showed any importance. The variable, number of sisters, as mentioned above, was altered slightly by the addition of number of relatives with breast or ovarian cancer. Although the odds ratio did not change (0.5) the 95% confidence interval narrowed slightly (to 0.3-0.9) to achieve significance. Treatment with radiotherapy had an odds ratio of 0.01 (95%CI of 0-0.5).

Table 8 shows categorical analysis of some continuous variables. Cutoffs were chosen based on frequency and prior knowledge in the literature. Two variables, number of pregnancies and number of sisters, did not converge and were left as continuous for any future models. Age of menarche, duration of Tamoxifen use and weight at age 40 were the only variables showing a dose-response relationship: odds of ovarian cancer increased with; older age of menarche and Tamoxifen use over 5 years, and decreased with increased weight at age 40. There was an increased odds ratio for greater than four relatives with breast or

ovarian cancer (OR=1.4) but was not non-significant (95%CI 0.1-23.5). Of all the categorical variables, only chemotherapy for less than 6 months and 6-12 months were significant at the 5% level with an odds ratio for ovarian cancer of 6.2 (95% CI 1.2-31.9) and 29.6 (95%CI 2.93-298.9) respectively. There were borderline non significant results for radiotherapy for 20-29 weeks, odds ratio of 0.4 (95% CI 0.2-1.1) and age of menopause of 45-54 with an odds ratio of 2.6 (95%CI 0.95-7.2).

Table 9 shows the complete conditional logistic regression model for those categorical variables that had at least one level with a p-value of less than 0.2, plus number of relatives with breast or ovarian cancer. There were non-significant odds ratios under unity for the number of relatives with breast or ovarian cancer (0.01 for 1-3 relatives and 0.76 for 4 or more relatives) and both had very wide confidence intervals. There was no categorical variable that was significant. The only individual category that was borderline non-significant was 7-12 months of chemotherapy (OR=905.7, 95%CI 0.9-922,100). It is possible that there might have been some dose-response results with the number of relatives with cancer (ORs from 1.0,7.9, 42.1) and duration of Tamoxifen use (ORs from 1.0, 1.1, 5.9) but there were too few subjects to achieve significance. It is also interesting to note that for the variable weight at age 40, the odds ratio for ovarian cancer shows a protective effect until the weight of 70-79 kg (ORs range from 0.02-0.1). If the weight at age 40 was reported as 80+ kg then the odds ratio for ovarian cancer was 18.9 (95%CI 0-45,510). Because the categorical estimates were for the most part non-significant, they are probably too imprecise to enter into future models and

continuous variables were used for the final model.

Table 10 shows the final model that was chosen. No categorical variables were entered since none appeared to be as stable as their continuous counterparts. The number of relatives with breast or ovarian cancer, a surrogate for family history, was found to have an increased odds ratio for ovarian cancer of 1.27, however, this was not significant (95%CI 0.6-2.9). Having chemotherapy for breast cancer was shown to increase the odds ratio for ovarian cancer to 52.7 (95%CI 1.7-1651.0). This means that those women who undergo chemotherapy for breast cancer have 53 times greater odds of ovarian cancer than those that do not. This estimate varied greatly depending on the other variables entered in the model at any particular time, so it is assumed to be inaccurate. The other significant variables in the model were all shown to decrease the odds of ovarian cancer. For every sister a woman had, the risk of ovarian cancer dropped by a factor of 0.5 (95%CI 0.3-0.9). If a woman's usual weight was over 50kg, then every kilogram over 50 resulted in a decreased odds by a factor of 0.9 (95%CI0.8-1.0). For those women who underwent radiotherapy treatment for breast cancer, every week of therapy more than 20 weeks reduced the risk of subsequent ovarian cancer, OR=0.9 (95%CI 0.8-1.0).

Table 4: Univariate Analysis of Potential Risk Factors-Dichotomous Variables, Unmatched

Variable	Exposed Cases	Exposed Controls	OR	95% Confidence Interval Lower	Upper
Any Relative with Cancer	44	58	1.18	0.58	2.40
Any Relative with Breast or Ovarian Cancer	26	31	1.28	0.66	2.50
Bilateral Cancer	11	11	1.44	0.58	3.57
Breast Surgery	32	63	0.37	0.19	0.75
Catholic Religion	38	54	1.17	0.39	3.50
Chemotherapy	28	36	1.65	0.82	3.33
Diploma	31	38	1.19	0.61	2.29
Treated at English Hospital	33	48	0.84	0.44	1.60
Ever Employed	56	77	0.73	0.26	2.05
Fertility Medication	2	1	2.85	0.25	32.26
Menopause Medication	11	22	0.67	0.30	1.52
Never Pregnant	14	18	1.05	0.48	2.31
Oral Contraceptive Use	21	31	1.01	0.51	2.01
Proxy Respondent	24	25	1.43	0.72	2.83
Radiotherapy	37	66	0.48	0.23	1.01
Regular Smoker	29	39	0.98	0.51	1.88
Regular Talc Use	26	31	1.11	0.56	2.20
Reproductive surgery	35	41	1.36	0.70	2.63
Tamoxifen Use	32	45	1.04	0.53	2.04

OR: Odds Ratio

Table 5: Univariate Analysis of Potential Risk Factors-Matched Analysis

	Odds Ratio	95% Confidence Interval Lower	Upper
Relatives with Breast or Ovarian Cancer	1.14	0.718	1.810
Relatives with Cancer	1.16	0.846	1.585
Potential Confounding Variables			
Age at First Child Born	0.99	0.96	1.03
Age at Menarche	1.03	0.85	1.25
Age at Menopause	1.03	1.00	1.06
Age of Oral Contraceptive use	1.00	0.97	1.03
Bilateral Cancer	1.49	0.43	5.12
Breast Fed	0.88	0.63	1.23
Duration of Oral Contraceptive Use	0.96	0.84	1.08
Ever Pregnant	0.85	0.27	2.64
Fertility Medication	1.09	0.80	1.48
Height	1.00	0.99	1.02
Number of Abortions	0.94	0.51	1.74
Number of Live Births	0.94	0.69	1.29
Number of Miscarriages	0.77	0.33	1.81
Number of Total Pregnancies	0.91	0.70	1.19
Oral Contraceptive Use	0.91	0.33	2.54
Regular Talc Use	0.94	0.36	2.49
Reproductive Surgery	0.10	0.41	2.64
Years of Reproduction	1.04	0.99	1.10
Demographic Variables			
Current Weight	0.96	0.93	1.00
Diploma	0.93	0.38	2.28
Ever Employed	0.53	0.13	2.28
Number of Brothers	0.98	0.74	1.29
Number of Sisters	0.59	0.37	0.92
Packs Smoked per Week	1.02	0.92	1.13
Proxy Respondent	0.31	0.03	3.50
Regular Smoker	0.80	0.40	1.63
Usual Weight	0.96	0.92	1.00
Weight at age 20	0.99	0.96	1.01
Weight at age 30	0.99	0.97	1.02
Weight at age 40	0.97	0.93	1.01
Years in Canada	1.00	0.96	1.03
Years in School	1.03	0.90	1.19
Treatment Variables			
Chemotherapy	1.59	0.83	3.06
Duration of Chemotherapy	1.08	0.98	1.19
Radiotherapy	0.30	0.11	0.81
Duration of Radiotherapy	0.97	0.94	1.00
Mastectomy	2.64	1.20	5.81
Menopause Medication	0.45	0.12	1.71
Tamoxifen Use	1.00	0.81	1.24
Age of Tamoxifen Use	1.01	0.99	1.02
Duration of Tamoxifen Use	1.01	0.99	1.02

All analysis is performed with 33 matched sets.

Table 6: Multivariate Conditional Logistic Matched Analysis of Selected Variables

Selected Variables	Odds Ratio	95% Confidence Interval Lower	Upper
Relatives with Breast or Ovarian Cancer	4014.00	0.00	1.166e10
Age at Menopause	1.34	0.81	2.22
Mastectomy	127700	0.00	2.147e14
Chemotherapy	0.43	0.04	4.69
Current Weight	0.62	0.26	1.45
Duration of Chemotherapy	3.63	0.42	31.27
Duration of Radiotherapy	1.49	0.74	2.97
Number of Pregnancies	1.63	0.54	4.93
Number of Sisters	0.02	0.00	12.76
Radiotherapy	0.00	0.00	2.162e6
Usual weight	1.26	0.69	2.31
Weight at age 40	0.60	0.25	1.43
Years of Menstruation	0.50	0.14	1.82

All analysis is performed with 33 matched sets.

Table 7A: Model After Stepwise Regression Analysis

Variables	Odds Ratio	95% Confidence Interval Lower	Upper
Mastectomy	13.60	1.43	129.30
Chemotherapy	1.57	0.59	4.14
Duration of Chemotherapy	1.28	0.98	1.67
Number of Sisters	0.50	0.24	1.03
Radiotherapy	0.03	0.00	0.50
Usual weight	0.84	0.72	0.97

All analysis is performed with 33 matched sets.

Table 7B: Model After Stepwise Regression Analysis – Family History Included

Variables	Odds Ratio	95% Confidence Interval Lower	Upper
Relatives with Breast or Ovarian Cancer	2.43	0.76	7.80
Mastectomy	15.13	13.92	164.50
Chemotherapy	1.26	0.44	3.60
Duration of Chemotherapy	1.38	0.92	2.05
Number of Sisters	0.49	0.26	0.91
Radiotherapy	0.01	0.00	0.51
Usual weight	0.81	0.67	0.98

All analysis is performed with 33 matched sets.

