The Impact of Prophylactic Salpingo-oophorectomy on Health in Women who carry a *BRCA1* or *BRCA2* Mutation

by

Amy Philippa Mary Finch

A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy

Institute of Medical Science
University of Toronto

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Abstract

Prophylactic salpingo-oophorectomy, the preventive removal of the ovaries and fallopian tubes, is recommended to women who carry a *BRCA1* or *BRCA2* mutation in order to reduce the risk of breast, ovarian and fallopian tube cancer. The short and long term health and quality of life effects of this procedure are not well understood. We examined the actual and perceived reduction in cancer risk associated with this surgery. The impact of prophylactic salpingo-oophorectomy on health-related quality of life, psychological distress, cancer worry, menopausal symptoms, and sexual function during the year following surgery was also evaluated. In our prospective study, prophylactic salpingo-oophorectomy was associated with an 80% reduction in ovarian and fallopian tube cancer risk. The residual risk for primary peritoneal cancer was 0.2% per year or 4.3% at 20 years after salpingo-oophorectomy. Most women accurately perceived their risk of breast cancer. However, the risk for ovarian cancer was overestimated, particularly by women who carry a *BRCA2* mutation. Physical and mental health-related quality of life did not decrease in the year following surgery; and psychological distress was similar to levels experienced by the general population. Most women were significantly less worried about cancer after the surgery, however, a subset of women continued to experience significant cancer specific distress after prophylactic salpingo-oophorectomy. Women who underwent prophylactic salpingo-oophorectomy when premenopausal experienced a significant worsening of vasomotor symptoms and a decline in sexual functioning. Hormone replacement therapy mitigated these symptoms, but not to pre-surgical levels. Dyspareunia was somewhat alleviated by hormone replacement therapy, however, the decrease in sexual pleasure was not. Satisfaction with the decision to undergo prophylactic salpingo-oophorectomy was high regardless of these symptoms. These studies will provide women who are considering prophylactic salpingo-oophorectomy with information about the reduction in cancer risk associated with the surgery and the possible effects experienced during the year following surgery.
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Original Contributions

This doctoral thesis is the work of the author, Amy Finch and various collaborators. An analysis of outcomes was performed on two cohorts of interest.

The study “The Impact of Salpingo-oophorectomy on the Risk of Ovarian, Fallopian and Peritoneal Cancers in Women with a BRCA1 or BRCA2 Mutation” was conceived by Dr. Steven Narod and was the result of an international collaboration with the Hereditary Ovarian Cancer Clinical Study Group. Subjects for the study were recruited at 32 centres in Canada, the United States, Europe, Norway and Israel. Collaborators at each centre recruited participants and completed follow-up questionnaires with the assistance of the main study centre. Data for all subjects were amalgamated at the main study centre by Nicole Phillips, Anna Tulman and the team at the Familial Breast Cancer Research Unit. The author was responsible for confirming all incident cancer cases, and was involved in the analysis of the data in conjunction with Dr. Ping Sun. The author was responsible for writing the manuscript with the assistance of Dr. Mario Beiner and Dr. Steven Narod.

The studies “Breast and Ovarian Cancer Risk Perception after Prophylactic Salpingo-oophorectomy due to an inherited Mutation in the BRCA1 or BRCA2 Gene”, “The Impact of salpingo-oophorectomy on Quality of Life and Psychological Distress in Women with a BRCA Mutation” and “The Impact of Prophylactic Salpingo-oophorectomy on Menopausal Symptoms and Sexual Function in Women who Carry a BRCA Mutation” were conducted through the recruitment of study participants at a single centre in Toronto, The University Health Network. The author was responsible for the execution of the studies in their entirety. The study concept was conceived by Dr. Steven Narod. Dr. Barry Rosen and Dr. Joan Murphy also assisted with design of the study, assisted with patient recruitment and performed the surgeries for the women in these studies. Caitlin Springate and Rochelle Demsky also assisted with patient recruitment. The author created an Access database, and data was entered by Jaclyn Chiang. The author performed all data analysis with the guidance of statisticians Dr. Ping Sun and Charles Victor, and wrote all three manuscripts.
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Breast and ovarian cancer risk perception after prophylactic salpingo-oophorectomy due to an inherited mutation in the \textit{BRCA1} or \textit{BRCA2} gene. Clinical Genetics 75, 220-4 (2009)

1 CHAPTER ONE

1.1 Introduction

In order for prophylactic salpingo-oophorectomy, the preventive removal of the fallopian tubes and ovaries, to reduce the burden of ovarian and fallopian tube cancer in women with a \textit{BRCA1} or \textit{BRCA2} mutation, it has to be viewed as an acceptable option by both clinicians and women who carry a mutation. In studies of the preventive choices made by women who carry a \textit{BRCA1} or \textit{BRCA2} mutation, approximately 60% of women between the ages of 35 and 70 elected to undergo prophylactic salpingo-oophorectomy.[1],[2]

While the majority of women facing this surgical decision elect to proceed, a substantial proportion of women who know their \textit{BRCA} mutation status remain at high risk for gynecologic cancer. It is unlikely that the number of women electing salpingo-oophorectomy will increase until the effectiveness of the surgery is more widely understood. In addition, women at high risk for cancer may feel more prepared to undergo the procedure when the possible implications of surgery on all aspects of their health and quality of life are also better understood. There is a paucity of literature available to women who are making the decision to undergo prophylactic salpingo-oophorectomy. In this thesis, the impact of this surgery on many aspects of health and quality of life are investigated including the actual and perceived cancer risk reduction afforded by salpingo-oophorectomy. Changes in health-related quality of life, worry about cancer, general psychological distress, menopausal symptoms, and sexual functioning experienced during the year following surgery are examined. This information will allow women to make informed calculated decisions when managing their elevated cancer risk. It is hoped that, as more women who carry a \textit{BRCA1} or \textit{BRCA2} mutation proceed to prophylactic surgery, the burden of ovarian and fallopian tube cancer will be reduced.
This thesis is presented in eight chapters. The first three chapters include the introduction, a review of the literature, the objectives, the hypotheses and the conceptual framework for the research studies presented in this thesis. Chapters four, five, six and seven are comprised of four research studies investigating the impact of salpingo-oophorectomy on health and quality of life in women who carry a $BRCA1$ or $BRCA2$ mutation. Chapter eight includes the discussion highlighting the overall findings, limitations, conclusions and future directions.
2 CHAPTER TWO

Review of the Literature

2.1 Epidemiology of Ovarian and Fallopian Tube Cancer

Approximately 200,000 women are diagnosed with ovarian cancer around the world every year and 125,000 die of the disease. [3, 4] In Canada alone, 2500 cases of ovarian cancer are diagnosed each year, of whom roughly 1400 will die.[5] Although ovarian cancer accounts for roughly three percent of new cancer diagnoses, it is the fifth leading cause of all cancer-related deaths in women.[6] It is estimated that between one in fifty-five and one in seventy North American women will develop ovarian cancer in her lifetime.[7, 8]

Surface epithelial ovarian tumours are the most common neoplasms of the ovary and originate from the ovarian surface epithelium or its derivatives. These tumours have been classified based on histological subtypes which exhibit different biological behavior. The most common type is serous accounting for up to 60% of ovarian cancers.[9] The other subtypes are: mucinous, endometrioid, clear cell, transitional cell, undifferentiated and mixed epithelial.[9]

Known genetic predisposition syndromes account for approximately 14% of unselected ovarian cancers in the general population. These are predominantly due to an inherited mutation in the \textit{BRCA1} or \textit{BRCA2} genes (13%), and a smaller proportion are due to mutations in the mismatch repair genes (\textit{MLH1}, \textit{MSH2}) (~1%).[10, 11] The frequency of germline mutations in the mismatch repair genes \textit{MSH6} and \textit{PMS2} among women with ovarian cancer has not been determined.

Fallopian tube cancer, as currently defined, is much less common than ovarian cancer and accounts for less than 1% of cancers in women.[12, 13] Risk factors for fallopian tube cancer appear to be similar to those of epithelial ovarian cancer and they also share the
same histological subtypes, with serous as the predominant type for both.\cite{9,14} Because tumours of the ovary and fallopian tube are histologically indistinguishable, tumours must be located within the tube or its fimbriated end and the ovary and uterus must not contain carcinoma, unless clearly different from the fallopian tube lesion, in order to be considered primary fallopian tube cancer.\cite{9} This likely contributes to the rarity of this diagnosis.

Fallopian tube cancer has a strong genetic component, with up to 26.4% of unselected fallopian tube cancers due to inherited mutations in the \textit{BRCA}1 or \textit{BRCA}2 genes, compared with 13% for unselected ovarian cancer.\cite{10,15} There are case reports of fallopian tube cancers in women with Hereditary Non-Polyposis Colon Cancer syndrome, however, the rate of inherited mutations in related genes has not been reported in the literature.\cite{16}

### 2.2 \textit{BRCA}1 and \textit{BRCA}2: Molecular Genetics

Breast and ovarian cancer were recognized in the literature as clustering in some families more than 100 years ago.\cite{17} The majority of large families with multiple cases of breast and ovarian cancer can now be attributed to the \textit{BRCA}1 or \textit{BRCA}2 genes which were discovered in 1994 and 1995.\cite{18-22}

\textit{BRCA}1 is a tumour suppressor gene located on chromosome 17q21 and is composed of 22 coding exons and encodes a protein of 1863 amino acids.\cite{23} \textit{BRCA}1 interacts with several proteins involved in cellular pathways, including cell cycle progression, gene transcription regulation, DNA damage response, apoptosis and ubiquitylation.\cite{24-26}

\textit{BRCA}2, also a tumour suppressor gene, is located on chromosome 13q12 and is composed of 27 exons and encodes a protein of 3,418 amino acids.\cite{27} \textit{BRCA}2 is involved in DNA repair through homologous recombination, chromatin remodeling and cell cycle checkpoint control.\cite{28}
A study conducted in 1998 by the Breast Cancer Linkage Consortium found that among 237 families with at least four cases of breast cancer, regardless of cases of ovarian cancer, 52% were linked to \textit{BRCA1}, 32% were linked to \textit{BRCA2} and 16% were linked to neither gene, which suggests that other genes may be involved.[29] In this study, 81% of the families with breast and ovarian cancer were due to \textit{BRCA1} and 14% were due to \textit{BRCA2}. The majority of families with male breast cancer were linked to \textit{BRCA2} (76%).

\textit{BRCA1} and \textit{BRCA2} are inherited in an autosomal dominant manner. General population carrier frequencies have been estimated to be as high as 0.32% for \textit{BRCA1} and 0.69% for \textit{BRCA2}, based on a large population study conducted in Ontario, Canada.[10]

In well defined populations based on ethnicity, founder mutations in the \textit{BRCA1} and \textit{BRCA2} genes have been found to account for a higher proportion of breast and ovarian cancer than in the general population.[30] Examples of this include the three founder mutations in populations of Ashkenazi Jewish descent (\textit{BRCA1} (185 delAG, 5382insC) and \textit{BRCA2} (6174delT)), two in the French Canadian population (\textit{BRCA1} C4446T and \textit{BRCA2} 8765delAG), three in the Polish population (\textit{BRCA1} 5382insC, C61G, and 4153delA), one in the Icelandic population (\textit{BRCA2} 995del5) and more recently six founder mutations in the Bahamian population. [30-35]

The founder mutations in \textit{BRCA1} and \textit{BRCA2} in the Ashkenazi Jewish population are well studied. The combined frequency of mutations in \textit{BRCA1} (185 delAG, 5382insC) and \textit{BRCA2} (6174delT) exceeds 2%.[36-38] Approximately 40% of Ashkenazi Jewish women with ovarian cancer and 11% of Ashkenazi Jewish women with breast cancer carry one of the founder mutations in \textit{BRCA1} or \textit{BRCA2} compared with 13% and <5% in the general population.[10, 39, 40]
2.3 Risks for Cancer in Women and Men who carry a 

BRCA1 or BRCA2 Mutation

The penetrance of a BRCA1 or BRCA2 mutation is the likelihood of developing cancer when a deleterious mutation is present. The penetrance of BRCA1 and BRCA2 appears to be variable given that different families with the same mutation have different cancer risks.[41] Some individuals who carry a BRCA mutation do not develop cancer, and the age of diagnosis and type of cancer are variable in those who do develop cancer.

Earlier studies estimated cancer risk associated with BRCA1 and BRCA2 mutations in families with multiple members diagnosed with cancer at young ages.[42]. As the number of affected family members will influence whether or not they will attend a familial cancer clinic, these studies were likely subject to ascertainment bias.[28]

In 1993, Easton et al. with the Breast Cancer Linkage Consortium published the first study to look at penetrance in 214 families who were participants in linkage studies to localize BRCA1. Prior to identification of the gene they estimated penetrance of 76-82% by age 70.[43]

Ford et al. published another study estimating the risks for cancer among BRCA1 carriers.[44] They selected 33 families with evidence of linkage to BRCA1 and estimated the risks of breast and ovarian cancer from the occurrence of second cancers in individuals with breast cancer. Twenty-six contralateral breast cancers and 23 primary ovarian cancers led to a breast cancer risk estimate of 87% to age 70 and an ovarian cancer risk estimate of 44% to age 70. Significant excesses of colon and prostate cancer were observed in these families.

A similar study published in 2002 also conducted by Thompson et al. and the Breast Cancer Linkage Consortium examined incidence of cancers other than breast and ovarian cancer in BRCA1 carriers.[45] It was a cohort study comparing observed incidence of cancer with expected incidence (in the general population) in more than 11,000 individuals from 699 families with a BRCA1 mutation. They found an increased risk for
pancreatic, uterine, and cervical cancer and prostate cancer in men under age 65. Overall, risks for other cancers were elevated in women but not significantly in men.[45]

The penetrance of \textit{BRCA2} was estimated by the Breast Cancer Linkage Consortium in 237 families in 1998.[29] The penetrance was 84% by age 70 for breast cancer, similar to observations for \textit{BRCA1}, and 27% by age 70 for ovarian cancer, somewhat lower than observed for \textit{BRCA1}. Further study of families with a \textit{BRCA2} mutation provided evidence for genotype-phenotype correlations in \textit{BRCA2}.[46] Mutations in the central portion of the gene bounded by nucleotides 3059-4075 and 6503-6629 termed the ‘Ovarian Cancer Cluster Region’ or ‘OCCR’ were associated with a significantly higher risk of ovarian cancer (RR=1.99, 95% CI=1.08-3.33, p=0.026) and a lower risk of breast cancer (RR=0.63, 95% CI=0.46-0.84, p=0.0012).[46]

Cancer risks other than breast and ovarian due to \textit{BRCA2} were estimated in a cohort of over 3,700 individuals from families with an identified mutation.[47] Statistically significant increases in risks were observed for prostate cancer, pancreatic cancer, gallbladder and bile duct cancer, stomach cancer and malignant melanoma. This risk for prostate cancer was shown to be higher in men under 65 than in those 65 years of age or older. Thus the cancer risks for \textit{BRCA2} are quite different from those for \textit{BRCA1}.

Fallopian tube cancer also came to be recognized as one of the cancers associated with \textit{BRCA1} and \textit{BRCA2}. Fallopian tube cancer was initially observed as part of the \textit{BRCA1} phenotype as early as 1995 and later also became recognized as part of the \textit{BRCA2} phenotype.[48-53]

Liede et al. reviewed the literature regarding cancer risks for male carriers of \textit{BRCA1} and \textit{BRCA2} mutations.[54] They reported an increased risk for breast cancer, prostate cancer, and pancreatic cancer in men with a \textit{BRCA1} or \textit{BRCA2} mutation. The risk for breast cancer and pancreatic cancer was higher in men who carried a \textit{BRCA2} mutation (7% and 2-5% respectively) than in men who carried a \textit{BRCA1} mutation (% not specified and 3-4% respectively). Increased risk for melanoma (5% lifetime risk) and ocular melanoma (% not specified) were also observed. Liede et al. reported that the literature was not consistent with regard to colon cancer risk in male \textit{BRCA} carriers.
A number of studies have estimated the risks for cancer among people of Ashkenazi Jewish descent who carry one of the founder mutations \((BRCA1\ 185\text{delAG}, \ BRCA1\ 5382\text{insC}, \text{and } BRCA2\ 6174\text{delT})\).[55-57] Struweing et al. estimated breast cancer risk to be 56% to age 70, ovarian cancer risk to be 16%, and prostate cancer risk to be 16%. No excess of colon cancer was observed.[55] King et al. estimated the lifetime risks for cancer among the relatives of Ashkenazi Jewish women with unselected primary invasive breast cancer who tested positive for one of the three Jewish founder mutations.[56] Of 1008 Ashkenazi Jewish women with invasive primary breast cancer, 104 (10.8%) carried one of the three founder mutations. Lifetime risks for breast cancer among women who carried the founder mutations were estimated to be over 80% by age 80 with no observed difference between \(BRCA1\) and \(BRCA2\) with the exception of lower risk before age 65 in women with a \(BRCA2\) mutation. Ovarian cancer risks were estimated to be 54% for \(BRCA1\) and 23% for \(BRCA2\). Ascertainment bias is likely a factor in this study as only relatives with confirmed \(BRCA1\) or \(BRCA2\) mutations were included in the risk analysis. Sib ships were omitted from the analysis if all sisters in the sib ship could not be genotyped.

Interestingly, King et al. reported that the risk of cancer increased with time. Breast cancer risk in women born before 1940 was estimated to be 24% by age 50, compared with 67% by age for 50 for those born after 1940. While this finding may have a biological basis, it is also possibly due to selection bias of families based on the ability to determine the genotype of family members born before 1940 or decreased likeliness of discussion of breast cancer among family members born before 1940.

A recent meta-analysis of \(BRCA1\) and \(BRCA2\) penetrance by Chen and Parmigiani (2007) included ten studies included both Jewish and non-Jewish populations.[58] The mean cancer risks for mutation carriers to age 70 were: breast cancer risk of 57% (95% CI, 47-66%) for \(BRCA1\), and 49% (95% CI, 40-57%) for \(BRCA2\); and ovarian cancer risk of 40% (95% CI, 35-46%) for \(BRCA1\) and 18% (95% CI, 13%-23%) for \(BRCA2\).

\(BRCA\) mutation carriers diagnosed with breast cancer remain at risk for contralateral breast cancer and ovarian cancer. The 10-year risk for contralateral breast cancer ranges
from 20-42% in \textit{BRCA} carriers compared with 5-6% in non-carrier controls.[59, 60] The 10-year risk for ovarian cancer after breast cancer is also significant at 12.7% for \textit{BRCA1} carriers and 6.8% for \textit{BRCA2} carriers.[61] \textit{BRCA} carriers with a previous diagnosis of ovarian, fallopian tube or peritoneal cancer likely remain at risk for breast cancer, however, studies have not been done to quantify this risk.

2.4 The Role of Genetic Counseling and Genetic Testing

Genetic counsellors are health professionals with specialized graduate degrees and experience in the areas of medical genetics and counseling. “Genetic counselling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease.” (National Society of Genetic Counselors, 2005) This process includes interpretation of family and medical histories, education about inheritance, genetic testing, management options, and prevention. The purpose of this counseling is also to promote informed decision making. (National Society of Genetic Counselors, 2005)

In the familial cancer clinic setting, genetic counselling is a multistep process. Patients are initially seen for risk assessment and initiation of genetic testing when indicated. A follow-up appointment is then scheduled to disclose genetic test results and review cancer risk management options. During this process, genetic counsellors gather a multi-generation family history (including ancestry, ages of family members and details of cancer diagnoses or other illnesses) and obtain pathology reports to confirm diagnoses of cancer in the family and determine histology. The genetic counsellor then estimates the likelihood of a germline mutation in the \textit{BRCA1} or \textit{BRCA2} gene taking into account ancestry, the number of males and females in the family, types of cancer and pattern of cancer diagnoses in the family, ages at diagnosis, tumour characteristics such as histology and any relevant genetic testing that has been performed in the family.

Models have been designed for use in clinical practice to estimate the likelihood of an individual carrying a mutation such as the Couch Model, Frank Model, \textit{BRCA4Pro}, the
Tyrer-Cuzick model (also known as IBIS), the Penn II Risk model and BoadiCea.[62-68] The Couch model is one of the earliest.[64] It does not distinguish between cancers diagnosed in first and second degree relatives and only estimates the likelihood of carrying a $BRCA1$ mutation. The model developed by Frank et al. estimates the likelihood of a $BRCA$ mutation based on family history of breast and ovarian cancer. [67] Limitations of this model are that it does not take into account Ashkenazi Jewish ancestry or bilaterality of breast cancer. Family history must include at least two relatives with breast cancer under age 50 or ovarian cancer.

Widely used, the $BRCA$Pro Model estimates the likelihood that an individual carries a $BRCA$ mutation using Bayes rules, given family history.[65, 66] This model includes ancestry (Ashkenazi Jewish or other) and information from first and second degree relatives if age or age at death is known. No provision is made for consanguinity, monozygotic twins or more distant relatives. The Tyrer-Cuzick, Penn II, and BoadiCea are more recent models that are available online free. Similar to $BRCA$Pro, the Tyrer-Cuzick model uses Bayes rules to determine carrier risk but for unaffected women only. The Penn II model provides a quick online assessment of both breast cancer risk and likelihood of carrying a $BRCA$ mutation, also taking into account male breast, prostate and pancreatic cancer.[63] BoadiCea is a model where susceptibility is explained by mutations in $BRCA1$ and $BRCA2$ together with a polygenic component.[68]

In the setting of familial breast and ovarian cancer, genetic counsellors interpret positive, negative and inconclusive genetic test results for $BRCA1$ and $BRCA2$ based on the a priori risk of carrying a mutation. Recommendations for management of cancer risks are outlined in accordance with estimated cancer risks given the genetic test results and all other factors. The genetic counsellor provides a detailed discussion of the options available for management of risk and provides referrals. The need for additional services, such as support and counseling, is also assessed.

Identification of families with Hereditary Non-Polyposis Colon Cancer Syndrome (HNPCC) is also an important part of the genetic counseling process in families with a history of ovarian cancer and possibly other HNPCC-related cancer such as colon,
endometrial, small bowel, hepatobiliary tract, pancreas and brain.[69] A discussion of the risks for ovarian, endometrial, colon and other cancers that are part of HNPCC, the age at which these cancer are diagnosed, and the options for risk management are integral parts of the genetic counseling process. Women with HNPCC have a lifetime risk of ovarian cancer of 10-12% with average age of diagnosis of 42.[70] The risk of endometrial cancer is 40-60%, which equals or exceeds the risk of colon cancer.[69, 71] Prophylactic salpingo-oophorectomy with total abdominal hysterectomy may also be offered to women who carry an HNPCC mutation at 35 or after childbearing is complete and has been shown to reduce the risk for both ovarian and endometrial cancer.[71] Although prophylactic surgery in women with HNPCC is not the focus of this thesis, many investigations into the impact of salpingo-oophorectomy in women who carry BRCA mutations are likely also relevant for women with HNPCC.

2.5 Management Options for Women who carry a BRCA1 or BRCA2 Mutation

2.5.1 Breast cancer risk

Breast cancer risk management for women with a BRCA mutation consists of breast screening (clinical breast exam, mammography and magnetic resonance imaging (MRI)), chemoprevention with Tamoxifen, and surgical reduction of risk with prophylactic bilateral mastectomy.[72]

Current recommendations for breast screening include clinical breast exam every 6 months beginning at age 25 or five to ten years before the earliest diagnosis in the family.[72] Annual mammography should begin at the same time. Studies have shown that MRI is more sensitive than mammography in women who carry a BRCA mutation, and it is now also part of the annual screening recommendations.[73] Breast ultrasound also plays a role in breast imaging of women who carry a BRCA mutation, particularly as
a diagnostic tool rather than for screening.[74] Breast self exam may be performed once per month, however, it has not been shown to reduce breast cancer mortality.[75]

Initial studies of Tamoxifen as a chemopreventive agent in women with a BRCA mutation showed that it reduced the risk of contralateral breast cancer mutation by 50%.[76] Tamoxifen has since been shown to reduce breast cancer risk in women with a BRCA1 or BRCA2 mutation.[77] Tamoxifen has also been shown to be effective in reducing the risk of primary breast cancer in women at high risk for the disease.[78]

Prophylactic mastectomy, the preventive removal of all breast tissue, is the most effective breast cancer prevention strategy for women with a BRCA mutation and reduces the risk for breast cancer by more than 90%.[74, 79]

Men who carry a BRCA mutation should have breast screening including monthly breast self-exam and annual clinical breast exam.[80] Mammography is an option if gynecomastia or parenchymal/glandular breast tissue is present or for suspicious findings.[81]

### 2.5.2 Ovarian and fallopian tube cancer risk

Management options for women at high risk for ovarian and fallopian tube cancer consist of screening with transvaginal ultrasound and CA125 blood test, chemoprevention through the use of oral contraceptives, and surgical reduction of risk through tubal ligation or prophylactic salpingo-oophorectomy.[82]

The current practice is to offer transvaginal ultrasound and CA125 blood test, however, there is no compelling evidence to support this. The efficacy of ovarian cancer screening with transvaginal ultrasound and CA125 blood test has been studied in women with a family history of the disease and in women who carry a BRCA1 or BRCA2 mutation. These studies have shown that the screening does detect ovarian cancer, but only at advanced stages (III-IV) when survival rates for the disease are very low.[83-86] To
date, there is no proven screening method for the detection of ovarian and fallopian tube cancer in this population.

The recommendation for prophylactic salpingo-oophorectomy is based on the supposition that an equivalent reduction in cancer mortality cannot be achieved through ovarian cancer screening. The evaluation of ovarian cancer screening in the general population with transvaginal ultrasound and CA125 blood test is ongoing in the Prostate Lung Colorectal and Ovarian screening trial (PLCO). One objective in this trial is to assess whether this screening reduces ovarian cancer mortality in healthy women aged 55 to 74 years.[87] Women were included in this study if they had not been diagnosed with cancer other than basal cell or squamous cell carcinoma.

Results from the initial screening round showed a relatively high number of oophorectomies in comparison to ovarian cancer diagnoses. The majority of women (80%) who were diagnosed were found to have late stage cancers (stage III and IV).[88] A second report of four rounds of screening in this population found similar results with a high ratio of surgeries to screen detected cancers and a high proportion of late stage cancers (72%). The effect of screening on mortality has not yet been determined.[87]

Another randomized trial, the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) is also underway and is also designed to assess the impact of this screening on mortality in women age 50-74 years.[89] This trial has three arms, a control arm with no intervention, one screening arm with annual CA125 and transvaginal ultrasound as a second-line test, and a second screening arm with transvaginal ultrasound only. To date they have reported on the initial or prevalence screen.[89] They reported that the sensitivity in the two screening arms was encouraging (89.4% and 84.9%) and state that the screening strategies are feasible. They are awaiting the results of the future screens to determine the effect of this screening on mortality.

Oral contraceptives are an effective means of reducing ovarian cancer risk in this population, with up to a 60% risk reduction if taken for 3-5 years.[90-92] A similar degree of protection from ovarian cancer has also been observed in the general population.[93] However, the oral contraceptive pill is associated with a small increase in
breast cancer risk in BRCA1 carriers, observed primarily in BRCA1 carriers who took the pill before 1975, those who took when younger than age 30, and those who took it for more than five years.[94] This increase in risk was not observed in BRCA2 carriers.

Studies of ovarian cancer risk reduction associated with tubal ligation in BRCA carriers are mixed.[91, 95] Earlier studies found a decreased risk of ovarian cancer after tubal ligation in BRCA1 carriers (OR=0.39; 95% CI, 0.22-0.70) but not in BRCA2 carriers.[95] A more recent study did not find a significant reduction in risk for BRCA1 or BRCA2 carriers.[91] Tubal ligation has been shown to provide protection from ovarian cancer in women in the general population.[96] The mechanism for ovarian cancer protection from tubal ligation is not clear.

Prophylactic salpingo-oophorectomy has been shown to reduce the risk of ovarian and fallopian tube cancer substantially in women who carry a BRCA mutation. Estimates of risk reduction range from 75-96%. [97-99] This procedure also reduces the risk of breast cancer by up to 50% if performed prior to menopause due to decreased circulating estrogen.[100, 101] This will be reviewed in greater detail in the next section: 2.6 Prophylactic Salpingo-oophorectomy.

2.5.3 Other cancers

Men who carry a BRCA1 or BRCA2 mutation should have annual screening for prostate cancer with digital rectal examination and Prostate Specific Antigen (PSA) test.[80] Women and men who carry a BRCA2 mutation should have regular annual screening for malignant melanoma of the skin and eye.[54] Currently no clinical guidelines for the screening of pancreatic cancer exist, although some centres do have research protocols involving ultrasound and magnetic resonance imaging (MRI).[102, 103] General population guidelines for colon cancer screening should followed with colonoscopy beginning at age 50 in the absence of a family history of the disease.
2.5.4 Other modifiers of cancer risk:

**Pregnancy and breast feeding**

Parity is associated with a decreased risk of ovarian cancer both in the general population and in *BRCA1* and *BRCA2* carriers.[104] Parity appears to be associated with a modestly decreased risk for breast cancer in *BRCA1* carriers. This was observed in *BRCA1* carriers who have had four or more births (OR = 0.62; 95% CI = 0.41-0.94) but not when comparing parous to nulliparous women. Conversely, increasing parity in *BRCA2* carriers is associated with an increase in breast cancer risk.[105] Breast feeding provides some protection from breast cancer in *BRCA1* carriers, but not in *BRCA2* carriers.[106]

2.6 Prophylactic Salpingo-oophorectomy

2.6.1 The history of salpingo-oophorectomy

As reviewed in Love et al., Robert Battey, an American physician, was the first to perform bilateral oophorectomy on August 17, 1872 and publish a report on the procedure he called ‘ovariectomy’. [107, 108] He reported that he performed the surgery for the absence of regular menses, reasoning that removal of the ovaries would remove the source of the patient’s illness.[107] Oophorectomy for the treatment of breast cancer was first proposed by Albert Schinzinger in 1889.[109] He noted that the prognosis of breast cancer was better in older women than younger women and proposed that removing the ovaries would prematurely age women and atrophy the breast and the breast cancer.[109] The case for bilateral oophorectomy for the treatment of breast cancer was strengthened by case reports of women who experience remission of their breast cancer at the time of menopause.[108, 110] Boyd published the first series of five patients treated for breast cancer with bilateral oophorectomy in 1897.[111] Bilateral oophorectomy is now recognized as an acceptable hormonal treatment option for breast cancer.[112]
Bilateral oophorectomy to reduce ovarian cancer risk was not reported in the literature until much later. In 1978 a report was published about ovarian cancer in multiple members of two families and the author observed that the mode of inheritance fits autosomal dominant transmission of a single gene. The difficulty of genetic counselling in these families was highlighted noting that few cases have been reported in the literature. In 1979 Lurrain et al. published a report of five cases of ovarian cancer in a three generation family. In 1982 they published another report about a similar family with four members affected with ovarian cancer.[113] Based on their clinical experience and reports in the literature of familial ovarian cancer dating back to the 1930s, the authors stated that “If autosomal dominant transmission is established, genetic counseling for prophylactic oophorectomy at an appropriate age may lead to a decrease in deaths from ovarian cancer in such families.”[113]

In 1995 Struewing et al. published one of the earliest studies to observe a reduced risk for gynecologic cancer after prophylactic oophorectomy in hereditary breast and ovarian cancer families.[114] The authors analyzed twelve large families and noted an excess of ovarian cancers in non-oophorectomized family members compared with oophorectomized family members suggesting oophorectomy is protective against ovarian cancer. Fallopian tube cancer was soon recognized as one of the cancers associated with BRCA1 and BRCA2 and the importance of removal of the fallopian tubes at the time of oophorectomy was emphasized.[53, 115]

Salpingo-oophorectomy is now recommended to women who are found to carry a BRCA1 or BRCA2 mutation at 35 or after childbearing is complete.[116] Oophorectomy is also now considered an elective procedure at the time of hysterectomy for other indications to reduce ovarian cancer risk. It is estimated that 1000 cases of ovarian cancer could be prevented each year in the United States if women over the age of 40 in the general population undergoing hysterectomy also elected to undergo salpingo-oophorectomy.[117] However the costs of early menopause must be weighed against benefits of decreased cancer risk, particularly in women at population risk for ovarian cancer.
2.6.2 Predictors of salpingo-oophorectomy

Studies have evaluated who is most likely to proceed to prophylactic salpingo-oophorectomy after receiving positive genetic test results for *BRCA1* and *BRCA2*. Significant predictors of proceeding to surgery include age, education, perception of health, perception of risk, and perceived incurability of ovarian cancer.[118, 119] Women who were older, had lower education levels, higher perception of risk, poorer health perception, who viewed ovarian cancer as incurable, and women who believed in the benefits of surgery were more likely to proceed. Personal history of breast cancer and family history of ovarian cancer are also associated with the decision to have prophylactic salpingo-oophorectomy.[120]

2.6.3 Incidental findings at salpingo-oophorectomy

Lu et al. were among the first to publish a series of women undergoing salpingo-oophorectomy for familial risk or known *BRCA* mutation.[121] They found occult cancer in four of 33 subjects (12%) who had a risk of carrying a mutation of greater than 25%. All four carried a *BRCA* mutation. They highlighted the need for careful pathologic examination of the surgical specimens as three of the four cancers were only detected on final pathology examination. Many studies examining the reduction in risk associated with salpingo-oophorectomy have since reported incidental findings of occult fallopian tube and ovarian cancer discovered at the time of surgery.[98, 100, 101, 122] Case reports have also been published.[51, 115, 123-125] Other incidental findings at salpingo-oophorectomy have included occult endometrial cancer, peritoneal cancer, and breast cancer metastatic to the endometrium and ovary.[126-129]

Many studies have now been published reporting the rate of occult cancer detection and the likely tissue of origin of the occult cancers.[98, 122, 126-128, 130-135] Rates of occult cancer range from 2.3-18%. A series from our group was one of the largest to report the rate of occult cancers (4.4%) and tissue origin of the tumours after careful pathologic examination of the salpingo-oophorectomy specimens.[127] A greater proportion of occult cancers were diagnosed in women with a *BRCA1* mutation (6.4%)
compared with women with a BRCA2 mutation (1.5%) and this is likely due to the comparative risk for gynecologic cancer and the age at surgery in both groups. In addition, we found that not only did a high proportion of the occult cancers originate in the fallopian tube, but that the fimbria appeared to be the site of very early carcinogenesis in BRCA carriers.