Table 8: Categorical Analysis of Selected Continuous Variables

	n (total=126)	Odds Ratio	95% Confidence Interval Lower	Upper
Relatives with Breast or Ovarian Cancer				
0	77	1.00	–	–
1-3	42	0.92	0.35	2.46
4+	3	1.41	0.09	23.57
missing	4			
Relatives with Cancer				
0	39	1.00	–	–
1-3	73	1.02	0.40	2.60
4+	10	1.70	0.38	7.59
missing	4			
Age of Menarche				
<10	1	1.00	–	–
10-14	85	1.22	0.11	14.08
15+	15	1.67	0.12	23.41
missing	25			
Age of Menopause				
<45	25	1.00	–	–
45-54	69	2.61	0.95	7.15
55+	11	0.41	0.04	4.37
missing	21			
Duration of Chemotherapy				
none	75	1.00	–	–
<6 months	31	6.20	1.21	31.87
7 - 12 months	12	29.60	2.93	298.90
13+ months	8	0.65	0.05	8.52
Duration of Oral Contraceptive Use				
none	86	1.00	–	–
< 6 months	29	0.96	0.32	2.89
7-12 months	8	0.31	0.03	2.98
13+ months	3	0.99	0.09	11.19
Duration of Radiotherapy				
none	43	1.00	–	–
<20 weeks	6	0.38	0.03	5.03
20-29 weeks	67	0.42	0.16	1.08
30+ weeks	10	0.16	0.02	1.54
Duration of Tamoxifen Use				
none	67	1.00	–	–
<5 years	41	1.08	0.40	2.92
5+ years	18	4.11	0.76	22.40

Table 8: Categorical Analysis of Selected Continuous Variables (cont.)

	n (total=126)	Odds Ratio	95% Confidence Interval Lower	Upper
Number of Pregnancies				
0	27	1.00	–	–
1-4	93	1.11	no convergence	
5+	6	0.00		
Number of Sisters				
0	26	1.00	–	–
1-4	85	0.31	no convergence	
5+	11	0.00		
missing	4			
Usual Weight				
<50 kg	9	1.00	–	–
50-59 kg	52	0.71	0.12	4.06
60-69 kg	28	0.91	0.14	5.77
70-79 kg	22	0.17	0.02	1.57
80 + kg	10	0.20	0.01	3.28
missing	5			
Weight at Age 40				
<50 kg	10	1.00	–	–
50-59 kg	55	0.22	0.04	1.22
60-69 kg	40	0.25	0.05	1.44
70-79 kg	9	0.16	0.03	1.46
80 + kg	5	0.12	0.01	1.85
missing	6			
Total Years of Menstruation				
<30	20	1.00	–	–
30-34	16	0.87	0.22	3.48
35-39	40	0.92	0.64	1.31
40+	17	0.48	0.11	2.08
missing	33			

All analysis is performed with 33 matched sets.

Table 9: Multivariate Analysis of Selected Categorical Variables

Selected Variables	Odds Ratio	95% Confidence Interval Lower	Upper
Relatives with Breast or Ovarian Cancer			
0	1.00	–	–
1-3	0.01	0.00	13.88
4+	0.76	0.00	7235.00
Relatives with Cancer			
0	1.00	–	–
1-3	7.92	0.19	328.30
4+	42.13	0.04	49190
Age of Menopause			
<45	1.00	–	–
45-54	12.92	0.54	308.20
55+	0.01	0.00	20.63
Duration of Chemotherapy			
none	1.00	–	–
<6 months	193.70	0.31	121700
7 - 12 months	905.70	0.89	922100
13+ months	8.38	0.05	1310
Duration of Radiotherapy			
none	1.00	–	–
<20 weeks	0.03	0.00	7.10e7
20-29 weeks	0.09	0.00	2.12
30+ weeks	0.05	0.00	124.80
Duration of Tamoxifen Use			
none	1.00	–	–
<5 years	1.10	0.06	21.27
5+ years	5.87	0.12	287.00
Weight at Age 40			
<50 kg	1.00	–	–
50-59 kg	0.02	0.00	3.62
60-69 kg	0.06	0.00	8.94
70-79 kg	0.12	0.00	6.46
80 + kg	18.85	0.00	45510
Duration of Oral Contraceptive Use			
none	1.00	–	–
< 6 months	0.06	0.00	5.36
7-12 months	0.00	0.00	1.11e7
13+ months	0.19	0.00	1.13e7

All analysis is performed with 33 matched sets.

Table 10: Final Conditional Logistic Model of the Risk of Subsequent Ovarian Cancer After Breast Cancer

Variables	Odds Ratio	95% Confidence Interval Lower	Upper
Relatives with Breast or Ovarian Cancer	1.27	0.55	2.91
Chemotherapy	52.74	1.69	1651.00
Number of Sisters	0.53	0.31	0.88
Usual Weight	0.89	0.82	0.98
Duration of Radiotherapy	0.89	0.80	0.99

All analysis is performed with 33 matched sets.

Discussion

This study sought to examine if women with breast cancer and a family history of breast and ovarian cancer were more likely to develop primary ovarian cancer. The secondary objectives of this study are to examine how reproductive factors such as age of menarche and menopause and the use of hormone replacement therapy and oral contraceptives affect the risk of subsequent ovarian cancer. Treatment factors for breast cancer; radio- and chemotherapy and Tamoxifen use were also examined for their potential role in increasing the risk of subsequent ovarian cancer. The benefits in treating and preventing breast cancer are clear, but if the risk of ovarian cancer is heightened as a result, then the benefits are lost.

A phone interview, rather than a self administered questionnaire, was chosen to increase the response rate and to ensure clarification of results. In a phone interview, any questions or misinterpretations can be clarified more easily than on a self-administered questionnaire. This questionnaire has been used in other similar studies with rare problems in interpretation. Responses were then corroborated with the information presented on their medical chart. However, both interviewers were aware of the case/control status during the interviews. There is a possibility that when interviewing cases, information on family history and other variables could have been ascertained more thoroughly than in controls.

Whether to match by status, alive or proxy, was a concern. Proxy information is considered not to be as reliable as the original source. The question of whether to use living or deceased controls has been debated in journals in the past (Gordis, 1982; Greenland, 1982). The debate centres on whether to obtain the most appropriate control for a case or whether to obtain the most accurate and valid information possible. Gordis (1982) mentions that proxy respondents might provide more accurate or less accurate information depending on the context (such as information on "Bad Habits", for example). The quality of this information would worsen over time. In our study, any deceased subjects had to have died less than 5 years previous to the start of the study for inclusion. However to select dead controls for the dead cases would effectively be matching on death. This may not be warranted for a particular study. Death could actually act as a confounder in certain studies, but it is not a confounder in the sense that it could alter an exposure outcome pathway. Deceased cases and controls represent an important subgroup and may be analysed separately. Again in the commentary by Gordis (1982) there are only a few studies that have compared the validity of proxy information. The studies either asked the next of kin when they were alive or their proxy was asked questions that the investigators could corroborate, either with administrative data or had asked the case before death. These studies generally found that for non specific information, the proxies were usually correct (occupation, age etc.). However when questions were asked in detail, the quality of the information was reduced. Using matching dead controls may increase the comparability and the consistency of the controls (not always for the better) but it does not guarantee a

valid study. Deceased controls were selected where available and where they were not, live controls were used. The problem still remains of the lower quality of data, especially considering the personal nature of some of the information required (weight at age 20, age at menarche etc.) and the fact that much of it was historical. Future studies may wish to extend the time for accruing cases and controls, limiting the sample to live subjects.

Stepwise procedures were used in the logistic regression analysis due to the large number of variables that were needed to be tested. By using an automated procedure to aid in the selection of a logistic regression model, one can save time, yet be confident that a significant factor was not missed from the final model.

Findings

Most cases and controls finished at least Grade 12 (about 38% for cases and 33% for controls) and there were 10% of cases and controls had finished Grade 13. This may be due to the differences between the Ontario and Quebec school systems (Quebec has no Grade 13). Figures 3 and 4 show the distributions of weight at age 20 and current weight. For both, most women weighed between 50-59 kilograms. The proportion of women in this weight group was much higher for weight at age 20 (approximately 50% compared with 30% for current weight), suggesting that the women gained weight over time. This effect may be real or it may be due to rounding and recall bias, that is women might believe that they

weighed less in the past.

The distribution of the age at diagnosis for breast cancer is in Figure 15. This distribution appears bimodal, with peaks at 45-49 and 60-64. This is expected due to the differences in pre- and post-menopausal breast cancer.

The cumulative incidence curves showed that the relatives of women who had breast cancer at an early age are at an increased risk of breast cancer. This has been demonstrated in the literature previously (Evans and Prosser, 1992; Narod et al., 1993 and Schottenfeld and Fraumeni, 1996). This result is thought to be due to hereditary factors. This would explain why the relatives of a case with breast cancer less than 50 are more likely to develop breast cancer at an earlier age. This study found that the results were significant only when accounting for second degree relatives as opposed to just first degree. Thirty-five percent of our sample included proxy respondents and this information could be suspect. However, it is more likely that a proxy respondent would underestimate the number of second degree relatives with cancers and their person-years of risk. Therefore the true difference between the two groups could be even larger. It was surprising not to find a difference between cases and controls: one would think that women with multiple primary cancer would have more relatives with cancer than controls would. The lack of significance could be due to the quality of information asked of respondents about their relatives or to sampling error.

The main hypothesis of this study was that women with breast cancer and a family history of breast and ovarian cancer were more likely to develop ovarian cancer than women without a family history. There was an increased risk of ovarian cancer found in those with a family history, however it was not significant (OR =1.27, 95%CI 0.55-2.91). Previous studies (Shah et al, 1993; Schildkraut et al. 1995, and Easton et al. 1996) have shown an increased risk of ovarian cancer in women with a family history of breast and ovarian cancer, so it seems plausible that there would be an increased risk of ovarian cancer in women with a family history and previous breast cancer. Perhaps the number or relatives affected was not a good measure of family history of breast and ovarian cancer. Although the number of relatives with breast or ovarian cancer was not significant, having a large number of sisters decreased the risk of ovarian cancer (OR=0.53, 95%CI 0.31-0.88).

Many variables were examined to identify risk factors that could increase the risk of a woman with breast cancer developing ovarian cancer later in life. Higher education, smoking, parity and talc, all of which were reported to increase the risk of ovarian cancer (Parazzini et al., 1991 and Whittemore, 1994) were not found to be significant in this study. Some of the variables that were examined, age at menarche, weight at age 20 and age at menopause, although they approached significance, did not show a large magnitude of risk (ORs of 1.03, 0.99 and 1.03 respectively), even when dose-response relationships were examined. Perhaps another unknown factor is at work, or possibly age and age of breast cancer were too strong predictors that, when matched for, resulted in null associations. More

likely it is due to the fact that the sample size is too small, leading to large uncertainty.