The finding of many early occult fallopian tube cancers at the time of salpingo-oophorectomy has called into question the tissue of origin of ovarian cancers in women who carry a BRCA1 or BRCA2 mutation. Serous ovarian, fallopian tube and peritoneal cancers are histologically indistinguishable and exhibit similar clinical behavior, complicating the question further.[136] The fallopian tube, and more specifically the fimbria, has since become the target for many studies examining early events in pelvic serous carcinoma, and had been posited as the origin of gynecologic cancers in BRCA carriers.[137, 138]

One of the main predictors of finding an occult cancer at the time of prophylactic salpingo-oophorectomy is the age at the time of surgery. Age at diagnosis of ovarian cancer in the general population is estimated to be 60.8 years (SEER, Surveillance, Epidemiology and End Results Program) compared with a mean age of 53.5 as observed among women with familial ovarian cancer in the Gilda Radner Familial Ovarian Cancer Registry.[139] This is similar to findings in a large series of unselected ovarian cancer in Ontario.[10] Age at diagnosis of ovarian cancer was 52.6 among women found to carry a deleterious BRCA1 mutation, 58.8 among women with a BRCA2 mutation and 57.3 among women with no mutation. If prophylactic salpingo-oophorectomy is performed close to the mean age of diagnosis of ovarian cancer, it is more likely that an early stage occult cancer will be identified. Another important factor is the level of detail of the pathology exam, as many occult cancers have been reported to be microscopic.
2.6.4 Cancer risk reduction associated with salpingo-oophorectomy

The diagnosis of primary peritoneal cancer after prophylactic salpingo-oophorectomy is a failure of the procedure to reduce the risk of ovarian and ovarian-like cancer. Peritoneal cancer may arise from the peritoneum after salpingo-oophorectomy. It is also possible that undetected microscopic disease in the ovaries or fallopian tubes at the time prophylactic salpingo-oophorectomy is diagnosed as primary peritoneal cancer after surgery. Fallopian tubes left in-situ or ovarian remnants are another possible source of gynecologic cancer in women after prophylactic oophorectomy, particularly for women who had surgery before the importance of the removal of these tissues was recognized.

Tobacman et al. published the first report of peritoneal cancer in 1982, titled “Intra-abdominal carcinomatosis after prophylactic oophorectomy in cancer prone families”.[140] They reported three cases of primary peritoneal cancer after oophorectomy in 28 women from 16 families. They concluded that derivatives of the coelemic epithelium other than the ovary are susceptible to cancer development. In 1993 Piver et al. examined the records of 324 women who were part of the Gilda Radner Familial Ovarian Cancer Registry and found six cases of primary peritoneal cancer diagnosed from 1-27 years after surgery.[141]

Many retrospective, cross-sectional, and prospective studies have since estimated the ovarian, fallopian tube, and breast cancer risk reduction associated with prophylactic salpingo-oophorectomy in women who carry a BRCA1 or BRCA2 mutation.[98-101, 114, 122, 142-146]

One of the first studies to prospectively evaluate the effect of salpingo-oophorectomy on risk of breast and ovarian cancer was published by Kauff et al. in 2002.[98] The authors followed 170 women from prophylactic surgery, or from receipt of genetic test results (for those who chose surveillance), for a mean of approximately two years. The end point, time to cancer diagnosis, was based on a total of 330 person years with a combined hazard ratio for subsequent breast cancer or BRCA-related gynecologic cancer of 0.25
(95% CI, 0.08-0.74). The hazard ratio for gynecologic cancer and breast cancer outcomes were not significant when analyzed separately, likely due to the size of the cohort.

A similar study published by Rebbeck et al. in the same journal issue was a larger but retrospective multicentre study of 259 women who underwent salpingo-oophorectomy and 292 controls, matched for mutation (BRCA1 or 2), year of birth, age at time of surgery, and centre, with a minimum follow-up of eight years in both groups.[122] The incidence of breast cancer was also determined in a subgroup of women who had not had breast cancer and had not undergone prophylactic mastectomy. The hazard ratio for primary peritoneal cancer after salpingo-oophorectomy was 0.04 (95% CI, 0.01-0.16) and for breast cancer was 0.47 (95% CI 0.29-0.77). Rebbeck et al. posited that salpingo-oophorectomy aided in the early detection of ovarian cancer as all six women diagnosed with occult cancer at surgery were stage I compared with six of the 58 women diagnosed with ovarian cancer with ovaries intact.[122] This study, although sufficiently large to identify a significant benefit from salpingo-oophorectomy, is limited by its retrospective design.

Both studies followed the women from the date of surgery not from the date of ascertainment. A possible source of survival bias is introduced if subjects are followed from ascertainment, as the women must have remained free of ovarian cancer from ascertainment to surgery to be included. Optimally the person years before oophorectomy will be attributed to the non-oophorectomy group, and then the subject will be transferred to the oophorectomy group at the time of surgery. Both studies also excluded women who were diagnosed with occult cancer at the time of salpingo-oophorectomy as including them would increase the apparent risk for ovarian cancer in the oophorectomy group. It cannot be assumed that these women would have been diagnosed with ovarian cancer during the duration of the study as the time from stage one ovarian cancer to clinical presentation is not known.

These two studies provided strong evidence for the recommendation of salpingo-oophorectomy to women who carry a BRCA mutation, but both had limitations. A large prospective study is the optimal study design for the most accurate estimation of risks for
ovarian, fallopian tube, and peritoneal cancer in BRCA carriers with and without ovaries intact. This is the subject of Chapter 5 of this thesis. This study was published in 2006 and was the largest study to date, with 1828 women followed for a mean of 3.5 years. We found that salpingo-oophorectomy reduced the risk of ovarian and fallopian tube cancer by 80% (HR, 0.80; 95% CI, 0.07-0.58). The residual risk for primary peritoneal cancer after salpingo-oophorectomy was 0.2% per year of follow-up, a cumulative incidence of 4.3% at 20 years.

Following our study, Kauff et al. published a study of 1079 women followed for a mean of three years with the intent of evaluating the efficacy of salpingo-oophorectomy in BRCA1 and BRCA2 carriers independently. While they did find a significant reduction in gynecologic cancer risk in BRCA1 carriers (HR, 0.15; 95% CI, 0.04-0.56) and breast cancer risk in BRCA2 carriers (HR, 0.28; 95% CI, 0.08-0.92), they did not find a statistically significant reduction in BRCA1 associated breast cancer (HR, 0.61; 95% CI, 0.30-1.21). There were no events of gynecologic cancer after salpingo-oophorectomy in women with a BRCA2 mutation (HR, 0.00; 95% CI, not estimable).

Three studies have investigated the reduction in breast cancer risk associated with salpingo-oophorectomy in BRCA1 and BRCA2 carriers.[100, 101, 143] These studies all found a similar reduction in risk of breast cancer with hazard ratios ranging from 0.38 (95% CI, 0.15-0.97) to 0.53 (95% CI, 0.33-0.84). The study by Eisen et al. was the largest study and estimated the risk reduction for BRCA1 (HR, 0.44; 95% CI, 0.29-0.66), and for BRCA2 (HR, 0.57; 95% CI, 0.28-1.15). They found that the risk reduction was greater if the surgery was performed before age 40 (HR, 0.36; 95% CI, 0.20-0.64) in BRCA1 carriers than if performed after age 40 (HR, 0.53; 95% CI, 0.30-0.91).

In 2009, a meta-analysis of ten studies examining breast and ovarian cancer risk reduction was published by Rebbeck et al.[147] The authors found that prophylactic salpingo-oophorectomy was associated with a significant reduction in risk of breast cancer for both BRCA1 and BRCA2 independently and combined (HR, 0.49; 95% CI, 0.37-0.65) and with a significant reduction in ovarian and fallopian tube cancer (HR,
The reduction in risk for ovarian and fallopian tube cancer was exceedingly close to our estimation (HR, 0.20; 95% CI, 0.07-0.58).

2.6.5 Surgical considerations

Salpingo-oophorectomy is the minimum procedure required to reduce the risk of ovarian and fallopian tube cancer in BRCA1 and BRCA2 carriers.[148] It is imperative that as much tissue as possible be removed at the time of salpingo-oophorectomy to minimize the possibility of an ovarian remnant, a tissue shown to be susceptible to cancer development after oophorectomy.[148, 149] Peritoneal washings should also be taken at the time of surgery, which may aid in the detection of occult disease.[125, 150]

There is ongoing debate about the role of hysterectomy at time of prophylactic salpingo-oophorectomy in BRCA carriers. Factors in favour of salpingo-oophorectomy alone include increased infections, hematomas and blood loss when hysterectomy is included in the procedure [151], and the lack of case reports of fallopian tube cancer originating in the interstitial fallopian tube in the cornua of the uterus.[152]

Factors in favour of including hysterectomy include the decreased theoretical risk for fallopian tube cancer development associated with leaving the uterus and intramural fallopian tube in place, the decreased risk for cancer of the endometrium, particularly with Tamoxifen therapy, and the simplicity of hormone replacement therapy (HRT).[152-154] One study estimated the length of fallopian tube left in place after prophylactic salpingo-oophorectomy in a series of consecutive hysterectomy specimens from premenopausal women.[155] They found the median length of the remnant to be 12mm (range 6-15mm).

Studies have found that the majority of the occult fallopian tube cancers detected at salpingo-oophorectomy occur in the distal end of the fallopian tube.[127, 129, 133] However, hysterectomy has not been included in the risk-reducing procedure at all institutions who report this information. It is possible that occult fallopian tube cancers that occur in the interstitial fallopian tube in the cornua of the uterus will present after
salpingo-oophorectomy as primary peritoneal cancer, the rates of which have not yet been reported at the majority of centres.

As clinically occult ovarian and fallopian tube cancers have been reported in 2.3-18% of women undergoing salpingo-oophorectomy with a *BRCA* mutation, serial sectioning every 2-3mm of all ovarian and fallopian tissue and thorough examination by a pathologist is essential.[122, 129, 131, 148] (see figure 2.1) Crum et al. have further described this protocol as SEE-FIM: Sectioning and Extensively Examining the FIMbria as the fimbria appears to be the preferred site of origin of these cancers.[156] Their protocol entails lengthwise (sagittal) sectioning of the fimbriated portion and sectioning in 2-3mm intervals for the remainder of the fallopian tube.[138, 156]
Figure 2.1: Recommendation of serial sectioning and detailed pathologic examination of tissue obtained at prophylactic salpingo-oophorectomy in a BRCA1 or BRCA2 mutation carrier.

The entire surgical specimen should be sectioned in 2- to 3-mm intervals, thoroughly examined for the possibility of microscopic disease. Courtesy of Mark H. Greene, MD, Clinical Genetics Branch, National Cancer Institute, Bethesda, MD.[148]
Surgeons who perform prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy in women for an inherited mutation in one of the mismatch repair genes (Hereditary Non-Polyposis Colon Cancer syndrome) or HNPCC must also be aware of the importance of pathologic examination of all tissue including the fallopian tubes for occult cancer.[16]

Surgical complications are another aspect of salpingo-oophorectomy to be discussed with women prior to surgery. Elit et al. examined the records of 263 patients who underwent prophylactic oophorectomy from 1992 to 1998 and found a surgical complication rate of 14%.[157] Laparotomy was used exclusively in 155 cases, laparoscopy in 79, and vaginal access in 12 cases. Seventeen cases required conversion from laparoscopy to laparotomy. More recent studies show that surgical complications are low.[98, 158, 159] Kenkhuis reported intraoperative and post operative complication rates of 1.3% and 3.1% among 159 women who underwent the procedure for a BRCA mutation or for familial cancer risk. The median age of the women was 43.8 and 98% had a laparoscopic procedure.[158]

2.6.6 Hormonal changes after salpingo-oophorectomy

Prior to menopause, estrogen production occurs primarily in the ovary and is secreted as estradiol. The ovary also produces progesterone.[160] Estrogen is produced in smaller amounts by the adrenal glands and adipose tissue through conversion from androgens by the enzyme aromatase.[161] Androstenedione (the primary androgen in young women) is produced in equal amounts by the ovaries and the adrenal glands. Dehydroepiandrosterone (DHEA) and testosterone are also produced by the ovaries and adrenal glands.

Natural menopause occurs due to the depletion of ovarian follicles at a median age of 51.[160] Estrogen levels decline gradually during the years prior to menopause and then decline dramatically after menopause. Estrogen production continues at low levels by the adrenal glands and through peripheral conversion in adipose tissue.[161]
Androstenedione decreases by approximately 50% after natural menopause whereas testosterone levels remain fairly constant after natural menopause.[162, 163]

After surgical menopause in young women (bilateral oophorectomy), estradiol declines to very low levels (similar to levels observed in naturally postmenopausal women). Circulating androstenedione decreases by approximately 50% and levels of DHEA decrease by approximately 70%.[162, 164, 165] Testosterone levels also decrease significantly after oophorectomy. The majority of circulating testosterone after oophorectomy is produced by peripheral conversion of androstenedione produced by the adrenal glands. The remaining is produced by the adrenal glands directly.[162] Androstenedione decreases by a small but significant amount in post-menopausal women who undergo oophorectomy demonstrating that the ovary continues to produce some androstenedione after natural menopause.[162]

2.7 Impact of Prophylactic Salpingo-oophorectomy

2.7.1 Perception of risk

Few studies have examined perception of risk in relation to prophylactic surgery to reduce the risk of ovarian cancer.[166-169] Elit et al. asked women who had undergone oophorectomy to rate their risk of ovarian cancer before and after prophylactic oophorectomy.[168] Mean estimated risk of ovarian cancer before surgery was 59.1% and after surgery was 31.9%. Thirty-nine percent indicated no risk after surgery. In a similar retrospective study, Robson et al. asked women who had undergone oophorectomy to report their perceived risk of ovarian cancer in the absence of oophorectomy.[169] Fifty-six percent of women reported a lifetime risk of ovarian cancer of greater than 50%. Ninety percent estimated this risk to be greater than 25%.

Madalinska et al. asked participants (both women who were having gynecologic screening and women who had salpingo-oophorectomy) what their current perceived risk
of developing breast cancer was.[167] They also asked the subgroup of women who had undergone salpingo-oophorectomy what they thought their risk of breast cancer was before surgery. As expected, current perceived risk was lower among women who had surgery compared to women who were having screening. Perceived risk of breast cancer decreased by 29 points (out of 100) in the oophorectomy group. They did not ask about perceived risk of ovarian cancer.

The study presented in Chapter four is the only study to date that evaluates perceived risk related to prophylactic surgery among *BRCA* carriers to date.[170]

### 2.7.2 Quality of life

Studies of the impact of salpingo-oophorectomy on quality of life have either been retrospective or small prospective studies.[167-169, 171-174] Various aspects of quality of life after salpingo-oophorectomy have been evaluated including general health, depression, cancer worry, menopausal symptoms, sexual functioning and satisfaction with the decision to have the surgery.

In 2001, Elit et al. published one of the first studies to evaluate quality of life after prophylactic oophorectomy for a family history of ovarian cancer.[168] It was a retrospective study of 40 women who underwent surgery on average five years prior, and examined the potential costs associated with the surgery such as menopausal symptoms and sexual functioning. Satisfaction with the decision to have the surgery was also reported. The mean age of women at the time of the study was 54.8, 49.9 at the time of surgery. All participants had a first degree relative with ovarian cancer, 66% were taking hormone replacement at the time of the study and 15% had a previous diagnosis of breast cancer. They found that while overall quality of life was comparable to the general population, menopause-specific quality of life was compromised and satisfaction with sexual functioning was compromised in up to 54% of women.

Also in 2001, Fry et al. published a retrospective study comparing 27 women who had elected prophylactic oophorectomy from one to five years previously with 28 women
who chose screening (i.e. did not have prophylactic surgery).[171] Nine women in the surgical group had a previous breast cancer; two women in the screening group had a previous breast cancer. They evaluated general health, quality of life, sexual functioning and cancer worry in the two groups. General health scores were higher in the surgical group however they had poorer scores for social functioning and menopausal symptoms. The authors found no difference between the two groups for sexual functioning or cancer worry. They also found that premenopausal women were more vulnerable to psychological distress and required longer recovery time after surgery.

Robson et al. published a retrospective study in 2003 with a similar design to the study by Elit et al.[169] Fifty-nine women who underwent prophylactic surgery completed standardized questionnaires on average two years after surgery. Participants were a mean of 51 years of age at surgery, 29% were premenopausal at the time of surgery, 83% had a personal history of breast cancer, and 10% were current users of HRT. The questionnaires evaluated overall quality of life, depression, cancer worry, sexual functioning and satisfaction with surgery. Similar to the study by Elit et al., overall quality of life was comparable to that of the general population. Menopausal symptoms affecting sexual function were the most significant predictors of satisfaction with surgery. 35% of participants reported that vaginal dryness was “quite a bit” or “extremely” bothersome and 28% of participants reported dyspareunia or “pain with sex” to be bothersome. While levels of depression were the same as levels in the general population, almost 21% of women continued to experience cancer specific worry almost two years after surgery.

In 2005 and 2006 Madalinska et al. published two complementary cross-sectional retrospective studies based on the same population of women.[167, 173] The first compared women who elected to have prophylactic salpingo-oophorectomy with those who chose screening and evaluated quality of life effects such as endocrine symptoms, sexual function and cancer worry after salpingo-oophorectomy.[167] The second evaluated the impact of HRT on endocrine symptoms and sexual functioning in premenopausal women who underwent salpingo-oophorectomy (and subsequently
surgical menopause) compared with premenopausal women undergoing gynecologic screening.[173]

The first was a cross-sectional observational study of 369 women who elected prophylactic salpingo-oophorectomy and 477 women who elected gynecologic screening. Questionnaires were administered on average three years (median two years) after surgery and evaluated general quality of life, cancer worry, endocrine symptoms and sexual functioning. Subjects who elected surgery were significantly older (49 years) than women who elected screening (47 years) (p=0.001). Of the women who elected to have surgery, 38% were premenopausal at the time of surgery, and 49% had a personal history of breast cancer. At the time of questionnaire 62% of women who elected screening were premenopausal, and 34% had a history of breast cancer. A greater number of women who had surgery (37%) took hormone replacement after surgery compared with the screening group (6%).

Women in both groups had quality of life scores similar to the general population. Women who had surgery had fewer cancer related worries than women having screening. However, they had more menopausal symptoms, more vaginal dryness and dyspareunia, and less pleasure and satisfaction during sexual activity.[167] Although the authors did not show the data, they report that there were no significant differences in menopausal symptoms and sexual function between HRT users and non-users.

In the second study Madalinska et al. limited their analysis subset of premenopausal women, comparing 164 women who had undergoing salpingo-oophorectomy with 286 women who were having gynecologic screening.[173] Of the 164 women who had surgery, 77 women were taking HRT and 87 were not. A comparison of symptoms was made between HRT users and non-users, and between HRT users and the screening group. HRT users were younger (45 vs. 47, p<0.05) and had prophylactic surgery at younger age (41 vs. 44, p<0.01) than non-users.

Women who were taking HRT reported significantly fewer endocrine related menopausal symptoms than women who were not taking HRT (p<0.05).[173] When symptoms were evaluated one by one, only hot flushes and cold and hot sweats were significantly
different between the groups (i.e. $p<0.05$). Women who had surgery and were taking HRT experienced significantly more menopausal symptoms than women in the screening group ($p<0.05$). These symptoms included hot flushes, cold and hot sweats, vaginal dryness, pain with intercourse, and loss of interest in sex. Sexual functioning after surgery was comparable between women who were taking HRT and women who were not. Women who underwent surgery and were taking HRT experienced significantly more sexual discomfort.

These two studies are the largest to date to evaluate outcomes after salpingo-oophorectomy in women at high risk for ovarian cancer to date and provide considerable information about the effects of salpingo-oophorectomy, particularly in women who are premenopausal at surgery. However, they are limited by their retrospective cross-sectional design. They identify differences in symptoms between women who have undergone surgery and those who have screening as a method of determining changes in quality of life, menopausal symptoms, sexual function and cancer worry resulting from surgery. The authors use multivariate models to account for characteristics that differ significantly between the two groups such as age, $BRCA$ status, history of breast cancer, menopausal status at surgery, and HRT.

In 2009, Fry et al. published the first small prospective study to compare women who elected to have screening ($n=37$) with women who elected to have prophylactic surgery ($n=38$) over a one year period from surgery.[174] Use of HRT was not mentioned in the study. Overall, women in the surgical group reported more hot flashes and vaginal dryness compared to the screening group both before and after surgery. They found that frequency of sexual activity decreased in the short term after surgery but returned to usual levels one year after surgery. No differences were noted between the groups in terms of depressive symptoms or body image.

Standardized questionnaires were widely used, however some were designed specifically for their study of oophorectomy and were not validated. The same standardized questionnaires were not used across all studies limiting comparisons across studies.
While the two largest studies did include breast cancer as a variable in their multivariate models, studies to date have been too small to evaluate the relevance of previous breast cancer diagnosis with regard to the findings.[167, 173] Only the study by Madalinska et al. was sufficiently powered to analyze the effect of hormone replacement on menopausal symptoms and sexual function but the interpretation of the findings was limited by the retrospective cross-sectional design.[173] The only prospective study to date did not mention whether or not subjects were using HRT before or after surgery.[174]

2.7.3 Long term health after salpingo-oophorectomy

Bone health

Bone loss begins around age 35 and accelerates after menopause.[175] It has also been observed that women who experience earlier menopause have lower bone density later in life.[176] Premenopausal oophorectomy is associated with an increased risk of osteopenia and osteoporosis.[177, 178] This was shown in a study by Aitken et al. who compared 163 women who underwent hysterectomy and oophorectomy with 95 women who underwent only hysterectomy.[177] Oophorectomy before age 45 was found to be associated with an increased prevalence of osteoporosis within three to six years of surgery. This was not observed in women over age 45 who were three to six years post surgery. Melton et al. have proposed that women who undergo oophorectomy may also experience greater bone loss later in life than women who have ovaries intact due to the lack of testosterone and androstenedione produced by the ovaries after menopause.[179] They cite the role of these hormones in the production of extragonadal endogenous estrogen after menopause, a protective factor in bone loss.[179] Hormone replacement therapy after surgical menopause may provide some benefit, however the duration of use required is not clear.[180, 181] This has not been studied in women who carry a \textit{BRCA} mutation.
Cardiac health

Coronary heart disease is a leading cause of death in older women. Various factors which increase after menopause are thought to account for this, specifically an accelerated increase in cholesterol level.[182-184] Bilateral oophorectomy is a risk factor for coronary heart disease in the general population.[185] One study compared women who were approximately 20 years post-menopause who had undergone hysterectomy with bilateral oophorectomy with those who underwent hysterectomy alone, and found that women who had bilateral oophorectomy had increased lipids, lipoproteins, glucose and insulin levels compared with the women with hysterectomy alone.[186] A large prospective cohort by Colditz et al. studied the relationship of menopause (natural and surgical) to the subsequent risk of coronary heart disease in 121,700 women between 30 and 55 years of age.[185] After controlling for age and cigarette smoking, women who had natural menopause with or without the use of estrogen did not have an increased occurrence of coronary heart disease. Women who underwent bilateral oophorectomy who had never taken hormone replacement had an increased risk (rate ratio, 2.2, 95% confidence interval (CI), 1.2-4.2). This risk was not increased in women who underwent bilateral oophorectomy and took hormone replacement as compared with premenopausal women (rate ratio, 0.9, 95% CI, 0.6-1.6).[185]

A meta-analysis performed in 2006 showed that, while natural menopause did not increase the risk for cardiovascular disease, bilateral oophorectomy around age 50 was shown to increase the risk (RR, 2.62, 95% CI, 2.05-3.35), and oophorectomy before age 50 increased the risk dramatically (RR 4.55, 95% CI, 2.56-8.10).[187] Studies of this kind have not been performed specifically in women who carry a BRCA mutation.

Cognitive function

Studies have examined the question of long-term health after oophorectomy for both family history and for other indications.[188-191] These studies are largely based on the Mayo Clinic Cohort of Oophorectomy and Aging which followed women who had had unilateral or bilateral oophorectomy before menopause for non-cancer indication and women who had not had oophorectomy from 1950 to 1987.[192] The main purpose of
the follow-up arm of this cohort was to detect age-related diseases such as dementia and Parkinson’s disease.

From this cohort, the risk of cognitive impairment or dementia appears to be increased in women who underwent unilateral or bilateral oophorectomy before menopause compared with women who did not (HR, 1.46; 95% CI, 1.12-1.90). This effect only approached significance when bilateral oophorectomy was analyzed separately (HR, 1.33; 95% CI, 0.98-1.81). When the analysis was restricted to women who underwent bilateral oophorectomy before 49 years of age and who were not treated with estrogen until at least 50 years of age the risk increased (HR, 1.89; 95% CI, 1.27-2.83).

Parkinsonism was also evaluated in this cohort. Women who underwent bilateral oophorectomy before menopause had an increased risk of Parkinsonism compared with women who had not had an oophorectomy (HR, 1.80; 95% CI, 1.00 to 3.26).[193] The findings were not significant for Parkinson’s disease alone.

2.7.4 Survival after salpingo-oophorectomy

The benefits of prophylactic salpingo-oophorectomy in terms of cancer risk must be weighed against the potential costs of the surgery in terms of long term health and survival.

Domchek at al. were the first to examine cancer-specific mortality after salpingo-oophorectomy in a prospective cohort of BRCA1 and BRCA2 carriers.[142] With a mean follow-up time of 2.5 years from surgery to censoring or death, they found a hazard ratio of 0.05 (95% CI, 0.01-0.46) for ovarian cancer specific mortality and 0.10 (95% CI, 0.02-0.71) for breast cancer specific mortality when comparing women who have had salpingo-oophorectomy with women who have not.

To date, the same group have published the only other study that investigates this question with a prospective multicentre cohort study.[194] 2482 women with a BRCA1 or BRCA2 mutation were followed at one of 22 centres for a mean of roughly four years.
Dates of ascertainment were 1974-2008 and follow-up continued until 2009. Compared with women who did not have salpingo-oophorectomy, women who did undergo salpingo-oophorectomy had lower all-cause mortality (HR, 0.40; 95% CI, 0.26-0.61), lower breast cancer specific mortality (HR, 0.44; 95% CI, 0.26-0.76) and lower ovarian cancer specific mortality (HR, 0.21; 95% CI, 0.06-0.80).

While this study is the largest to confirm a benefit of prophylactic salpingo-oophorectomy in terms of reduction in mortality, some aspects of the methods were not clear. Ascertainment of subjects with \textit{BRCA} mutations began in 1974, 20 years prior to the discovery of \textit{BRCA1} and \textit{BRCA2}. Women in the study who underwent salpingo-oophorectomy in the 1970s and 1980s may not have had optimal surgical technique and pathological review, which is directly related to the efficacy of the surgery in terms of cancer prevention. Women who underwent salpingo-oophorectomy were followed from the date of surgery, and women who did not were followed from the date of ascertainment; follow-up time was longer among women who did not have surgery. Finally, when data was missing, the subject was dropped from that aspect of the analysis. The authors stated this was most applicable to ovarian cancer endpoints. Thus the incidence of ovarian cancer diagnoses and deaths may have been underestimated.

Kurian et al. used a Monte Carlo simulation model that uses empiric data from the literature about the effectiveness of screening and treatment options to estimate survival probabilities among \textit{BRCA1} and \textit{BRCA2} carriers.[195] They simulate the life histories of a 1980 birth cohort of 100,000 female carriers from age 25 to 100. This model is entirely dependent on the accuracy of the literature in terms of risk reduction and makes assumptions about degree of prevention afforded by prophylactic surgeries and mortality associated with other illnesses related to the aging process in conjunction with the Berkeley Mortality Database 1980 birth cohort table.

They found that the survival probability to age 70 with no intervention was 53\% for \textit{BRCA1} and 71\% for \textit{BRCA2}.[142] Prophylactic oophorectomy by age 40 in women with a \textit{BRCA1} mutation was found to be the most effective single intervention with an increase in survival of 15\%. The combination of prophylactic mastectomy and oophorectomy
improved survival by 24% for BRCA1 carriers and 11% for BRCA2 carriers. This model was proposed as an aid in decision making for women who carry a BRCA mutation.

The Mayo Clinic Cohort of Oophorectomy and Aging was also studied to assess mortality associated with bilateral oophorectomy.[189] Subjects for this analysis were 1091 women with bilateral oophorectomy, 1274 with unilateral oophorectomy, and 2383 with no oophorectomy. Mean follow-up time in all three groups was 25 years or greater. They found that women who underwent bilateral oophorectomy did not have an increased risk of death compared with women who did not undergo oophorectomy. However, women who underwent bilateral oophorectomy before age 45 did have an increased risk of death (HR, 1.67; 95% CI, 1.16-2.40). When stratified by use of hormone replacement, only women who did not take hormone replacement had this increased risk. The authors reported that of the 33 deaths in the group of women who had oophorectomy before age 45, five were affected with uterine cancer and one with breast cancer at the time of oophorectomy, two of whom had an estrogen-related cancer. This is a possible source of bias, as women with these conditions will be more likely to proceed to oophorectomy, thus increasing the mortality in this group. However, this increased risk for mortality was not observed across other groups where this bias was equally likely.
3 CHAPTER THREE

3.1 Objectives

Two prospective cohorts of women who carry a BRCA1 or BRCA2 mutation were developed to address the following objectives:

1. To determine the reduction in ovarian and fallopian tube cancer risk associated with prophylactic salpingo-oophorectomy and the residual risk of primary peritoneal cancer after salpingo-oophorectomy.

2. To determine the change in perception of risk for the development of breast and ovarian cancer after prophylactic salpingo-oophorectomy.

3. To assess changes in health-related quality of life after prophylactic salpingo-oophorectomy.

4. To assess changes in psychological distress and worry about cancer after prophylactic salpingo-oophorectomy.

5. To assess changes in menopausal symptoms and sexual functioning after prophylactic salpingo-oophorectomy with respect to menopausal status at the time of surgery and hormone replacement therapy use after surgery.

6. To evaluate satisfaction with the decision to undergo prophylactic salpingo-oophorectomy in women who have undergone the procedure.

3.2 Rationale

Comprehensive prospective studies of the impact of prophylactic salpingo-oophorectomy in women who carry a BRCA mutation have not been published in the literature to date. Reasons for this may include:
1. The relatively short period of time since an identifiable genetic predisposition to breast and ovarian cancer was discovered (genetic mutations in \textit{BRCA1} and \textit{BRCA2}).