There has been limited research of other malignancies after breast cancer treatment; however the outcomes examined are mostly endometrial or colon cancer and leukemia (Lavey, 1990 and Shapiro, 1994). Those that do mention ovarian cancer (Lavey, 1990) did not find a significant excess of cancer. There are a few chemotherapeutic agents that are toxic to the ovary and can impair its function (Shapiro, 1994); however, they do not appear to be carcinogenic. Many of the drugs such as cyclophosphamide, melphan and methotrexate were administered to a large proportion of the cases and controls. This study found an increased risk of chemotherapy (OR=52.7, 95%CI 1.69-1651); however, the confidence intervals were very wide and varied greatly depending on the other variables in the model. Duration of chemotherapy was not associated with any change in the risk of ovarian cancer, even when duration was stratified.

The estimated odds ratios for mastectomy, while high and significant, fluctuated greatly with the presence of any other variables. Because of this instability this variable was not selected for the final model. Duration of radiotherapy was found to be protective against subsequent cancer and was significant (OR 0.89, 95% CI 0.78-0.99). This could be due to the stage of the cancer and more aggressive treatment, as more advanced cancer requires more intensive treatment.

Usual weight was found to decrease the risk of subsequent ovarian cancer (OR=0.89, 95%CI 0.82-0.98). Vatten and Kvinnsland (1992) found that increased BMI lead to a reduction in risk for breast cancer. They hypothesized that the inverse relationship with BMI could be related to a lower rate of cell division in breast cells in obese women. It is not know if this would affect ovaries the same way.

Half of the cases were excluded from the risk factor analysis because the ovarian cancer occurred before the breast cancer. Some instances of this were expected, considering the relative rarity of ovarian cancer, however, 50% seemed high. There is a possibility that similar analyses could be performed for those who had ovarian cancer first, but age-matched ovarian cancer controls would be required. Considering the rarity of ovarian cancer, this would be very difficult and time consuming. In a study of double primary tumours, Shah et al. (1993) found that in the vast majority of breast ovarian double primary cases, the breast cancer occurred first. In their sample of 113 cases, 93 (77%) had breast cancer before ovarian cancer. In our study this would correspond to 50 cases with breast first and 15 with ovarian cancer first which was not the case. It was mentioned that ovarian metastases often occur in women with breast cancer. There is one case report where the breast was the site of metastases from a primary ovarian (Twaalhoven, 1992); however, it is doubtful that this occurred in our study.

The Breast Cancer Detection Demonstration Project (BCDDP) modeled the

risk of breast cancer by examining particular risk factors. The final model included age at menopause, number of biopsies, age at first live birth, number of mothers and sisters with breast cancer, age and the interaction terms of age by number of biopsies and age of first live birth by number of first degree relatives affected (Claus, 1994):

Log odds=0.74948+0.09401(agemen)+0.52926(nbiops)+0.21863(ageflb)+
0.95830(numrel)+0.0108(agecat)-0.28804(nbiops*agecat)-0.19081(ageflb*numrel)

It is difficult to compare our study with the BCDDP because this study did not have biopsy information or any interaction terms. Age of menopause was not found to be significant in our study and neither was age of first birth. Age was a matching variable, thus could not be analysed separately. Although we did have the number of sisters in the final model (odds ratio 0.53), this was not the number of first degree relatives with cancer, which was also not significant in this study.

The hypothesis for the analysis of Tamoxifen use reducing the interval between the breast and ovarian cancer came from a small study at Memorial Sloan-Kettering Cancer Centre in New York City (Schneider, 1995). That study did not use controls and was essentially a chart review of the hospital's medical files. Age was not controlled for in their analysis. Older women are more likely to be prescribed Tamoxifen (Narod, 1995) and older women are more susceptible to cancer (NCIC, 1997), thus age should be taken into account. Schneider (1995)

found that the interval between women with multiple primary breast and ovarian cancer was 23 months in women prescribed Tamoxifen and 120 months in women without. This study controlled for age and family history and found no difference.

There is still debate on the risk of cancer and other diseases from five to ten years of Tamoxifen use. Despite recent studies (Fisher et al., 1997; EBCTG, 1998; Powels, 1998 and Veronesi et al., 1998) there is still no consensus on whether Tamoxifen reduces the incidence of breast cancer, although based on the evidence there probably is an effect.

Strengths and Weaknesses

This study obtained cases from the Quebec Tumour registry. This cancer registry is population based, meaning all diagnosed cases are forwarded to a central location. The benefit being that there is no selection bias due to under reporting in some areas. By selecting cases from a central registry, one can be sure that no sub-population (which could have different characteristics that would alter their risk of breast and/or ovarian cancer) would be missed. This sample included women from varying ethnic groups. As mentioned above, there are certain mutations that are more common in French-Canadians and those of the Jewish faith (Tonin et al., 1998 and Gotlieb et al., 1998). By sampling from this cosmopolitan population we can again be sure that no sub-population would be overlooked. Cases and controls were asked a wide variety of questions regarding reproduction,

exogenous hormone use and treatment received in addition to family history. By analysing these factors in conjunction with family history, we can have some assurance that any effect we found was not due to confounding effects.

The use of a telephone interview could have led to observer bias. Since the interviewers (Ms. Chantal Perret and myself) knew the status of the interviewee, detailed prompting might have occurred in cases and not in controls. This would lead to an over estimation of some of the results. The use of interviewers blind to the case/control status would eliminate this potential problem. Recall bias could also be present in this study. Some of the questions, such as age of menarche and weight at age 20, occurred as much as 60 years previous in some of the women. Some women might have guessed at the answer, or unintentionally gave information that they thought we wanted to hear. Finally the use of proxy subjects could have been a problem in this study. As reported above by Gordis (1982) and Greenland (1982), proxy information is less accurate than information directly from the intended case or control.

Prevention of Cancer in Those with High Risk

With the discovery of the BRCA1 mutation, population screening is possible. However, since no cure is available, some new issues are raised. Lerman et al. (1996) examined a group of families (279 total members) in order to find out who gets tested and why. The authors found that only 60% of those who completed a

pre-test interview requested results. Women who had health insurance were more likely to request testing (odds ratio of 3.7, 95% CI 2.1-6.8). Those women that had first degree relatives with breast cancer (odds ratio of 1.6, 95%CI 1.2-2.2) and more knowledge about the mutation (odds ratio of 1.9, 95%CI 1.4-2.5) were more likely to request testing. As expected those identified as non-carriers had a reduction in stress levels. In addition, those identified as carriers did not show any increase in depression or functional impairment.

Combined with what is already known about the genetics of the breast ovarian cancer syndrome, a clinician could be in a position to help prevent the incidence of another cancer. If the clinician takes a family history of breast and ovarian cancer, and keeps a careful watch of any ovarian problems then it is possible that some of these cancers could be prevented. If a woman seems to have a strong family history of breast and/or ovarian cancer then perhaps different preventive and therapeutic interventions would be warranted. Lynch et al. (1993) recommend that women in high risk families undergo a semi-annual exam starting at age 20 and mammography beginning at age 25, every second year until 35. They also recommend bilateral mastectomy in women with a first cancer who are also members of a high risk family, especially from one where the cancers occurred at an early age. High risk women should also be given the option of bilateral oophorectomy once their families have been completed.

Since there are no clinical signs or biomarkers that can be used, other than

family history of breast and ovarian cancer as a crude estimate, Lynch et al, (1993) linked one high risk family consisting of 198 members, in order to estimate the risk of breast and ovarian cancer. The study involved asking the patient's views on a number of issues (including genetic knowledge, reasons for screening, plans for the results, planned disclosure and surveillance strategies) before and after telling them the results of the linkage. There were also follow-up interviews 3 to 6 weeks after disclosure of the results. All participants, when asked if they would go through the same process again, said yes. All of the women <45 reported that they would go for annual breast and pelvic exams compared with 50% and 0% of those >45, 94% of the younger women would tell their siblings but none would tell their children compared with 50% and 75% in the older age group. This method was well received because the information was presented before disclosure of the linkage status and allowed them to cope better after the follow-up interview.

Screening issues were also raised by Weber, Giusti and Liu (1995). Current screening methods for breast cancer include prophylactic mastectomy, increased frequency of screening and use of chemotherapeutic agents. According to the authors, the efficacy of these methods in preventing breast cancer is currently unknown. With the advent of a commercially available test in a few years, new questions will arise as to the benefits and risks of the test, and of any similar procedure. It has been speculated that after a mastectomy, prolactin levels in the blood rise and this can actually increase breast cancer risk. There are also risks associated with screening. First, the number of false positives and false negatives

with advancing age is not well known. Second, the potential risk of ionizing radiation from repeated mammography is not known, especially for long term screening in younger women. Another decision facing a high risk woman is whether to have a prophylactic mastectomy. Because of the limitations with mammography and the equivocal benefit of Tamoxifen, mastectomy may be an option. One study showed that the risk for contralateral breast cancers among women with breast cancer and the BRCA1 mutation was 85% by age 70 (Narod, 1994) . Because of this many women choose this option. Mammography has not been shown to reduce mortality in younger women, but those with a strong family history of breast and ovarian cancer have not been studied as a whole. There have been a few reports of women with a strong family history of breast and ovarian cancer having their breast cancer diagnosed through self-exam or other methods even though they were undergoing routine mammographic screening. Mammography may be more suited to screening for post menopausal breast cancer.

In an editorial on the important concerns of mastectomies, Stefanek (1995) added two points to consider. Only 44% of all physicians (the proportion in plastic surgeons was 84%) believe that mastectomies are appropriate for women with a high risk of breast cancer. All women interviewed reported satisfaction with the procedure at six months post-surgery. Finally, it should be noted that prophylactic mastectomy (lumpectomy or total mastectomy) may reduce but not eliminate the risk of breast cancer.