2. The long period of time needed to establish a cohort of women and follow them for relevant outcomes.

3. Prophylactic salpingo-oophorectomy has not been uniformly accepted as an option for the reduction of ovarian cancer risk in women who carry a \textit{BRCA} mutation.

4. The majority of medical centres caring for women for an inherited cancer risk likely see only a small number of women. A prospective cohort study requires either a multicentre collaboration or a single centre with a larger number of women proceeding to surgery.

Why conduct large prospective cohort studies of women who elect prophylactic salpingo-oophorectomy due to a \textit{BRCA1} or \textit{BRCA2} mutation?

1. Retrospective studies may have inherent bias such as selection bias or survival bias.

2. Prospective cohort studies can reveal changes over time more accurately than retrospective cross-sectional studies.

3. As more and more women are diagnosed with a \textit{BRCA1} or \textit{BRCA2} mutation, the number of women seeking information about the impact of salpingo-oophorectomy will increase.

4. Uptake of salpingo-oophorectomy in women who carry a \textit{BRCA} mutation is likely dependent on information available regarding the physical and psychological consequences of the surgery.

5. Until screening can detect ovarian and fallopian tube cancer at a curable stage, or individuals who will develop cancer can be identified by biomarkers, salpingo-
6. Women who carry a *BRCA* mutation may have different and unique experiences with salpingo-oophorectomy and surgical menopause compared with women who have the surgery for family history alone or for other medical indications.

### 3.3 Hypotheses

1. Salpingo-oophorectomy will significantly reduce the risk of ovarian and fallopian tube cancer in women who carry a *BRCA1* or *BRCA2* mutation.

2. Perceived risk of ovarian cancer will decrease significantly as a result of prophylactic salpingo-oophorectomy.

3. Women will experience a decrease in cancer worry and psychological distress after prophylactic salpingo-oophorectomy.

4. Women who undergo salpingo-oophorectomy before menopause will experience greater changes in menopausal symptoms and sexual function than women who undergo the procedure after menopause.

5. Hormone replacement therapy will relieve the symptoms of surgical menopause in women who have prophylactic salpingo-oophorectomy before natural menopause.

6. Increased menopausal symptoms and decreased sexual functioning after surgery will negatively impact satisfaction with the decision to undergo prophylactic salpingo-oophorectomy.

### 3.4 Conceptual Framework

The goal of this thesis is to evaluate the impact of prophylactic salpingo-oophorectomy on various aspects of health in women who carry a *BRCA1* or *BRCA2* mutation. The
studies that comprise this thesis follow an important study conducted by Elit et al. which highlighted areas for continued research.[168] Seven areas of focus are examined in four complementary studies. These areas of focus are:

1. The impact of salpingo-oophorectomy on ovarian, fallopian tube and peritoneal cancer risk.

2. The perceived impact of prophylactic salpingo-oophorectomy on breast and ovarian cancer risk.

3. The impact of salpingo-oophorectomy on health-related quality of life.

4. The impact of salpingo-oophorectomy on general psychological distress and cancer worry.

5. The impact of salpingo-oophorectomy on menopausal symptoms.

6. The impact of salpingo-oophorectomy on sexual functioning.

7. Satisfaction with the decision to undergo prophylactic salpingo-oophorectomy.

These areas of focus can be better understood by defining them further in terms of:

1. **Timeframe:** Are the effects experienced immediately after surgery or are they experienced years after the surgery?

2. **Duration of effect:** Are the effects short term, lasting for weeks or months, or do they last for years?

3. **Degree of effect:** Are the effects life altering or only slightly bothersome?

4. **Body systems affected:** Are the effects physical in nature, psychological, or both?

5. **Characteristics of women electing to have surgery:** Are the characteristics of each woman proceeding to surgery related to the effects of surgery? Examples of these characteristics are previous diagnosis of breast cancer, menopausal status at the time of surgery, age at surgery, and choice regarding HRT after surgery.
The rectangle on the left represents each woman who elects to undergo salpingo-oophorectomy. Characteristics of each woman which may be related to outcomes after salpingo-oophorectomy are listed here. The shaded shapes on the right side of the diagram represent areas of focus for this thesis. Risk of cancer and perceived risk of cancer are investigated in relation to mutation status (BRCA1 or BRCA2). The impact of surgery on aspects of health and quality of life are investigated in relation to previous diagnosis of breast cancer, menopausal status at the time of surgery, age at surgery and choice regarding HRT after surgery.
4  CHAPTER FOUR

The Impact of Salpingo-oophorectomy on the Risk of Ovarian, Fallopian and Peritoneal Cancers in Women with a BRCA1 or BRCA2 Mutation

Adapted from: Amy Finch MS, Mario Beiner MD, Jan Lubinski MD, PhD, Henry T Lynch MD, Pal Moller MD, Barry Rosen MD, Joan Murphy MD, Parviz Ghadirian PhD, Eitan Friedman MD, William D Foulkes MD, Charmaine Kim-Sing MD, Teresa Wagner MD, Nadine Tung MD, Fergus Couch PhD, Dominique Stoppa-Lyonnet MD, Peter Ainsworth MD, Mary Daly MD, Babara Pasini MD, Ruth Gershoni-Baruch MD, Charis Eng MD, Olufunmilayo Olopade MD, Jane McLennan MD, Beth Karlan MD, Jeffrey Weitzel MD, Ping Sun PhD, SA Narod MD and the Hereditary Ovarian Cancer Clinical Study Group. Salpingo-oophorectomy and the Risk of Ovarian, Fallopian and Peritoneal Cancers in Women with a BRCA1 or BRCA2 Mutation. JAMA 2006 296; 2: 185-192.[99]
4.1 Abstract

**Context:** Women with *BRCA1* or *BRCA2* mutation are often advised to undergo preventive oophorectomy. The effectiveness of this intervention has not been prospectively evaluated in a large cohort of women.

**Objectives:** To estimate the incidence of ovarian, fallopian tube and primary peritoneal cancer in women who carry a deleterious mutation in *BRCA1* or *BRCA2*. To estimate the reduction in risk of these cancers associated with a bilateral prophylactic salpingo-oophorectomy.

**Design, Setting, and Participants:** Women known to carry a *BRCA1* or *BRCA2* mutation were identified from an international registry between 1992 and 2003. A total of 1828 carriers at one of 32 centres in Canada, the United States, Europe, Norway and Israel completed questionnaires at baseline and follow-up. Participants were followed from the date of study entry until: diagnosis of ovarian, fallopian tube, or peritoneal cancer; death; or the date of the most recent follow-up.

**Intervention:** Participants were divided into those who had undergone bilateral prophylactic oophorectomy and those who had not.

**Main Outcome Measure:** The incidence of ovarian, peritoneal, and fallopian tube cancer was determined by survival analysis. The risk reduction associated with prophylactic salpingo-oophorectomy was evaluated by time-dependent survival analysis, adjusting for covariates.
**Results:** After a mean follow-up of 3.5 years, 50 incident ovarian, fallopian tube, and peritoneal cancer cases were reported in the cohort. Of the 1828 women, 555 (30%) had a bilateral prophylactic salpingo-oophorectomy prior to study entry, 490 (27%) had an oophorectomy after entering the study, and 783 (43%) did not undergo bilateral prophylactic salpingo-oophorectomy. There were 32 incident cancers diagnosed in women with intact ovaries (1015/100,000 per year). Eleven cancer cases were identified at the time of prophylactic oophorectomy and seven were diagnosed after oophorectomy (217/100,000 per year). The estimated cumulative incidence of peritoneal cancer is 4.3% at 20 years after oophorectomy. The overall (adjusted) reduction in cancer risk associated with bilateral oophorectomy is 80% (multivariate hazard ratio = 0.20; 95% confidence interval, 0.07-0.58; p = 0.003).

**Conclusion:** Oophorectomy is associated with reduced risk of ovarian and fallopian tube cancer in high-risk women, although there is a substantial residual risk for peritoneal cancer in *BRCA1* and *BRCA2* mutation carriers following prophylactic salpingo-oophorectomy.
4.2 Introduction

Women with a deleterious mutation in the \textit{BRCA1} or \textit{BRCA2} gene have a lifetime risk of ovarian cancer (range, 15\% - 54\%).[29, 55, 56, 196, 197] Mutations in either of these genes increase susceptibility to cancers of the ovary, fallopian tube and peritoneum. It is difficult to distinguish between these three forms of cancer because the clinical symptoms are similar and because the pathological appearance of the three tumour types is almost identical. It is important to generate risk estimates separately for peritoneal cancer for \textit{BRCA1} and \textit{BRCA2} carriers after oophorectomy because this endpoint is an indicator of the effectiveness of preventive surgery. The level of cancer risk reduction associated with prophylactic oophorectomy has been estimated to be as high as 95\%. However, most of the studies to date that have evaluated the risk of ovarian, peritoneal, and fallopian tube cancer have used either historical or cross-sectional designs, [29, 55, 56, 196, 197] and these are subject to bias. In this prospective study, we estimate the absolute risks for developing ovarian, fallopian tube and peritoneal cancers in an international cohort of \textit{BRCA1} and \textit{BRCA2} mutation carriers. The risk reduction associated with prophylactic salpingo-oophorectomy is then estimated, after adjustment for a number of cofactors.

4.3 Patients and Methods

\textbf{Study population}

Eligible study participants were women at one of 32 centres in Canada, the United States, Europe, Norway and Israel who carry a deleterious \textit{BRCA1} or \textit{BRCA2} mutation. All participants provided written informed consent for genetic testing and for participating in the prospective study. The ethics committees of all participating centres have approved the study. In most cases, genetic testing was offered initially to women who were affected either by breast or ovarian cancer. When a mutation in either \textit{BRCA1} or \textit{BRCA2} was found in a proband or in her relative, testing was offered to other at-risk women in her family, both affected and unaffected. In some cases, mutation testing was offered
directly to unaffected women, when no affected family member was available for testing. The criteria for genetic testing varied from centre to centre, but all centres offered testing to both affected and unaffected women. Mutation detection was performed using a range of techniques, but all abnormal nucleotide sequences were confirmed by the direct sequencing of deoxyribonucleic acid. A woman was eligible for the study when the molecular analysis established that she was a mutation carrier. She was then asked to participate in this prospective study and to complete a baseline questionnaire. This study deals only with women who were free of ovarian cancer at the time of genetic testing. All study participants received genetic counseling and all received their genetic test result prior to study entry. Participants were enrolled in the study from 1992 to 2003. The majority of participants completed the baseline questionnaire at the time of genetic testing or within one year of receiving their result. Because this is a dynamic cohort the lengths of follow-up varied from individual to individual. Participants completed a baseline questionnaire and at least one follow-up questionnaire, a minimum of two years following the baseline questionnaire. The baseline and follow-up questionnaires requested information regarding reproductive history, surgical history (including preventive oophorectomy and mastectomy) and screening practices for breast and ovarian cancer. Questions about exposures to birth control pills and hormone replacement therapy (HRT) were also included. Follow-up questionnaires were either mailed to each study participant to complete and return, or were administered over the telephone by a genetic counsellor or a research assistant at each centre.

Participants were excluded if they were diagnosed with ovarian, fallopian tube or peritoneal cancer prior to the baseline questionnaire. However, participants who had a diagnosis of breast cancer before study entry were not excluded. Subjects who had only one ovary removed prior to study entry were considered to be at risk for ovarian cancer.

Participants were followed from the date of completion of the baseline questionnaire or age 30 (whichever was later). The members of the cohort were followed from study entry to: 1) the date of completion of the follow-up questionnaire; 2) the development of ovarian, peritoneal or fallopian tube cancer; 3) age 75, or 4) death. Study participants were divided into those who had undergone oophorectomy before the completion of
questionnaire and those who had both ovaries intact at study entry. Women who elected to have an oophorectomy after the questionnaire was completed were transferred from the first cohort to the second cohort at the date of surgery in the survival analysis.

A total of 2891 eligible participants were identified at the 32 centres. We received information regarding 2171 of these (75%). There were 135 women who declined to participate in the follow-up study. Fourteen women had died, but details of the cause of death were not known and these cases were excluded. 194 additional women were excluded because of missing data or loss to follow-up. After exclusions, the study population consisted of 1828 women (63% of the total).

All ovarian, fallopian tube and peritoneal cancers that were diagnosed in the cohort during the follow-up period were confirmed by review of medical records and/or pathology reports. The medical records of the subjects who died during the follow-up period were requested to determine the age and cause of death. The pathology reports were reviewed in order to correctly assign the diagnosis of ovarian, fallopian tube or primary peritoneal cancer. The diagnosis of primary fallopian tube cancer was made when the tumor predominantly involved the fallopian tube. The diagnosis of primary peritoneal carcinoma was based on the criteria of the Gynecology Oncology Group: [198] 1) both ovaries are of normal size; 2) extra-ovarian involvement is greater than the involvement on the surface of either ovary; 3) the ovarian component was nonexistent (or the ovaries had been removed previously); or 4) the cytological characteristics were of the serous type. All cases of serous peritoneal cancer diagnosed after prophylactic-oophorectomy were considered to be primary peritoneal cancer. A single case of primary peritoneal cancer was diagnosed in a woman with intact ovaries. She had ovaries of normal size, with microscopic tumor ovarian involvement. She had metastatic serous papillary cancer in the omentum and throughout the peritoneum. Stage was defined using 1988 International Federation of Gynecology and Obstetrics criteria based on the clinical and the pathologic reports.[199]

**Statistical analysis**
Initially, the overall incidence of ovarian, fallopian tube and peritoneal cancer was determined in the entire cohort by survival analysis, using the Kaplan-Meier method. For this estimate, all women were considered to be at risk and all incident cancers were included. Secondly, we estimated the actuarial risks of ovarian, fallopian tube and peritoneal cancer in the subgroups of women with both ovaries intact and following oophorectomy. Women in the first group were followed from study entry until they were diagnosed with cancer, underwent an oophorectomy, death, or completion of the follow-up questionnaire. The second group of women were followed from the date of oophorectomy or study entry (whichever came last) until they were diagnosed with cancer, death, or completion the follow-up questionnaire. This sub-cohort only included women who were free of cancer at the time of oophorectomy. Women who underwent an oophorectomy during the study follow-up period were transferred from the first group to the second group at that time (see below).

The derived incidence rates for women with intact ovaries were then used to estimate the penetrance of ovarian cancer to age 75 years. Penetrance estimates for \textit{BRCA1} and \textit{BRCA2} carriers were derived by applying the calculated age-specific rates to a theoretical cohort of women from the age of 30 years until age 75 years. These rates were applied both for women with and without breast cancer.

The expected numbers of ovarian cancers for each subgroup were then calculated using age- and country-specific incidence rates derived from the IARC Scientific Publication “Cancer Incidence in Five Continents”.[200] Expected numbers were calculated separately for each of the six countries, by five-year age groupings, beginning at age 30 years and ending at age 75 years. The observed women-years of risk in each age-country category were multiplied by expected cancer incidence to estimate the total expected number of cancers for each category. The standardized incidence ratios (SIRs) were determined by summing the observed and expected numbers of cancers. Statistical significance was evaluated using the Poisson test.

The Cox proportional hazards model was used to determine the hazard ratio (HR) of cancer in women after oophorectomy, compared with women with two ovaries intact.
Oophorectomy was included in the model as a time-dependent covariate. The hazard ratio was adjusted for age at study entry, oral contraceptive use (ever vs. never), breastfeeding (number of months), parity (0, 1, 2, 3, 4+), mutation (BRCA1 or BRCA2) and country of origin. For purposes of this comparison, the 11 women in the cohort in whom ovarian cancer was identified at the time of prophylactic oophorectomy were considered to be at risk for ovarian cancer from the date of the baseline questionnaire until the date of the oophorectomy, and were withdrawn from the cohort at that time (i.e. their cancer was assigned to neither subgroup).

4.4 Results

There were 1828 women in the cohort who completed a baseline questionnaire and who provided follow-up information. The mean age of the cohort at study entry was 47.3 years (range 30-74 years). 1380 participants (75.5%) carried a BRCA1 mutation, 440 (24.1%) carried a BRCA2 mutation and 8 (0.4%) carried both a BRCA1 and BRCA2 mutation.