If a woman was been identified with a BRCA1 mutation there are various management issues for ovarian cancer that a woman and her physician should discuss. The first is oophorectomy. Once a woman has completed her family she may decide to undergo this procedure. However the optimal age for this operation has not yet been estimated. The risk of ovarian cancer would be decreased, but there is the risk of surgical menopause leading to heart disease and osteoporosis. There is also the risk of peritoneal cancer (which has identical histology to ovarian cancer); however the rate is quite low (2.8%) and it is not known whether this is a complication or a new primary (Narod, 1993). Lynch et al. (1993) state that women at risk for ovarian cancer should be offered annual pelvic exams and ultrasound starting at age 25. Screening programs for families at risk should be initiated, for example the establishment of genetic registers. Gallion and Park (1995) outline three major issues for intervention strategies that should be developed for women at risk of ovarian cancer: first, identification of high risk women; second, assessment of the effectiveness of current screening techniques; and third, recommendations for clinical trial design. Women who are first or second degree relatives of a woman with ovarian cancer of a breast-ovarian family are considered to be high risk. In terms of screening, trans-vaginal ultra sound is highly effective in detecting early stage ovarian cancer. Prophylactic oophorectomy appears to be appropriate for women with BRCA1 mutations. The authors recommend that the effects of environmental and modifiable risk factors (e.g. oral contraceptives) need to be assessed in those with BRCA1 mutations.

There are a few methods of screening for ovarian cancer although none of the methods seem appropriate. They include physical exam, CA-125 (Cancer Antigen-125), and abdominal or trans-vaginal ultrasound. Screening for ovarian cancer using CA-125 has been proposed however, this method is known to have a poor specificity and a low positive predictive value (Narod 1993). Currently the CA-125 test has a sensitivity of 78% and a specificity of 77%. In most women, an increase in CA-125 levels up to 18 months before diagnosis has occurred (Bast et al. 1994). The ultrasound methods have poor specificity, therefore the positive predictive value is low (7.7%)(Narod 1993). As with any screening test the predictive value increases when one studies a high risk group.

No information could be found about ovarian chemotherapeutic agents and toxicity to the breast tissue (there was one article dealing with melphan for ovarian cancer and subsequent leukaemia, Forbes, 1992). It has been postulated that chemotherapy causes menstrual cycle to stop, altering gonadotropin levels in the woman and increasing her risk of cancer. Obviously this mechanism would only be appropriate for pre-menopausal breast cancer.

Even if a reliable test for BRCA1 was commercially available, there are still some issues that need to be discussed. One of the most important, for patients as well as clinicians, is the risk of loss of insurance coverage. While this is not a problem in Canada, it could lead to a loss of other benefits. There is at least one case of a woman being denied insurance coverage for a prophylactic

oophorectomy, despite have been linked to the BRCA1 mutation (Lynch, 1994). This case went to the state Supreme Court before being ruled in the patient's favour. These issues must be worked out, legislatively, before widespread screening starts.

Conclusion

The main objective of this study was to examine the role of family history of breast and ovarian cancer in women with breast cancer who subsequently develop primary ovarian cancer. The results hinted at an increased risk but were inconclusive. There was an increased cumulative incidence of breast cancer in relatives of a case, if the case was diagnosed with breast cancer under age 50.

The secondary objectives of this study were to examine how other factors influence the risk of ovarian cancer in women with previous breast tumours. Reproductive factors (age of menarche and menopause, hormone replacement therapy and oral contraceptives) or treatment factors (radio- and chemotherapy and Tamoxifen use) did not conclusively alter the risk or ovarian cancer in women with previous breast cancer. There is suggestion of an increased risk with chemotherapy, however the estimate of the odds ratio was not reliable.

If a significant association is found between those factors and the development of a second primary cancer, the course of treatment of the breast cancer should be altered in order to help reduce the risk of an ovarian tumour. This knowledge may also be used to increase the frequency of screening visits for specific detection of ovarian tumours, which otherwise would be missed.

Using the figures presented earlier (5100 breast deaths and 1350 ovarian),

one could estimate that there are between 154-247 cases (2%-4% for breast cancer 5% for ovarian) in Canada per year that could be preventable.

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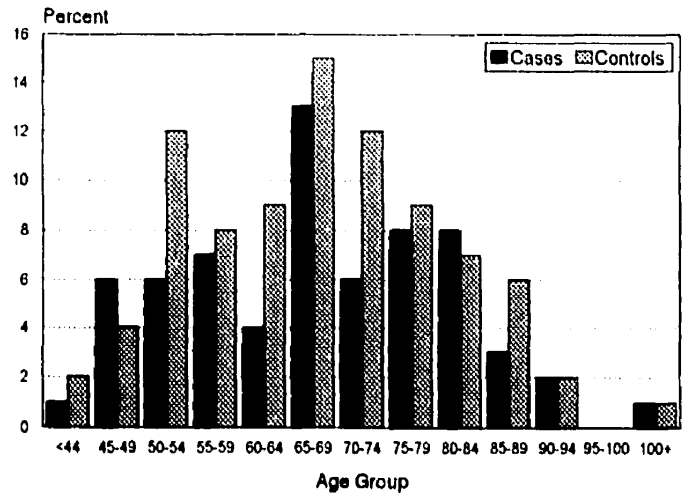

Figure 1: Distribution of Cases and Controls by Age Group

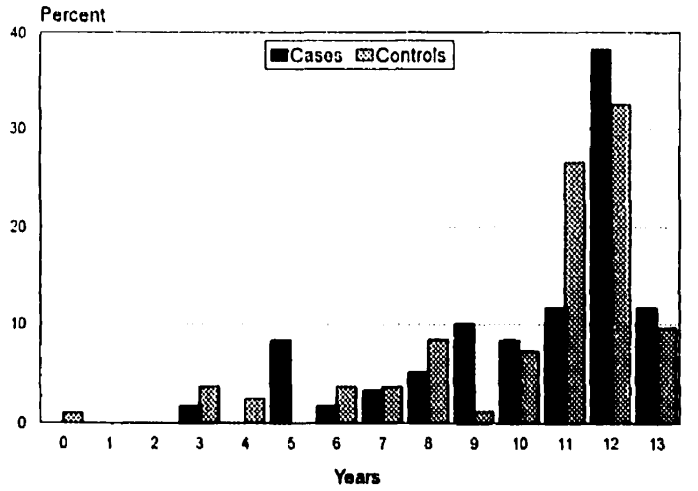

Figure 2: Total Years of School Completed

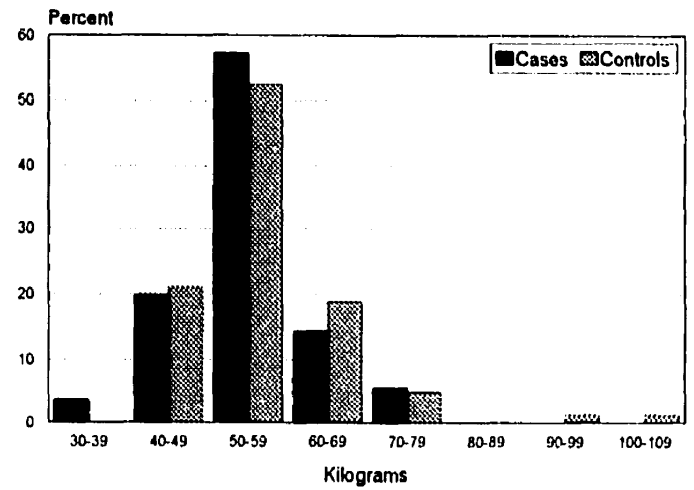

Figure 3: Weight at age 20

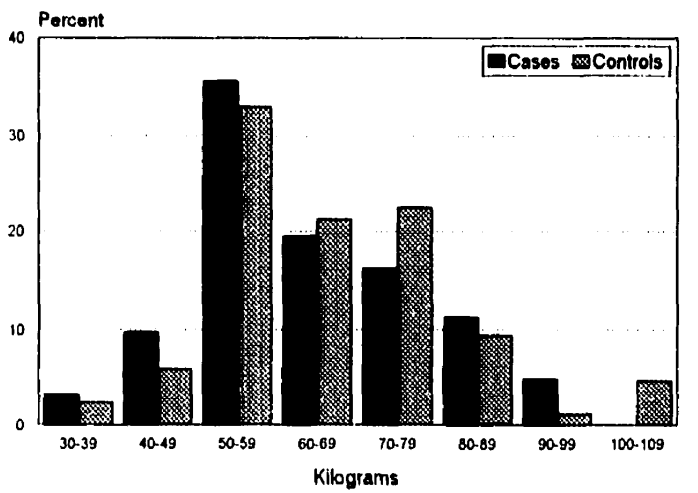

Figure 4: Current Weight

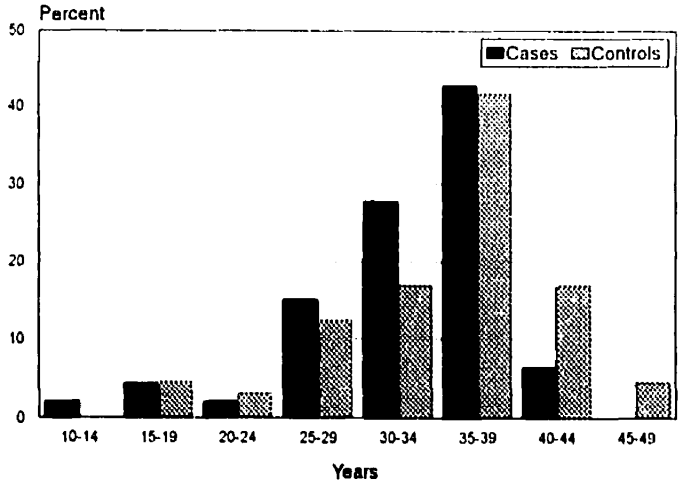

Figure 5: Total Years of Menstruation

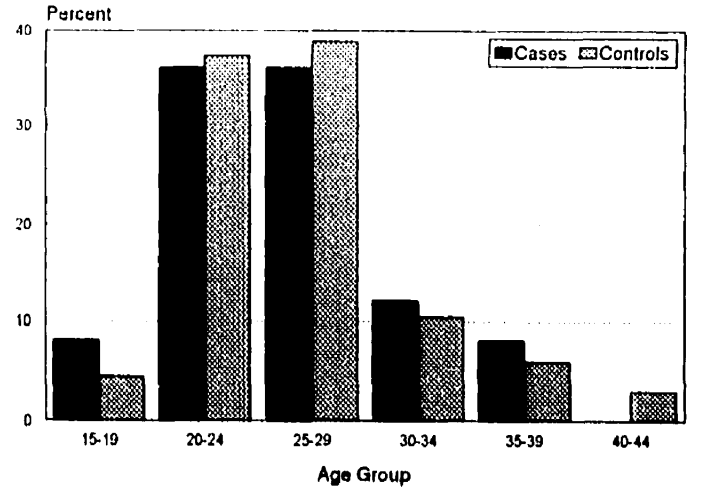

Figure 6: Age When First Child was Born

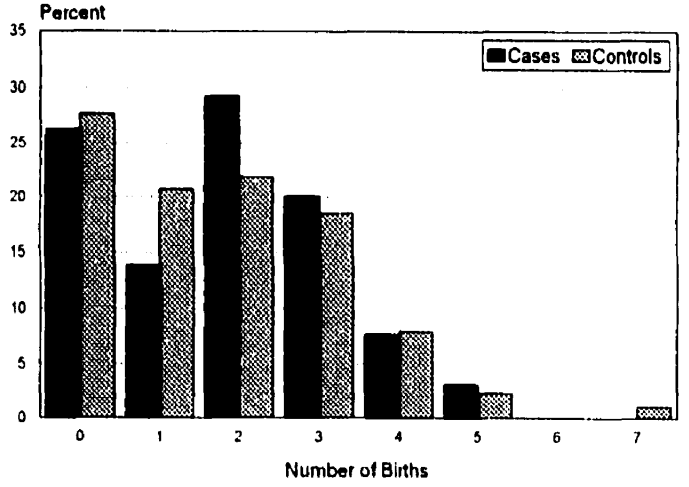

Figure 7: Number of Live Births

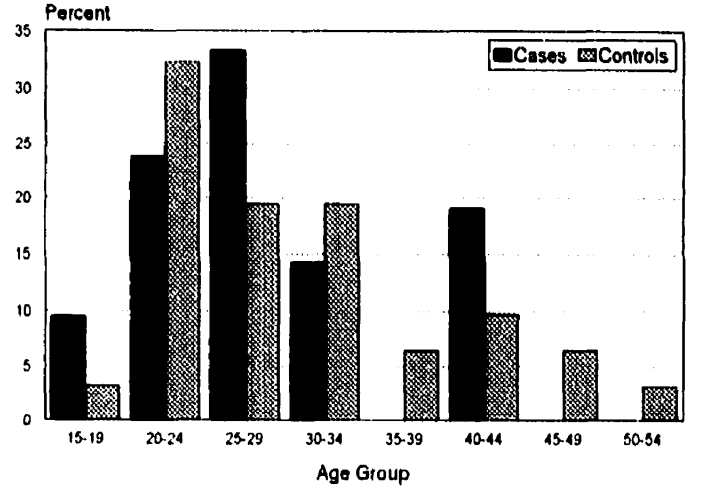

Figure 8: Age When Started Oral Contraceptive Use

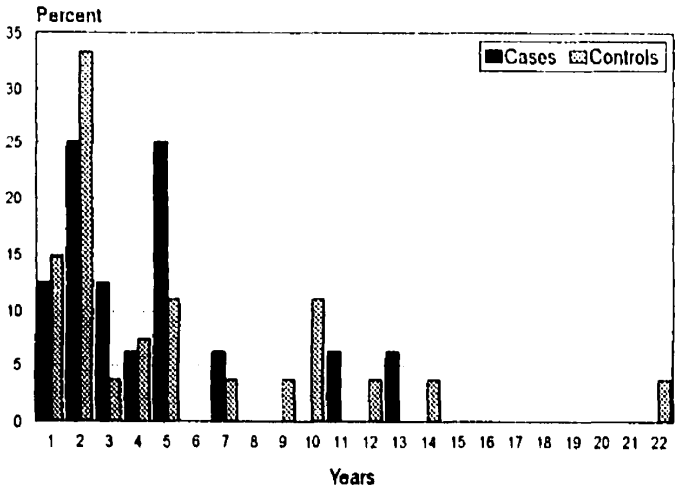

Figure 9: Duration of Oral Contraceptive Use

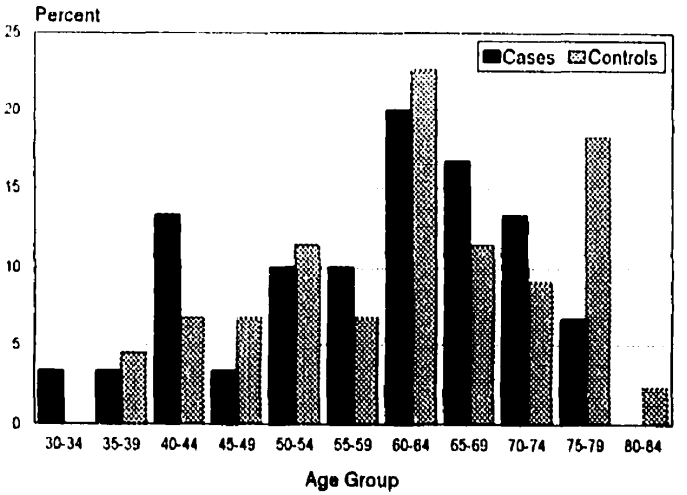

Figure 10: Age When Prescribed Tamoxifen