Of the 1828 subjects, 555 (30.4%) subjects had a prophylactic bilateral salpingo-oophorectomy prior to study entry and 1273 subjects had not had bilateral salpingo-oophorectomy. Of the 1273 women who had intact ovaries, 490 (38.5%) underwent an oophorectomy during the follow-up period. The women who had an oophorectomy were, on average, 3.8 years older than women who had intact two ovaries (45.1 years versus 48.9 years; p < 0.001). There were 834 out of 1045 women (80%) who carried a BRCA1 mutation, compared with 546 out of 783 (70%) of women with intact ovaries (p < 0.001). However, the women who did and who did not have oophorectomies were similar with respect to past history of breast cancer, parity and the use of oral contraceptives and HRT. The characteristics of the participants are presented in table 4.1.

The women were followed for a mean of 3.5 years. Among the women with intact ovaries, 32 cancers were observed (29 ovarian, two fallopian tube and one primary
peritoneal cancer). The mean age at diagnosis was 53.8 years (range 34 to 72 years). Twenty-nine cancers developed in BRCA1 mutation carriers (mean age 53.5 years) and three cancers developed in BRCA2 mutation carriers (mean age 57.3 years). Twenty-four (75%) of the women had a personal history of breast cancer.

During the follow-up period, 490 women underwent a prophylactic oophorectomy. Of these women, 11 (2.2%) were diagnosed with occult cancer at the time of preventive surgery (table 4.2). Seven of the cancers were classified as ovarian and three were diagnosed as primary fallopian tube carcinoma. In one case, the peritoneal washings were positive for carcinoma but no source of cancer was found in either the ovaries or fallopian tubes. The mean age at the time of prophylactic surgery for women diagnosed with occult cancer was 47.7 years (range 38 years-68 years). The youngest cancer diagnosed at prophylactic oophorectomy was at age 38 years; eight of the 11 cases were diagnosed prior to age 50 years. Only one of the eleven patients had died of cancer, four years after her diagnosis of stage I disease. The other ten patients are alive after a mean of 2.2 years (range, 1-5 years).

Seven women were diagnosed with primary peritoneal cancer following after preventive oophorectomy (mean age 51.1 years). Six were BRCA1 mutation carriers and one was a BRCA2 mutation carrier. Four underwent bilateral salpingo-oophorectomy and three had their ovaries, fallopian tubes and uterus removed. On average, 5.3 years had elapsed from preventive surgery to cancer diagnosis (median 3 years; range 1 to 20 years) (table 4.3). Four of these seven women have died of their disease (average survival three years).

The risks for ovarian, fallopian tube and primary peritoneal cancers for women with intact ovaries, by age and mutation type, are presented in table 4.4. The highest incidence rate was observed for BRCA1 mutation carriers between the ages of 60 years and 70 years (annual risk, 3505/100,000). The risk of peritoneal cancer following oophorectomy was 217 per 100,000 per year (table 4.5). The risk was modestly higher for BRCA1 mutation carriers (230 per 100,000) than for BRCA2 mutation carriers (167/100,000) but the difference was non-significant. The observed numbers of cancers, by age group and mutation type, were then compared with the expected numbers, based
on cancer registry information (Cancer Incidence in Five Continents[200]). The ratios of observed to expected numbers are represented as Standard Incidence Ratios (SIR) (table 4.5). Based on the calculated incidence rates for women with two intact ovaries, the penetrance of ovarian cancer was estimated to be 62% to age 75 years for BRCA1 mutation carriers and 18% to age 75 for BRCA2 mutation carriers (figure 4.1).

The Kaplan-Meier probabilities of remaining cancer-free for BRCA1 mutation carriers, with and without intact ovaries, are presented in figure 4.2. A Cox proportional hazards model was then used to estimate the extent of risk reduction associated with prophylactic oophorectomy for BRCA1 and BRCA2 carriers combined. The multivariable model also included terms for age, gene, country of origin, past history of breast cancer, oral contraceptive use, breast-feeding and parity. The crude hazard ratio associated with oophorectomy was 0.26 (95% CI, 0.09 - 0.74). After adjustment for covariates, there was an 80% reduction in risk associated with oophorectomy in this study (HR, 0.20; 95% CI: 0.07 – 0.58.
4.5 Discussion

We estimate that the risk of ovarian, fallopian tube and peritoneal cancer is reduced by 80% for \textit{BRCA1} and \textit{BRCA2} mutation carriers who undergo a prophylactic oophorectomy. Ours is the largest prospective study of \textit{BRCA1} and \textit{BRCA2} mutation carriers to date to examine the risks for these cancers in women with, and without, ovaries. Based on the incidence rates calculated here, we estimate the risk of ovarian cancer to be 62% for \textit{BRCA1} carriers and 18% for \textit{BRCA2} carriers in women up to age 75 with both ovaries intact. The penetrance estimate for \textit{BRCA1} is higher than most previous estimates; but it is based on 29 incident cancers and chance may be a factor. However, there are other possible reasons for the high observed rates. Previous estimates have been based on reports of family histories [29, 55, 56, 196, 197] and in general, these have not excluded relatives who had undergone an oophorectomy from the at-risk group. Furthermore, patients may have incomplete knowledge about their relatives’ cancer histories. In contrast, we have included only confirmed cases of cancer in our study. Secondly, a high proportion of cancer cases in our study had a previous diagnosis of breast cancer (70%). We found suggestive evidence that the risk of ovarian, fallopian tube and peritoneal cancer was higher in women with previous breast cancer than in women without a history of breast cancer history (HR= 2.0; p = 0.07). This may be a chance finding but it is also possible that there are common risk factors for breast and ovarian cancer, or that some aspect of breast cancer treatment increases the risk of subsequent ovarian cancer. We have recently reported that tamoxifen treatment was associated with a small, but non-significant increase in the risk of ovarian cancer.[61] In this study, we estimated the risk for ovarian cancer following breast cancer to be 13% at ten years for \textit{BRCA1} mutation carriers and 7% for \textit{BRCA2} mutation carriers.

It is also possible that our risk estimate might be high because we did not obtain a follow-up questionnaire on all women who completed a baseline questionnaire. If there has been preferential reporting of the follow-up status for women who developed ovarian, fallopian tube or peritoneal cancer, then this might lead to a spurious risk increase. Furthermore, the 1828 subjects included our study were similar to the 1064 patients with no follow-up information, in terms of age of interview, and the proportions with a history
of breast cancer, or who had previously used oral contraceptives or HRT (data not shown).

The women in our study were tested because of a personal or family history of breast or ovarian cancer. These participants are representative of the women who are referred for genetic testing, but may experience a higher level of cancer risk than unselected women in the general population.

Liede et al.[57] examined cancer incidence in a population of Jewish women who were at risk for ovarian cancer in a historical cohort study. They estimated the 10-year risk for \textit{BRCA1} carriers for ovarian, peritoneal or fallopian tube cancer to be 21%, or approximately 2% per year. This is higher than our finding of an annual risk of 1.4% per year in \textit{BRCA1} mutation carriers. Liede et al.[57] also estimated the risk of peritoneal cancer to be much higher (20% at ten years), but their study was completed among women with ovaries and it is difficult to diagnose this condition in the presence of intact ovaries. We recorded only a single case of peritoneal cancer among women with intact ovaries, versus seven cases in women following oophorectomy. It is easier to estimate the risk of peritoneal cancer among women after the ovaries have been removed because the problem of misclassification is thereby diminished.

Ovarian cancer risk is age-dependent and age differences may account for variations in the risk estimates for various studies. It is also possible that the risk varies with the actual mutation. In the Liede study,[57] the majority of mutations were the common 185delAG mutation. Recently, Gronwald et al.[201] reported significant differences in ovarian cancer risk for each of the three founder \textit{BRCA1} mutations in Poland.

Women who carry a mutation in the \textit{BRCA1} gene are asked to consider prophylactic bilateral salpingo-oophorectomy at age 35, or thereabouts, in order to reduce the risk of ovarian, fallopian tube and breast cancer. [101, 202] Our observations support this recommendation. It may be reasonable to wait until a time closer to menopause to prevent ovarian and fallopian tube cancer in \textit{BRCA2} carriers but this delay will diminish the level of protection offered against breast cancer in this subgroup.[101]
We estimate the magnitude of the risk reduction for ovarian, fallopian tube and peritoneal cancer to be approximately 80%. Previous estimates of the effectiveness of prophylactic oophorectomy have varied widely, from 60%-95% [97, 98, 140, 141, 145, 203] but none of these estimates were based on a large prospective study. Earlier studies were based on family history alone[140, 141] or were retrospective studies,[97, 203] case-control studies,[145] or small prospective studies.[98]

Early studies did not take into consideration genetic status. Tobacman et al.[140] reported peritoneal cancer in three of 28 women after prophylactic oophorectomy, and Piver et al.[141] reported six primary peritoneal cancers in a cohort of 324 high-risk women, occurring from one to 27 years after prophylactic oophorectomy. In these two studies, all women had a family history of ovarian cancer but none had undergone genetic testing.

Rebbeck et al.[97] determined the incidence of ovarian cancer in 259 women who had undergone prophylactic oophorectomy and 292 matched controls that had not undergone the procedure. They reported that prophylactic oophorectomy significantly reduced the risk of ovarian cancer by 96% (hazard ratio of 0.04), based on two observed cases of papillary serous peritoneal carcinoma, which occurred four and nine years after prophylactic oophorectomy. However, this was not a prospective study and, in most cases, genetic testing had taken place after the diagnosis of the incident cancer. In a similar study from the Netherlands, Olivier et al.[203] reported that three of 84 BRCA1 mutation carriers developed primary peritoneal cancer after oophorectomy. In all three cases the fallopian tubes had been left intact, suggesting that these cases may actually have had tubal origins. Rutter et al.[145] identified five women with a BRCA1 mutation who developed peritoneal cancer following oophorectomy. Compared to a cancer-free control group, they estimated the cancer risk reduction associated with bilateral oophorectomy to be 71% (OR = 0.29; 95% CI 0.12-0.73).

In the only other purely prospective study reported to date, Kauff et al.[98] reported a hazard ratio of 0.25 for breast and gynecologic cancers combined in a cohort of 170 BRCA mutation carriers who chose prophylactic surgery, compared with those who were
followed by surveillance alone. They estimated the reduction in risk for ovarian, peritoneal and fallopian tube cancer to be 85%; however only a single case of cancer was diagnosed following oophorectomy and the risk reduction was not statistically significant. Powell et al.[131] reported two cases of primary peritoneal cancer after prophylactic salpingo-oophorectomy in a cohort of 67 participants. Both cancers were diagnosed five years after surgery.

The women in this study were aware of their genetic status and it is probable that most women underwent regular surveillance for early detection of ovarian cancer by vaginal ultrasound and/or CA-125 blood levels; however, most of the incident cancers were diagnosed after the patients experienced clinical symptoms of ovarian cancer, and were discovered at an advanced surgical stage. Three of seven cancers diagnosed through prophylactic oophorectomy were stage IA.

We identified eleven cancers in 490 women at the time of prophylactic oophorectomy, representing a prevalence of 2.4% of BRCA1 mutation carriers and 1.8% of BRCA2 mutation carriers undergoing the operation. The prevalence of occult carcinomas in previous studies of oophorectomy patients varies widely. Comparisons have been hampered by the lack of standardized pathologic exam of the tissue at the time of the surgery. In 1985, Chen et al. reported a case of a woman who underwent prophylactic oophorectomy and subsequently died of intra-abdominal carcinomatosis.[204]

On retrospective examination of the ovaries, a small focus of adenocarcinoma was found on the ovarian surface. Numerous other authors have also emphasized the need for rigorous pathologic examination.[115, 127, 131, 145, 150, 204]

Among 98 BRCA mutation carriers who underwent prophylactic oophorectomy at Memorial Sloan-Kettering Cancer Center, three early-stage neoplasms were found (3.1%).[98] Finch et al.[127] reported on seven cancers identified in 159 BRCA-mutation-positive women (4.4%) at prophylactic oophorectomy and Rebbeck et al. reported six (2.3%) diagnoses of occult stage I ovarian cancer among 259 women who underwent prophylactic oophorectomy.[97] Powell et al.[131] found six microscopic ovarian cancers and one apparent ovarian cancer among 41 BRCA mutation carriers at
oophorectomy (17%). It is possible that fewer peritoneal cancers will be diagnosed after oophorectomy if the comprehensive pathology review of the salpingo-oophorectomy specimens is conducted on all patients (undiagnosed cancers at the time of surgery will be considered primary peritoneal cancer when they become clinically apparent).

In order to estimate penetrance in an unbiased fashion, we did not include these cancers detected at prophylactic oophorectomy for the construction of our incidence rates. For the estimation of rates among women with ovaries intact, women were considered to be at risk until the time of the prophylactic oophorectomy. For the construction of the rate among women after oophorectomy, we considered women to be at risk from the date of oophorectomy.

We estimate the risk of peritoneal cancer in the twenty years following oophorectomy to be 4.3% - or roughly nine times greater than the ovarian cancer risk in the non-carrier population. On average, the peritoneal cancers were diagnosed five years after oophorectomy, but three cases were diagnosed within three years of surgery. It is possible that these are actually metastases of sub-clinical disease that was present at the time of surgery and that we have over-estimated the risk of incident peritoneal cancer. It is currently recommended that removed ovaries and fallopian tubes receive close examination to identify microscopic disease.[127]

In the future, it will be important to address the question of whether or not the risk of peritoneal cancer might be reduced by non-surgical means such as oral contraceptives.

The primary strength of our study is that this is the first large-scale prospective study of ovarian cancer risk in women with BRCA1 and BRCA2 mutations. Previous studies have either been very small (and the results non-significant) or they used a historical cohort design whereby genetic testing took place after the diagnoses of the incident cancers. Historical cohort studies are subject to bias because women who experience the endpoint of interest (ovarian, fallopian tube or peritoneal cancer) may be more (or less) likely to undergo testing than healthy women because of local genetic testing criteria or high mortality. The mortality experience of women with peritoneal cancer may be even greater. Our study supports the recommendation for prophylactic oophorectomy as a
highly effective means of reducing the risk of ovarian and fallopian tube cancer in 
BRCA1 and BRCA2 carriers. We estimate the magnitude of the risk reduction to be 
approximately 80% and the residual risk of 4% of peritoneal cancer is not sufficiently 
high to recommend against the procedure. It is important that both the fallopian tubes 
and ovaries be removed because either site may be the origin of cancer and both organs 
should be examined in fine detail to rule out the presence of microscopic disease.[127]
Table 4.1 Characteristics of 1828 participants in the cohort study

<table>
<thead>
<tr>
<th></th>
<th>No oophorectomy N = 783</th>
<th>Oophorectomy at baseline N = 555</th>
<th>Oophorectomy during follow-up N = 490</th>
<th>All subjects N = 1828</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline, mean (range)</td>
<td>45.1 (30-74)</td>
<td>51.3 (30-74)</td>
<td>46.3 (30-74)</td>
<td>47.3 (30-74)</td>
</tr>
<tr>
<td>Age at prophylactic oophorectomy, mean (range)</td>
<td>-</td>
<td>45.2 (13-74)</td>
<td>47.6 (19-76)</td>
<td>46.4 (13-78)</td>
</tr>
<tr>
<td>Mutation, No. %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1 (%)</td>
<td>546 (69.7)</td>
<td>460 (82.9)</td>
<td>374 (76.3)</td>
<td>1380 (75.5)</td>
</tr>
<tr>
<td>BRCA2 (%)</td>
<td>233 (29.8)</td>
<td>94 (16.9)</td>
<td>113 (23.1)</td>
<td>440 (24.1)</td>
</tr>
<tr>
<td>Both</td>
<td>4 (0.5)</td>
<td>1 (0.2)</td>
<td>3 (0.6)</td>
<td>8 (0.4)</td>
</tr>
<tr>
<td>Mean follow-up, years (range)</td>
<td>3.27 (0.01-9.6)</td>
<td>3.60 (0.1-9.6)</td>
<td>3.75 (0.3-9.8)</td>
<td>3.50 (0.01-9.8)</td>
</tr>
<tr>
<td>Previous breast cancer (%)</td>
<td>421 (53.8)</td>
<td>331 (59.6)</td>
<td>366 (54.3)</td>
<td>1018 (55.7)</td>
</tr>
<tr>
<td>Mean age of diagnosis (years)</td>
<td>41.3</td>
<td>43.3</td>
<td>41.4</td>
<td>42 (22-73)</td>
</tr>
<tr>
<td>Parity, mean (range)</td>
<td>2.0 (0-10)</td>
<td>2.2 (0-8)</td>
<td>2.1 (0-10)</td>
<td>2.1 (0-10)</td>
</tr>
<tr>
<td>OC use at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever (%)</td>
<td>516 (66.8)</td>
<td>369 (67.0)</td>
<td>352 (72.1)</td>
<td>1237 (68.3)</td>
</tr>
<tr>
<td>Mean duration (years)</td>
<td>5.8</td>
<td>5.3</td>
<td>6.0</td>
<td>5.7</td>
</tr>
</tbody>
</table>
Table 4.2 Description of cancers diagnosed at prophylactic oophorectomy