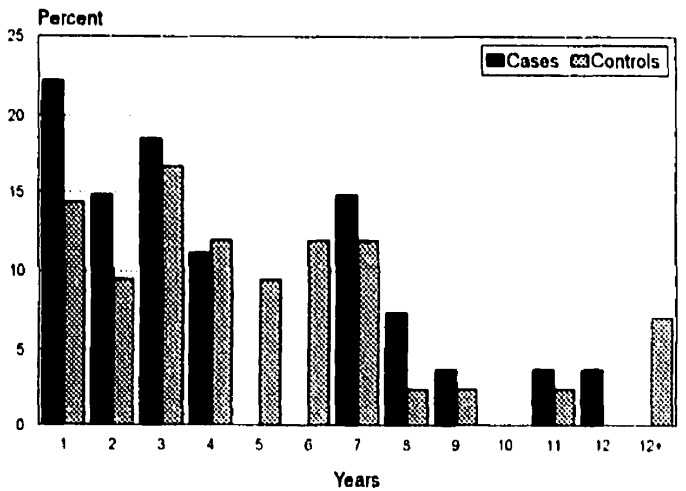

Figure 11: Duration of Tamoxifen Use

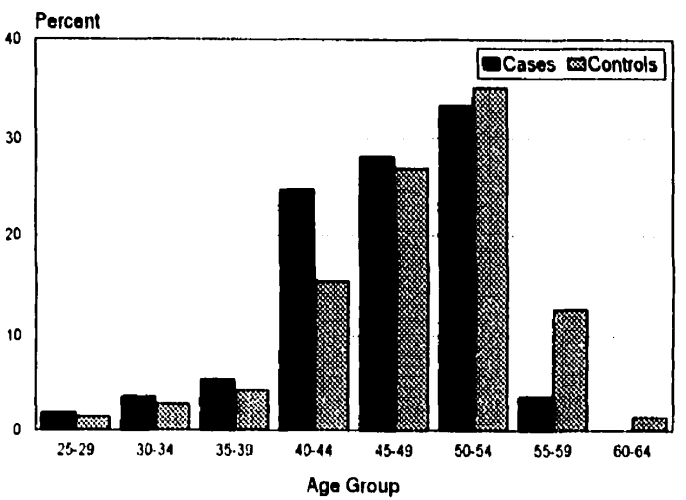

Figure 12: Age at Menopause

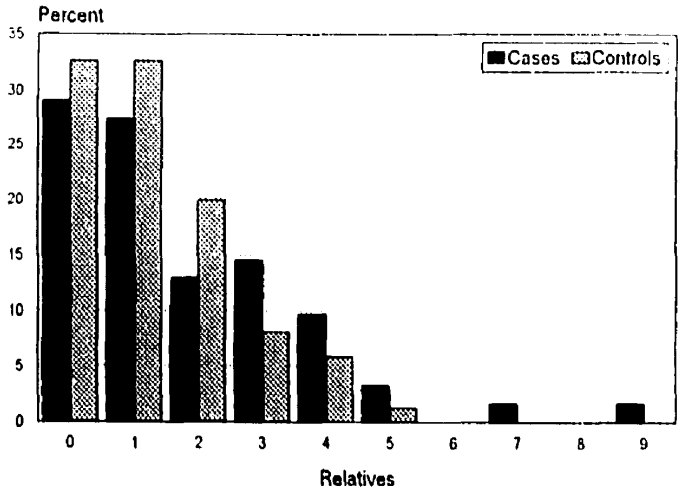

Figure 13: Number of Relatives With Cancer

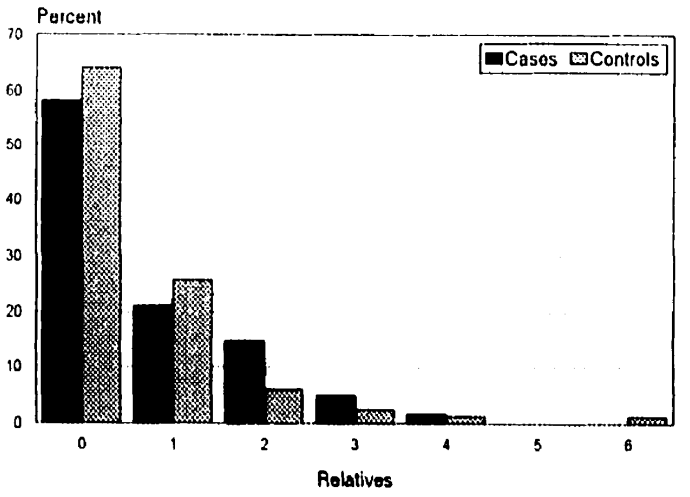

Figure 14: Number of Relatives With Breast or Ovarian Cancer

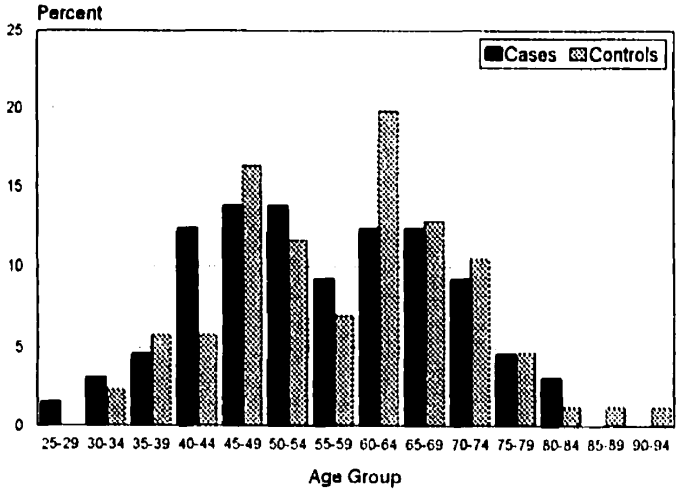

Figure 15: Age at Diagnosis of Breast Cancer

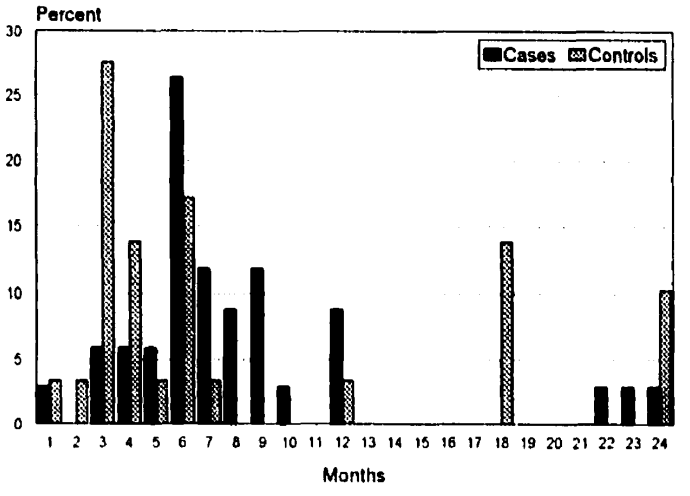

Figure 16: Duration of Chemotherapy

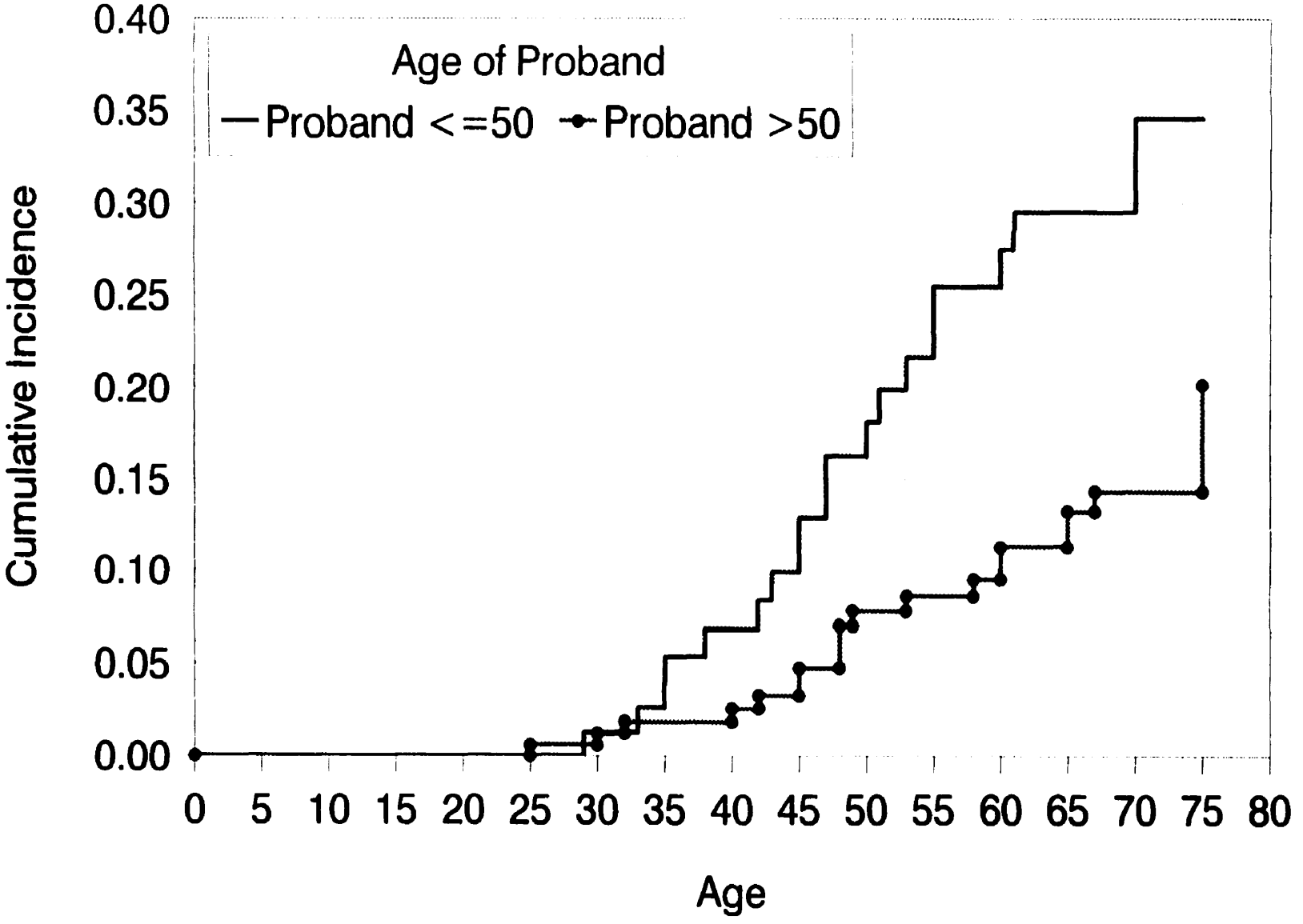

Figure 17: Cumulative Incidence of Breast Cancer in First and Second Degree Relatives - Until Age 75

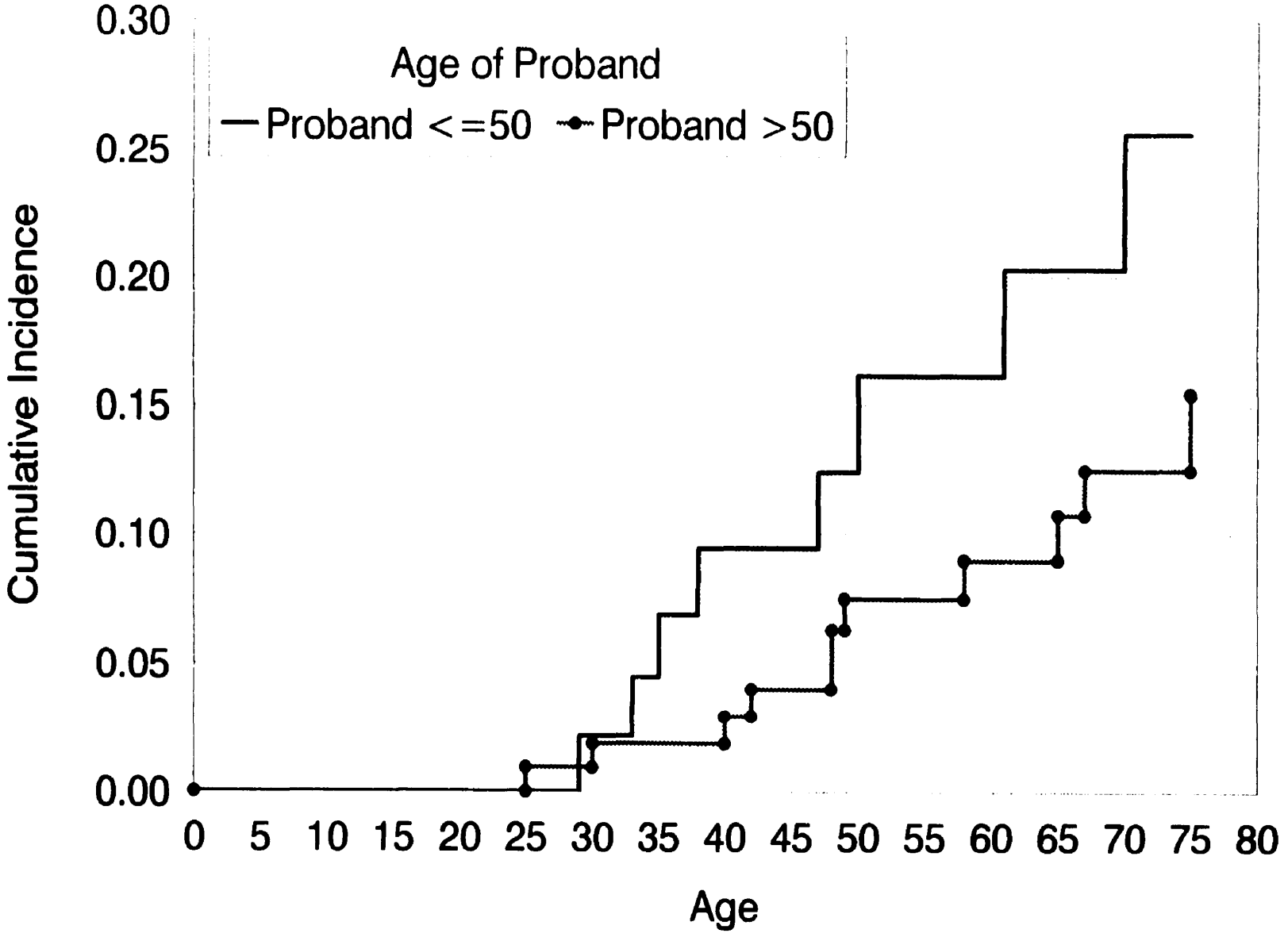

Figure 18: Cumulative Incidence of Breast Cancer in First Degree Relatives - Until 75