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Mutation</th>
<th>Age at PO*</th>
<th>Site</th>
<th>Surgical Stage</th>
<th>Previous Breast cancer</th>
<th>Vital Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BRCA1</td>
<td>49</td>
<td>Ovary</td>
<td>IIIC</td>
<td>Yes</td>
<td>Alive at 50</td>
</tr>
<tr>
<td>2</td>
<td>BRCA1</td>
<td>43</td>
<td>Ovary</td>
<td>IIIC</td>
<td>Yes</td>
<td>Alive at 46</td>
</tr>
<tr>
<td>3</td>
<td>BRCA1</td>
<td>51</td>
<td>Ovary</td>
<td></td>
<td>Yes</td>
<td>Alive at 56</td>
</tr>
<tr>
<td>4</td>
<td>BRCA1</td>
<td>38</td>
<td>Ovary</td>
<td>IIIC</td>
<td>Yes</td>
<td>Alive at 39</td>
</tr>
<tr>
<td>5</td>
<td>BRCA2</td>
<td>68</td>
<td>Tubal</td>
<td>IA</td>
<td>Yes</td>
<td>Alive at 69</td>
</tr>
<tr>
<td>6</td>
<td>BRCA1</td>
<td>49</td>
<td>Malignant cytology</td>
<td>-</td>
<td>No</td>
<td>Alive at 46</td>
</tr>
<tr>
<td>7</td>
<td>BRCA1</td>
<td>40</td>
<td>Ovary</td>
<td>IA</td>
<td>Yes</td>
<td>DOD** 44</td>
</tr>
<tr>
<td>8</td>
<td>BRCA2</td>
<td>51</td>
<td>Tubal</td>
<td>IA</td>
<td>No</td>
<td>Alive at 57</td>
</tr>
<tr>
<td>9</td>
<td>BRCA1</td>
<td>49</td>
<td>Tubal</td>
<td>IIIC</td>
<td>No</td>
<td>Alive at 51</td>
</tr>
<tr>
<td>10</td>
<td>BRCA1</td>
<td>45</td>
<td>Ovary</td>
<td></td>
<td>Yes</td>
<td>Alive at 46</td>
</tr>
<tr>
<td>11</td>
<td>BRCA1</td>
<td>46</td>
<td>Ovary</td>
<td></td>
<td>Yes</td>
<td>Alive at 47</td>
</tr>
</tbody>
</table>

*PO=Prophylactic Oophorectomy
**DOD=dead of disease
- Not available
Table 4.3 Description of primary peritoneal cancers diagnosed following prophylactic oophorectomy.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Mutation</th>
<th>Age at PO</th>
<th>Procedure</th>
<th>Age at Diagnosis</th>
<th>Previous Breast cancer</th>
<th>Vital Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BRCA2</td>
<td>46</td>
<td>TAH-BSO</td>
<td>49</td>
<td>No</td>
<td>DOD 52</td>
</tr>
<tr>
<td>2</td>
<td>BRCA1</td>
<td>44</td>
<td>BSO</td>
<td>45</td>
<td>Yes</td>
<td>DOD 49</td>
</tr>
<tr>
<td>3</td>
<td>BRCA1</td>
<td>38</td>
<td>BSO</td>
<td>43</td>
<td>No</td>
<td>DOD 46</td>
</tr>
<tr>
<td>4</td>
<td>BRCA1</td>
<td>51</td>
<td>BSO</td>
<td>71</td>
<td>No</td>
<td>Alive at 72</td>
</tr>
<tr>
<td>5</td>
<td>BRCA1</td>
<td>51</td>
<td>TAH-BSO</td>
<td>55</td>
<td>Yes</td>
<td>Alive at 57</td>
</tr>
<tr>
<td>6</td>
<td>BRCA1</td>
<td>36</td>
<td>TAH-BSO</td>
<td>38</td>
<td>No</td>
<td>Alive at 40</td>
</tr>
<tr>
<td>7</td>
<td>BRCA1</td>
<td>55</td>
<td>BSO</td>
<td>57</td>
<td>Yes</td>
<td>DOD 59</td>
</tr>
</tbody>
</table>

PO=Prophylactic Oophorectomy
TAH-BSO Total abdominal hysterectomy and bilateral salpingo-oophorectomy
DOD=dead of disease
Table 4.4. Annual risks of ovarian, peritoneal or fallopian tube cancer in $BRCA1$ and $BRCA2$ carriers with intact ovaries.

<table>
<thead>
<tr>
<th>Age group</th>
<th>$BRCA1$</th>
<th></th>
<th></th>
<th></th>
<th>$BRCA2$</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Cancers</td>
<td>Person years</td>
<td>Annual risk (per 100,000 per year)</td>
<td>N</td>
<td>Cancers</td>
<td>Person years</td>
<td>Annual risk (per 100,000 per year)</td>
</tr>
<tr>
<td>30-39</td>
<td>346</td>
<td>2</td>
<td>973.2</td>
<td>206</td>
<td>86</td>
<td>0</td>
<td>290</td>
<td>0</td>
</tr>
<tr>
<td>40-49</td>
<td>328</td>
<td>13</td>
<td>678.2</td>
<td>1918</td>
<td>133</td>
<td>0</td>
<td>385</td>
<td>0</td>
</tr>
<tr>
<td>50-59</td>
<td>164</td>
<td>9</td>
<td>297.0</td>
<td>3030</td>
<td>79</td>
<td>2</td>
<td>204</td>
<td>986.6</td>
</tr>
<tr>
<td>60-69</td>
<td>52</td>
<td>4</td>
<td>114.1</td>
<td>3505</td>
<td>38</td>
<td>1</td>
<td>108</td>
<td>927.1</td>
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<tr>
<td>70-74</td>
<td>21</td>
<td>1</td>
<td>59.3</td>
<td>1685</td>
<td>8</td>
<td>0</td>
<td>19.7</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>911</td>
<td>29</td>
<td>2121.9</td>
<td>1367</td>
<td>344</td>
<td>3</td>
<td>1006.7</td>
<td>298.5</td>
</tr>
</tbody>
</table>

11 cancers diagnosed at prophylactic oophorectomy were excluded.
<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Total person years</th>
<th>Observed cancers</th>
<th>Total expected cancers</th>
<th>Observed incidence (per 100,000 per year)</th>
<th>Expected incidence (per 100,000 per year)</th>
<th>SIR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>p-value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1828</td>
<td>6177</td>
<td>50</td>
<td>1.34</td>
<td>782</td>
<td>21.0</td>
<td>37.3</td>
<td>&lt;10&lt;sup&gt;-4&lt;/sup&gt;</td>
</tr>
<tr>
<td>BRCA1</td>
<td>1380</td>
<td>4751</td>
<td>44</td>
<td>0.98</td>
<td>926</td>
<td>20.6</td>
<td>44.9</td>
<td>&lt;10&lt;sup&gt;-4&lt;/sup&gt;</td>
</tr>
<tr>
<td>BRCA2</td>
<td>440</td>
<td>1606</td>
<td>6</td>
<td>0.33</td>
<td>373</td>
<td>20.8</td>
<td>17.9</td>
<td>&lt;10&lt;sup&gt;-4&lt;/sup&gt;</td>
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<td>Yes</td>
<td>1018</td>
<td>3503</td>
<td>34</td>
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<td>970</td>
<td>24.1</td>
<td>40.3</td>
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<td>2893</td>
<td>16</td>
<td>0.49</td>
<td>553</td>
<td>16.9</td>
<td>32.7</td>
<td>&lt;10&lt;sup&gt;-4&lt;/sup&gt;</td>
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<tr>
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<tr>
<td>All</td>
<td>1262</td>
<td>3152</td>
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<td>167</td>
<td>23.9</td>
<td>7.0</td>
<td>&lt;10&lt;sup&gt;-4&lt;/sup&gt;</td>
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</tbody>
</table>

<sup>a</sup>SIR=standardized incidence ratio
<sup>b</sup>p-values were calculated by Poisson test
<sup>c</sup>PO=Prophylactic oophorectomy
Figure 4.1 Penetrance of ovarian, fallopian tube and peritoneal cancer among carriers of *BRCA1* and *BRCA2* mutations.
Figure 4.2 Kaplan-Meier estimated incidence of ovarian, peritoneal and fallopian cancer for all \textit{BRCA1} mutation carriers.
5 CHAPTER FIVE

Breast and Ovarian Cancer Risk Perception after Prophylactic Salpingo-oophorectomy due to an Inherited Mutation in the \textit{BRCA1} or \textit{BRCA2} Gene

\textit{Adapted from:}

Amy Finch, Kelly Metcalfe, Janet Lui, Caitlin Springate, Rochelle Demsky, Susan Armel, Barry Rosen, Joan Murphy, Laurie Elit, Ping Sun, Steven Narod. Breast and Ovarian Cancer Risk Perception after Prophylactic Salpingo-oophorectomy due to an Inherited Mutation in the \textit{BRCA1} or \textit{BRCA2} Gene. \textit{Clin Genet} \textbf{75}, 220-4 (2009).[170]
5.1 Abstract:

Background: It is often recommended that women who carry a mutation in the \textit{BRCA1} or \textit{BRCA2} gene have their ovaries and fallopian tubes removed to reduce their risk of gynecologic cancer. The aim of the current study is to evaluate women’s perception of their risk of breast and ovarian cancer before and after prophylactic salpingo-oophorectomy.

Methods: We surveyed 127 women who carry a \textit{BRCA1} or \textit{BRCA2} mutation and who underwent prophylactic salpingo-oophorectomy at the University Health Network, Toronto. Subjects were asked to estimate their risks of breast and ovarian cancer, before and after surgery. Their perceived risks of cancers were then compared to published risks, based on their mutation status.

Results: \textit{BRCA1} carriers estimated their risk of breast cancer risk to be, on average, 69% before surgery and 41% after surgery. They estimated their risk of ovarian cancer to be 55% before surgery and 11% after surgery. \textit{BRCA2} carriers estimated their risk of breast cancer to be 69% prior to surgery and 45% after surgery, and their perceived risk of ovarian cancer to be 43% before surgery and 8% after surgery. Compared to published risk figures, the perceived risk of ovarian cancer before prophylactic salpingo-oophorectomy was overestimated by 47% of \textit{BRCA1} mutation carriers and by 61% of \textit{BRCA2} mutation carriers.

Conclusion: Most women who have undergone genetic counseling and subsequently choose prophylactic salpingo-oophorectomy accurately perceive their risk of breast
cancer. However, in this study, many women overestimated their risk of ovarian cancer, particularly women that carry a BRCA2 mutation.
5.2 Introduction:

Prophylactic salpingo-oophorectomy is recommended to women at high risk of ovarian and fallopian tube cancer [116]. The procedure has been shown to decrease the risk of gynecologic cancers in women of all ages and of breast cancer when carried out in premenopausal years [97-101].

The goals of cancer genetic counseling include the introduction of strategies to prevent or reduce the risk of cancer, and an achievement of an accurate understanding of cancer risk [205-207]. Many studies have focused on changes in risk perception among women with an increased susceptibility to cancer risk in response to genetic counseling and genetic testing [207-211]. Studies have also examined how personal and family histories of cancer relate to perception of risk and the uptake of screening and preventive measures [119, 166, 211]. There are few studies that examine the perception of risk following an intervention to reduce cancer risk [166, 168].

We asked women who carry a $BRCA1$ or $BRCA2$ mutation, and who chose to undergo prophylactic salpingo-oophorectomy, to estimate their risk of developing breast and ovarian cancer, before and after surgery.

5.3 Patients and Methods:

Women with a $BRCA1$ or $BRCA2$ mutation who elected to undergo prophylactic salpingo-oophorectomy at The University Health Network from January 1, 2000 to May 31, 2006 were invited to participate. Subjects were contacted from December 2002 until May 2007. To introduce the study, a letter of invitation and an information sheet was mailed from the gynecologic oncologist who performed the surgery. The subject was then contacted by telephone and the study was explained. Each study subject who elected to participate was mailed a questionnaire assessing satisfaction with their decision to undergo prophylactic salpingo-oophorectomy and their perception of risk, approximately one year following surgery. In this questionnaire, women were asked to estimate what they believed their lifetime risk of breast cancer and ovarian cancer to be before, and after, prophylactic salpingo-oophorectomy by
marking along a scale from 0 to 100 percent. A second follow-up questionnaire was sent approximately three years after surgery to a subset of these women (with sufficient follow-up time). Women who did not return their questionnaires were contacted one time by telephone as a reminder. All subjects had genetic counseling as part of the genetic testing process prior to participation in this study, including a discussion of risks for cancer and the reduction in risk associated with prophylactic salpingo-oophorectomy. The study was approved by the Research Ethics Board at the University Health Network.

Published estimates of risk for breast cancer and ovarian cancer in women who carry BRCA1 or BRCA2 mutations were used as standards, and compared to the perceived risks in this study. These estimates of risk for breast cancer are similar for BRCA1 and BRCA2 and range from 45% to 87% [29, 197]. The risk of ovarian cancer ranges from 39% to 54% for BRCA1 and 11% to 23% for BRCA2 [29, 55, 56, 197]. Studies have found that breast cancer risk can be reduced by up to 50% if salpingo-oophorectomy is performed prior to menopause and that ovarian cancer risk can be reduced by up to 95% [97-101, 212].

All data, including perception of cancer risks, were coded and entered in an Access database. The statistical package SAS (version 9.1) was used for analysis. The paired t-test procedure was used to compare perceived risk at one and three years post-surgery. The unpaired t-test procedure was used to compare the perceived change in breast cancer risk for women under age 50 and for women over age 50. The Pearson Correlation Coefficient was calculated to evaluate the relationship between age at the time of surgery and perceived risk of breast and ovarian cancer, before and after surgery. Statistical significance was defined at the level of \( p \leq 0.05 \). All statistical tests were two-tailed.

5.4 Results:

A total of 188 women with a BRCA1 or BRCA2 mutation underwent prophylactic salpingo-oophorectomy at a Canadian hospital between January 1, 2000 and May 31, 2006. One hundred and eighty women were contacted to participate in a study of the impact of the prophylactic surgery (five women were excluded from the study because they were diagnosed with occult
ovarian or fallopian tube cancer at the time of the surgery; one woman died of breast cancer prior to mailing of the follow-up questionnaire; and two women were not contacted due to illness). Of the 180 women, 127 (71%) women agreed to participate and returned the questionnaire regarding risk perception, between six months and four years after surgery. Eight (4%) women declined to participate and 45 (25%) women agreed to participate in the study, but did not return the questionnaire. The questionnaires were completed on average 17 months (range 6-48.5 months) after surgery. The characteristics of the study subjects are described in table 5.1.

As expected, women in this study perceived a significant reduction in risk of breast and ovarian cancer as a result of surgery (see table 5.2). The perceived reduction in risk from before to after surgery was significant, with a p-value of <0.0001 for risk of both breast and ovarian cancer.

The range of perceived risks was broad before and after surgery for both breast and ovarian cancer (table 5.2). The great majority of BRCA1 carriers (30 of 34 or 88%) estimated their breast cancer risk to be within 5% of the actual range for BRCA1, (45-87%). This number was similar for BRCA2; 25 of 29 (86%) women estimated their risk within the actual range (45-87%).

Twenty-eight of 74 (38%) BRCA1 carriers estimated their ovarian cancer risk prior to surgery within 5% of the range of published risk figures. Forty-seven percent overestimated their risk and 16% underestimated their risk. Nineteen of 51 (37%) BRCA2 carriers estimated their risk within 5% of published risk figures; 61% overestimated their risk, and 2% underestimated this risk. The range of perceived risk for ovarian cancer after surgery was 0% to 95%. Twenty-eight of 74 (38%) BRCA1 carriers estimated their risk of ovarian cancer after surgery to be less than five percent. Thirteen of the 74 (18%) estimated their risk to be zero. Twenty-seven of 51 (53%) BRCA2 carriers estimated their risk to be less than 5% and 11 of the 51 (22%) estimated their risk to be zero.