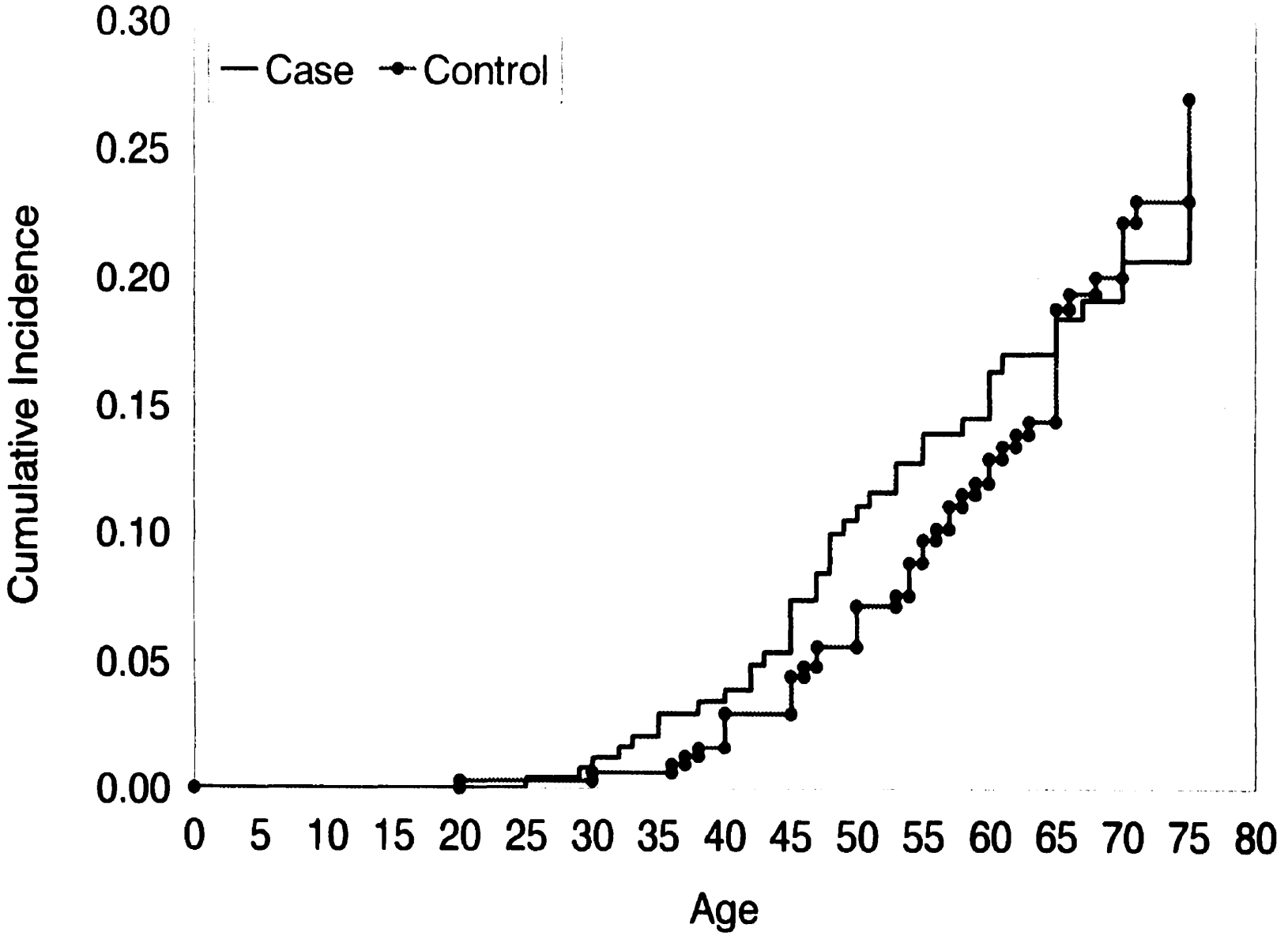

Figure 19: Cumulative Incidence of Breast Cancer of Cases and Controls in First and Second Degree Relatives - Until 75

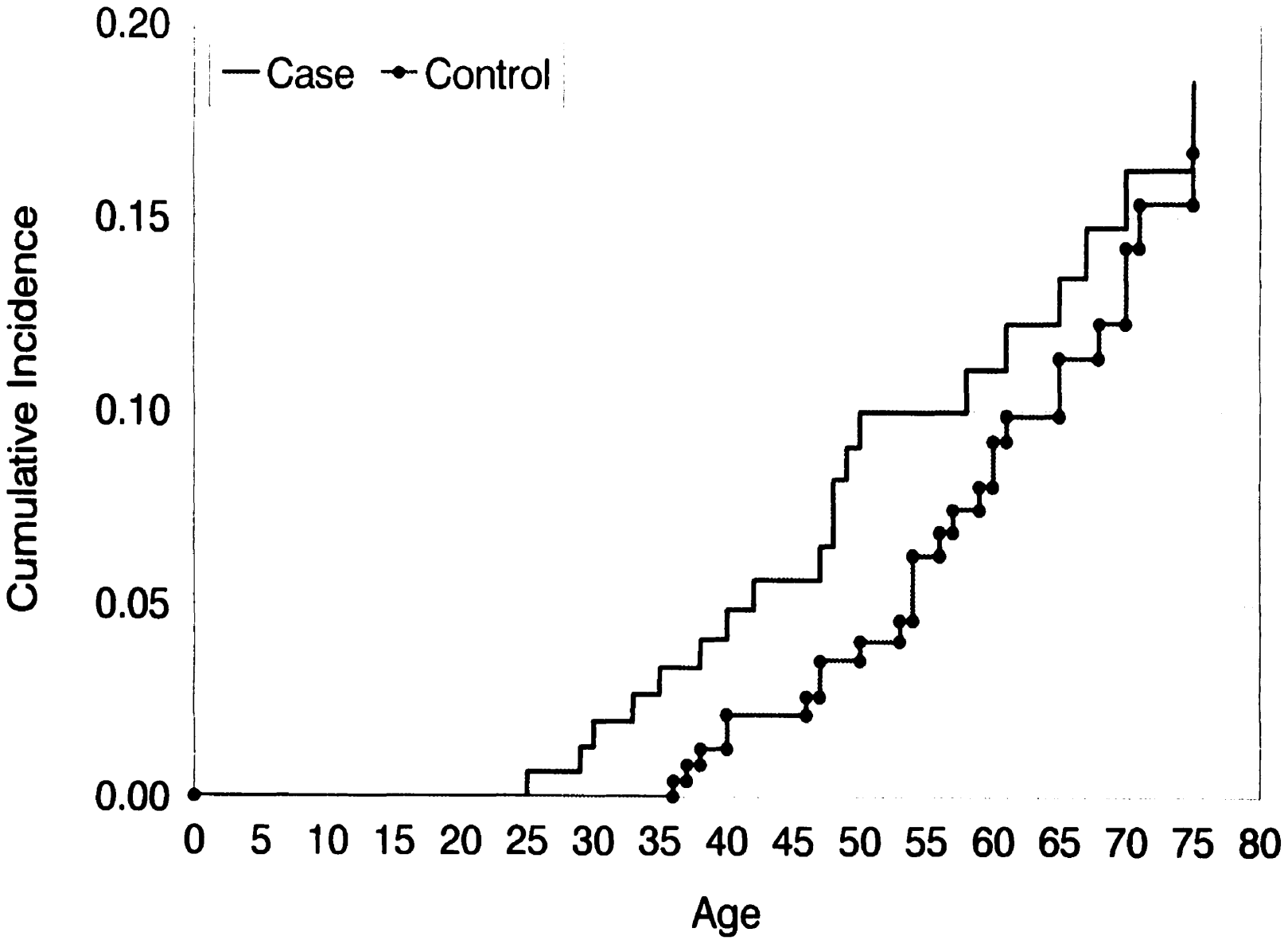

Figure 20: Cumulative Incidence of Breast Cancer of Cases and Controls in First Degree Relatives - Until 75

Appendix: Study of Multiple Primary Cancer (Breast/Ovary) and Peritoneal Cancer - Questionnaire

Epidemiology Research Unit
Research Institute
Hotel Dieu Hospital

Division of Medical Genetics
Department of Medicine
McGill University

Study of multiple primary cancer (breast/ovary) and peritoneal cancer

Questionnaire

Participating Center		⌊⌋
Category of cancer	1 : **multiple primary (breast/ovary)** 2 : **peritoneal**	⌊⌋
Family and individual number		⌊⌋⌊⌋⌊⌋ ⌊⌋⌊⌋⌊⌋ **f - ind**
Date of interview		⌊⌋⌊⌋ ⌊⌋⌊⌋ ⌊⌋⌊⌋ **DD MM YY**

Hello, my name is _____. I am calling from the epidemiology research unit of the Research Institute of Hotel Dieu Hospital of Montreal.
This questionnaire will permit us to identify the risk factors in the detection of breast and ovarian cancer with the goal of developing a prevention and diagnostic program.

|_|_|_|_| |_|_|_|
f ind

A. SOCIO-DEMOGRAPHIC CHARACTERISTICS

To begin, we have a few questions about your origins.

A.1 What is your date of birth? ____ / ____ / 19____. |_|_| |_|_| |_|_|
D - M - Y

A.2 Where were you born? _____ |_|_|_|

A.3 If other than Canada: how many years have you lived in Canada?
_____ |_|_|

A.4 What ethnic group did your paternal ancestors come from, before coming to Canada?
_____ |_|_|_|

A.5 What ethnic group did your maternal ancestors come form, before coming to Canada?
_____ |_|_|_|

A.6 Are you part of a religious group? 1: Yes
2: No (Go to B) |_|

A.7 If yes, which one? _____ |_|

B. PHYSICAL CHARACTERISTICS

B.1 How tall are you? _____ |_|_|_| |_| |_|_|
cm ft-in

B.2 How much do you currently weigh? _____ |_|_|_| |_|_|_|
kg lbs

B.3 What is your usual weight? _____ |_|_|_| |_|_|_|
kg lbs

B.4 What was your weight at: Age 20_____ |_|_|_| |_|_|_|
Age 30_____ |_|_|_| |_|_|_|
Age 40_____ |_|_|_| |_|_|_|
kg lbs

C. FERTILITY HISTORY

C.1 **Have you ever been pregnant?** **1: Yes**
2: No (Go to C.3) |_|

C.2 If yes, for each pregnancy, from the 1st to the last, tell us the date and how it ended. For each child, tell us how long you breast fed. (If you did not breast-feed, enter 0)

	Month	Year	Outcome of pregnancy: 1: live birth 2: still born or died at birth 3: miscarriage 4: abortion	Breast feeding Number of months
01				
02				
03				
04				
05				
06				
07				
08				
09				
10				

(For birth of twins: write J on the corresponding line)

C.3 At what age did you first menstruate? _____ |_|_|

C.4 Has you menstruation stopped? **1: Yes**
2: No (Go to D) |_|

C.5 If yes, what age did your menstruation stop? _____ |_|_|

C.6 Did they stop: **1: naturally**
2: surgically
3: by chemotherapy
4: other _____ |_|

D. MEDICATIONS

D.1 For Infertility

D.1.1 Have you ever taken medication (pills or injections) to increase your chances of becoming pregnant?

1: Yes
2: No (Go to D.2) |_|

D.1.2 If yes, for each cycle of treatment, tell us the name of the medication, what age you began taking it, and for how many months you took it.

	Medication	code	Age started	Duration (months)
01				
02				
03				
04				

D.2 For Birth Control

D.2.1 Have you ever taken oral contraceptives? 1: Yes
2: No (go to D.3) |_|

D.2.2 If yes, tell us from what age to what age (without omiting breaks).

01	From age	_____	to Age	_____
02	From age	_____	to Age	_____
03	From age	_____	to Age	_____
04	From age	_____	to Age	_____

D.2.3 Are you currently taking oral contraceptives? 1: yes
2: no |_|

D.3 For Menopause

D.3.1 Have you ever taken hormone replacement therapy for menopause as pills, injections or as a patch? (exclude vaginal cremes)

1: Yes
2: No (Go to E) |_|

D.3.2 If yes, tell us the name of the hormone and what age you began and stopped taking the drug.

	Hormone	code	from age	to age
01				
02				
03				
04				

D.3.3 Are you currently taking hormones? 1: Yes
2: No |_|

E. SURGICAL HISTORY

E.1 Breast

E.1.1 Have you ever been operated on your breast(s)? 1: Yes
2: No |_|

E.1.2 If yes, was it for breast cancer? 1: Yes
2: No |_|

E.1.3 Do you have one or two breasts affected? _____ |_|

E.1.4 For each breast effected, tell us the year of the operation, and what type of surgery you had (lumpectomy or mastectomy)?

	Year	Surgery	code: 1=lumpectomy 2=mastectomy
1st breast	19|_|_|		|_|
2nd breast	19|_|_|		|_|

E.1.5 Have you ever had radiotherapy on your breast?

1: Yes
2: No (Go to E.1.8) |_|

E.1.6 If yes, in what year? (Indicate the month, if possible)_____/19____. |_|_|/|_|_|
M - Y

E.1.7 What was the duration of the treatment? (number of days or of treatments)
_____ |_|_|

f ind

E.1.8 Have you had radiotherapy of other organs?
1: Yes
2: No (Go to E.1.10) ⌊⌋

E.1.9 If yes, indicate the areas_____ ⌊⌋

E.1.10 Have you ever received chemotherapy (excluding tamoxifen)?
1: Yes
2: No (Go to E.1.12) ⌊⌋

E.1.11 If yes, for each series of treatments, tell us the following:

	Name of medication(s)	Year began	Duration in months
01		19⌊⌋⌊⌋	⌊⌋⌊⌋
02		19⌊⌋⌊⌋	⌊⌋⌊⌋
03		19⌊⌋⌊⌋	⌊⌋⌊⌋
04		19⌊⌋⌊⌋	⌊⌋⌊⌋

E.1.12 Have you ever taken Tamoxifen? 1: Yes
2: No (Go to E.2) ⌊⌋

E.1.13 What year did you begin taking tamoxifen? (indicate the month if possible)
_____/19____. ⌊⌋⌊⌋⌊⌋⌊⌋
M - Y

E.2 Ovary

E.2.1 Have you ever had surgery on your ovaries? 1: Yes
2: No (Go to E.2.3) ⌊⌋

E.2.2 If yes, tell us the reason(s), year of surgery, and if the ovary (in part or the entire ovary) was removed.

	Reason	code	Year	Ovary removed 1: in part 2: whole
1st ovary:		⌊⌋⌊⌋⌊⌋⌊⌋	19⌊⌋⌊⌋	⌊⌋⌊⌋
		⌊⌋⌊⌋⌊⌋⌊⌋	19⌊⌋⌊⌋	⌊⌋⌊⌋
2nd ovary:		⌊⌋⌊⌋⌊⌋⌊⌋	19⌊⌋⌊⌋	⌊⌋⌊⌋
		⌊⌋⌊⌋⌊⌋⌊⌋	19⌊⌋⌊⌋	⌊⌋⌊⌋

E.2.3 Have you ever had surgery on any other reproductive organs: fallopian tubes, uterus, cervix, including tubal ligation. 1: Yes
2: No (Go to E.3) ⌊⌋

/6

E.2.4 If yes, what operation did you have, what was the reason and the year?

	Surgery or organ and reason	code	year
01		||| ||||	19|||
02		||| ||||	19|||
03		||| ||||	19|||
04		||| ||||	19|||

E.3 Other Abdominal Surgery

E.3.1 Have you ever had any abdominal surgery, such as a cholecystectomy, appendectomy, etc.

1: Yes
2: No (Go to F) |_|

E.3.2 If yes, for each operation, tell us the type of surgery and the year it was performed.

	Surgery or organ	code	year
01		|||	19|||
02		|||	19|||
03		|||	19|||
04		|||	19|||

F. OTHER ILLNESSES

F.1. Please describe briefly any other medical problems that have not yet been mentioned, especially those which required hospitalization.

	Medical Problem	code	year
01		||||	19|||
02		||||	19|||
03		||||	19|||
04		||||	19|||

G. EXPOSURE TO CERTAIN PRODUCTS

G.1 Talc

G.1.1 Have you ever been a regular user of talcum powder?
1: Yes
2: No (Go to G.2) |_|

G.1.2 If yes, did you apply it directly to the vaginal area?
1: Yes
2: No |_|

G.1.3 Do you use it on sanitary napkins or tampons?
1: Yes
2: No |_|

G.1.4 Do you use it for other purposes? 1:Yes
2: No |_|

G.1.5 If yes, describe:_____ |_|_|

G.2. Tobacco

G.2.1 Have you ever been a regular cigarette smoker? 1: Yes
2: No (Go to H) |_|

G.2.2 If yes, at what age did you begin to smoke regularly? _____ |_|_|

G.2.3 Do you currently smoke? 1: Yes (Go to G.2.5)
2: No |_|

G.2.4 If no, at what age did you stop? _____ |_|_|

G.2.5 On average, how many packs did/do you smoke per week? _____ |_|_| packs

H. OCCUPATIONAL HISTORY

H.1 How many years of primary and secondary school have you completed? _____ |_|_|

H.2 Do you have a diploma from a trade school or did you continue your post-secondary studies?
1: Yes
2: No (Go to H.4) |_|

H.3 If yes, describe: _____ duration: _____ |_|_|
_____ _____ |_|_|

H.4 Have you ever been employed?
1: Yes
2: No (Go to J) |_|

H.5 If yes, for each type of employment, can you tell me the nature of the product that the company produced, and the years that you held the job. Describe them from the most recent to the earliest.

	Job (detailed description)	code	years began		ended
01		| | |	19| | |	to	19| | |
02		| | |	19| | |	to	19| | |
03		| | |	19| | |	to	19| | |
04		| | |	19| | |	to	19| | |

J. FAMILY HISTORY

J.1 In total, how many brothers and half-brothers do you have (living and deceased)? _____ |_|_|

J.2 In total, how many sisters and half-sisters do you have (living and deceased)? _____ |_|_|

J.3 For each of your sisters and half-sisters, tell me their current age or their age and cause of death.

		code 1: living 2: deceased	current age or age of death	cause of death
01		||	|||	
02		||	|||	
03		||	|||	
04		||	|||	
05		||	|||	
06		||	|||	
07		||	|||	
08		||	|||	
09		||	|||	
10		||	|||	

J.4 With regards to your biological parents and first degree relatives, father, mother, brothers, sisters, half-brothers, half-sisters, sons, daughters, are there any that have suffered from cancer?

1: Yes
2: No (Go to J.5) |_|

J.5 If yes, for each of them, tell me their relationship, site of cancer and age of diagnosis.

1: father
2: mother
3: brother
4: sister
5: half-brother
6: half-sister
7: son
8: daughter

* to complete only if an individual has had multiples cancers
A: 1st cancer, B: 2nd cancer, C: etc

	Relationship	code	*	Site of cancer	code	age of diagnosis
01		||	||		||||	|||
02		||	||		||||	|||
03		||	||		||||	|||
04		||	||		||||	|||
05		||	||		||||	|||
06		||	||		||||	|||
07		||	||		||||	|||
08		||	||		||||	|||
09		||	||		||||	|||
10		||	||		||||	|||

f ind

J.6 How many maternal aunts (sisters of you mother) do you have? (living and deceased) _____ |_|

J.7 How many paternal aunts (sisters of your father) do you have? (living and deceased) _____ |_|

J.8 Concerning more distant biological relatives, grandmother, aunts, cousins, paternal or maternal, and nieces, are there any that suffer from breast or ovarian cancer?
1: Yes
2: No (end of interview) |_|

J.9 If yes, for each person, tell me their relationship, if the individual suffered from breast or ovarian cancer, and their age of diagnosis.

11: maternal grand-mother	12: paternal grand-father	19: grandmother (unknown side)
21: maternal aunt	22: paternal aunt	29: aunt
31: maternal cousin	32: paternal cousin	39: cousin
40: niece		

			Type of cancer			
	Relationship	code	Breast 1: Yes 2: No	age at diagnosis	Ovary 1: Yes 2: No	age at diagnosis
01		|||	||	|||	||	|||
02		|||	||	|||	||	|||
03		|||	||	|||	||	|||
04		|||	||	|||	||	|||
05		|||	||	|||	||	|||
06		|||	||	|||	||	|||
07		|||	||	|||	||	|||
08		|||	||	|||	||	|||
09		|||	||	|||	||	|||
10		|||	||	|||	||	|||

END OF INTERVIEW

Thank you for your participation

K. EVALUATION OF INTERVIEW

K.1	Interview done by:	1: telephone 2: in person	|_|
K.2.	Interview done with the patient?	1: Yes 2: No	|_|
K.3	If no, relationship of respondent:	1: sister 2: daughter 3: mother 4: spouse 5: other _____	|_|
K.4	Collaboration of respondent:	1: very good 2: good 3: average 4: poor 5: very poor	|_|
K.5	Credibility of the information:	1: very good 2: good 3: average 4: poor 5: very poor	|_|
K.6	Name of interviewer: _____		|_|_|