There was no significant correlation between current age and perceived risk of breast cancer, before or after surgery, or between age and perceived risk of ovarian cancer after surgery. However, there was a significant negative correlation between age and perceived risk of ovarian cancer before surgery (-0.20, p-value=0.02). Women under 50 at the time of surgery perceived a significantly greater risk reduction from prophylactic surgery (mean 30% reduction in risk)
compared to women over age 50 (mean 13% reduction in risk) (p-value=0.02) (women with a personal history of breast cancer or prophylactic mastectomy were excluded from this analysis).

A number of women were surveyed twice to determine if their perception of risk was stable over time. Forty-three women in this study completed two follow-up questionnaires; the first at a mean of 12 months post surgery (range 6-18 months) and the second at a mean of 37 months post surgery (range 35-42 months). Their perception of their breast and ovarian cancer risks did not change significantly over this time period (see table 5.3). Perceived risks reported by \( BRCA1 \) and \( BRCA2 \) carriers were combined for this analysis. When \( BRCA1 \) and \( BRCA2 \) were analyzed separately, there were no differences with the exception of \( BRCA2 \) carrier’s perception of their ovarian cancer risk before surgery. Their perception of risk increased from a mean of 31% at one year to 43% at three years post surgery (n=18, p-value 0.02).

5.5 Discussion:

One of the purposes of genetic counseling and genetic testing for \( BRCA1 \) and \( BRCA2 \) is to educate women about cancer risk and to facilitate the selection of cancer risk-reduction strategies. Studies reporting on perception of risk for breast and ovarian cancer, before and after genetic counseling, show inconsistent findings. Braithwaite et al performed a review of five controlled trials and 16 prospective studies which evaluated the impact of genetic counseling [213]. They found that knowledge of cancer genetics improved through counseling, but not all prospective studies showed that risk estimation was more accurate after counseling.

A study by Cull et al evaluated women’s perception of ovarian cancer risk prior to attending a familial ovarian cancer clinic [206]. Perceived risk was compared to actual risk based on family history. They found that more women underestimated than overestimated their ovarian cancer risk. Huiart et al studied the effects of genetic consultation on perception of familial risk of breast and ovarian cancer in low, moderate and high-risk women [210]. They found that genetic counseling did not affect the perceived risk of the women at high risk (who perceived their risk to be high prior to, and after, genetic consultation). McInerney-Leo et al looked at whether perception of breast and ovarian cancer risk changes following genetic counseling and receipt of
genetic test results [207]. Perception of cancer risk was assessed prior to testing and six to nine months after testing. They found that those who tested positive did not have a change in perception of breast cancer risk, but did have a significant increase in perception of ovarian cancer risk. These studies examined perception of cancer risk in individuals with a family history of cancer. In contrast, the current study evaluates perception of cancer risk only in women found carry a mutation in the \textit{BRCA1} or \textit{BRCA2} gene. In addition, we evaluated the impact of prophylactic surgery on risk estimation.

Our study shows that the women understood the effectiveness of the surgery for both breast and ovarian cancer risk. There was no relationship between age at surgery and perceived risk of breast cancer. Perceived risk of ovarian cancer before surgery was inversely correlated with age. Patients are not routinely counseled that lifetime risk is based on current age and this was evident in their perception of risk. A greater reduction in breast cancer risk was reported by women that were under age 50 at the time of surgery compared to women that were greater than age 50, consistent with the understanding that premenopausal prophylactic oophorectomy is associated with a decrease in breast cancer risk, whereas postmenopausal oophorectomy is not.

Although perceived risk of ovarian cancer decreased significantly after surgery, a large range was reported. Of note, approximately 20% of both \textit{BRCA1} and \textit{BRCA2} carriers believed that their ovarian cancer risk was eliminated following prophylactic surgery; though the risk of peritoneal cancer is small, this risk should be included in the counseling discussion.

Based on estimates taken at one and three years post-surgery in this cohort, we found that perceived cancer risk did not change over time. This contrasts with previous studies that have shown that perceived risk often reverts to pre-counseling levels [208, 214]. Watson et al. examined patient’s perception of risk before and after genetic counseling [208]. They showed that although subject’s perceived of risk of breast cancer was more accurate directly after counseling, the information was poorly retained following counseling, and the number of subjects reporting the correct risk declined at one year following counseling. Lloyd and colleagues (1996) reported similar results. They found that despite clinic attendance, 66% of women continued to over or under estimate their lifetime risk of developing cancer. However, in both of these studies, the women were not known \textit{BRCA1} or \textit{BRCA2} carriers.
Limitations:

A limitation of this study is the retrospective design. Study subjects were not asked to report their risk perception before undergoing surgery. As a result, the perception of risk of women that elected to have screening instead of surgery was not evaluated in this study. They may have had lower risk perception reflected by the willingness to forgo primary prevention in favor of screening. In addition, the pre-surgery perception of risk is reported months after surgery, a possible source of recall bias. The response rate may also introduce bias. Twenty-five percent of women agreed to participate but did not return the questionnaire. Lastly, although the data supports that perception of risk was stable over time, the range of time since surgery is broad (6-48.5 months). Perception of risk may have been different if subjects were surveyed at exactly one, two and three years after surgery.

Women who learn they carry a *BRCA1* or *BRCA2* mutation and subsequently go on to have prophylactic salpingo-oophorectomy have an accurate perception of their breast cancer risk, but many have an inflated perception of their ovarian cancer risk before and after surgery. This risk perception appears to be stable over time. Women who continue to perceive themselves at high risk for ovarian or ovarian-like cancers after prophylactic salpingo-oophorectomy may benefit from additional counseling.
Table 5.1: Characteristics of 127 study subjects

<table>
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<tr>
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<th>BRCA1</th>
<th>BRCA2</th>
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<tr>
<td>Number of subjects (N)</td>
<td>75</td>
<td>52</td>
</tr>
<tr>
<td>Age at surgery, mean (range)</td>
<td>45.3 (35-63)</td>
<td>48.8 (37-67)</td>
</tr>
<tr>
<td>Months since surgery</td>
<td>16.4 (6-39)</td>
<td>16.9 (10.5-48.5)</td>
</tr>
<tr>
<td>Previous breast cancer</td>
<td>48% (N=36)</td>
<td>41% (N=21)</td>
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</table>
Table 5.2: Perceived risks for breast and ovarian cancer as reported after prophylactic salpingo-oophorectomy

<table>
<thead>
<tr>
<th></th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast risk before surgery*</td>
<td>69% (N=34)  (range 10-100)</td>
<td>69% (N=29)  (range 20-100)</td>
</tr>
<tr>
<td>Breast risk after surgery*</td>
<td>41% (N=34)  (range 0-99)</td>
<td>45% (N=29)  (range 0-85)</td>
</tr>
<tr>
<td>Ovary Risk before Surgery†</td>
<td>55% (N=74)  (range 40-100)</td>
<td>43% (N=51)  (range 5-92)</td>
</tr>
<tr>
<td>Ovary risk after Surgery†</td>
<td>11% (N=74)  (range 0-90)</td>
<td>8% (N=51)   (range 0-95)</td>
</tr>
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</table>

* excludes subjects that did not report perceived risk for one type of cancer
† excludes subjects that had a previous diagnosis of breast cancer or prophylactic mastectomy
Table 5.3: Perceived risk of breast and ovarian cancer at one and three years following surgery

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<th>First Follow-up</th>
<th>Second Follow-up</th>
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<tr>
<td>Follow-up time: mean (range)</td>
<td>12 (6-18)</td>
<td>37 (35-42)</td>
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<tr>
<td>Breast risk before surgery* (n=17)</td>
<td>64%</td>
<td>65%</td>
</tr>
<tr>
<td>Breast risk after surgery* (n=17)</td>
<td>39%</td>
<td>28%</td>
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<tr>
<td>Ovarian risk before surgery (n=43)</td>
<td>44%</td>
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<tr>
<td>Ovarian risk after surgery (n=43)</td>
<td>5%</td>
<td>7%</td>
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</table>

*excludes women with breast cancer or prophylactic mastectomy
6  CHAPTER SIX

The Impact of Prophylactic Salpingo-oophorectomy on Quality of Life and Psychological Distress in Women who carry a *BRCA* Mutation

6.1 Abstract

**Objectives:** To measure the impact of prophylactic salpingo-oophorectomy on health-related quality of life and psychological distress in women who carry a *BRCA* mutation.

**Methods:** Women who underwent prophylactic salpingo-oophorectomy between August 20, 2003 and June 26, 2008 because of a *BRCA1* or *BRCA2* mutation were invited to participate. Participants completed three questionnaires (SF-12® Health Survey, Basic Symptom Inventory and the Impact of Events Scale) before prophylactic surgery and again one year after surgery. Measures of health-related quality of life, of general psychological distress and of ovarian cancer worry, before and after surgery were compared.

**Results:** Few women who underwent salpingo-oophorectomy experienced a worsening in physical or mental functioning after salpingo-oophorectomy. On average, women experienced less ovarian cancer-specific worry after surgery; 34.3% experienced moderate to severe ovarian cancer specific distress before surgery, compared to 18.6% after surgery.

**Conclusions:** For most women, physical and mental health-related quality of life did not deteriorate after prophylactic salpingo-oophorectomy and they were less worried about ovarian cancer. A subset of women continued to experienced moderate to severe cancer-specific distress. Identification of these women is important in order to provide continued counseling and support.
6.2 Introduction

In a Canadian study of the preventive choices made by women who carry a \textit{BRCA1} or \textit{BRCA2} mutation, approximately 60% of women between the ages of 35 and 70 elected to undergo prophylactic salpingo-oophorectomy.\cite{1} Similar results were found in an international study.\cite{2} Prior to surgery, women are interested in knowing how their general physical functioning and emotional health will change as a result of surgery.\cite{215} It is important that women are made aware of the possible risks and the benefits of this surgery.

To date, studies of health-related quality of life and psychological functioning associated with prophylactic salpingo-oophorectomy have been cross-sectional comparing women who have chosen screening vs. surgery at one point in time or small prospective studies.\cite{167-169, 171, 172, 174, 216} These studies included women who proceeded to surgery for a family history of ovarian cancer, but without a \textit{BRCA} mutation. This prospective study examines changes over time in psychological distress and health-related quality of life, before and after prophylactic salpingo-oophorectomy, in a series of women who carry a \textit{BRCA1} or \textit{BRCA2} mutation.

6.3 Patients and Methods

Subjects were women who elected to undergo prophylactic salpingo-oophorectomy to reduce their risk of ovarian, fallopian tube and breast cancer due to a mutation in the \textit{BRCA1} or \textit{BRCA2} gene. Subjects were recruited from the University Health Network in Toronto between August 20, 2003 and June 26, 2008. Women were between 30 and 70 years of age at the time of surgery. Women who had been diagnosed with breast cancer prior to surgery were included. Women diagnosed with occult cancer at surgery or diagnosed with breast cancer during the one year follow-up period were excluded. Women were invited to participate by letter, followed by a phone call during the month before surgery. Subjects provided written consent and completed a Medical History Questionnaire and three standardized questionnaires (described below). Women who completed the baseline questionnaires were contacted by mail one year after their surgery and asked to complete the questionnaires again. Those who did not respond were contacted by mail or telephone.
Instruments

The Medical History Questionnaire was designed specifically for this study and requests information about reproductive history, menopausal status, personal cancer history, prophylactic mastectomy, and all medications, including HRT.

The Short Form Health Survey (SF-12®) is derived from the widely used validated SF-36® Health Survey, a 36 item questionnaire used to measure eight domains of health related quality of life.[217] The eight items are: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and mental health. At least one item from each of the eight health domains measured by the SF-36® is included in the SF-12®. There are two summary component measures; physical (PCS) and mental (MCS) health. The standard version with a 4-week recall period was used. Raw scores are converted to standardized area T scores based on 1998 general population norms with a mean of 50 and a standard deviation of 10. Lower scores indicate lower functioning. A change in score from before to after surgery of five points for either component of the SF-12® Health Survey is considered clinically significant. In tests of validity and reliability, scores for the SF-12® were highly correlated with those of the SF-36® for both the physical component score ($R^2=0.911$) and the mental component score ($R^2=0.938$) and test-retest correlations (2 weeks) were 0.89 for the physical component score and 0.79 for the mental component score of the SF-12®.[218]

The Basic Symptom Inventory 18 (BSI® 18) is derived from the 53-item BSI®, a self-report symptom inventory.[219] It was designed to screen for psychological distress and psychiatric disorders in research settings, and medical and community populations and to measure treatment outcomes.[220] The BSI® 18 measures three domains, somatization (distress caused by bodily dysfunction such as faintness, dizziness, weakness, nausea, and numbness or tingling), depression (symptoms of dysphoric mood, self-deprecation, inability to experience pleasurable emotions, loss of hope and suicidal ideation) and anxiety (symptoms of nervousness, tension, restlessness, and apprehension).[220] Raw scores are converted to standardized area T scores based on female community norms with a mean of 50 and a standard deviation of 10. An overall
global severity score represents the subject’s overall level of psychological distress. Individuals with global scores of 63 or greater or with scores on any two of three dimensions of 63 or greater are considered at high risk for a psychiatric disorder or a “case”. The internal consistency (Cronbach’s Alpha) ranges from 0.74-0.89 for the three dimensions of the BSI® 18 and the global severity index. Test-retest reliability was 0.68 to 0.90 for the three domains and the global severity index that are common to the BSI® and the BSI® 18.[220] A large study of cancer patients has demonstrated that scores derived from the BSI® and the BSI® 18 are comparable.[221]

The Impact of Events Scale (IES) is a 15-item self-report questionnaire used to measure current subjective distress for a particular life event or situation (i.e. being at high risk for ovarian cancer). There are two subscales: 1) intrusion (intrusively experienced ideas, images, feelings or bad dreams) and 2) avoidance (consciously recognized avoidance of certain ideas, feelings or situations).[222] The possible range of responses for intrusion is 0-35 and 0-40 for avoidance. The global score is the sum of the intrusion and avoidance scores with a possible range of 0-75. Global scores from 26-43 indicate moderate distress. Global scores above 44 indicate severe distress. Internal consistency for the scale (Cronbach’s Alpha) is 0.78 for intrusion and 0.82 for avoidance. Test-retest reliability for a one-week interval is 0.87 for the total stress score with 0.89 for the intrusion sub-scale and 0.79 for the avoidance sub-scale.[222] Internal consistency and reliability was found to be similar among a group of women at increased risk for breast cancer.[223] Only a small proportion of variation in IES scores can be attributed to participant characteristics such as age and gender whereas type of event and time since the event are strong predictors of levels of stress reactions as measures by the IES.[224]

6.4 Analysis

The SF-12® Health Survey was scored using QualityMetric Health Outcomes™ Scoring Software 3.0 including Missing Data Estimation for missing items. The scoring software evaluates data quality for completeness, convergent validity and discriminant validity. The BSI® 18 test was scored according to the Administration, Scoring, and Procedures Manual published by NCS Pearson Inc.[220] The IES was scored according to published methods and
questionnaires of subjects who missed one or more items were excluded from the analysis.[222] Student’s paired t-test was used to evaluate differences in scores between baseline and follow-up for all measures. Unpaired t-test was used to evaluate differences in scores between subgroups (i.e. premenopausal vs. postmenopausal, breast cancer (yes/no), HRT at follow-up (yes/no). Pearson’s correlation coefficient was used to test for relationships between health-related quality of life scores and reproductive history/lifestyle factors. The statistical package SAS (version 9.1) was used for analysis.

6.5 Results

A total of 186 women with a BRCA mutation underwent prophylactic salpingo-oophorectomy at the University Health Network from August 20, 2003 to June 26, 2008. 183 of 186 were contacted to participate in the study prior to surgery and 126 (68.9%) women completed the baseline questionnaires prior to surgery. Of the 126 women, 12 (9.5%) were later excluded; six of these women were diagnosed with occult cancer at surgery; one woman was diagnosed with colon cancer just prior to prophylactic surgery; one woman died from a previous breast cancer; and four women were diagnosed with breast cancer during the one year follow-up period. An additional 18 (14.3%) women who completed the baseline questionnaires did not complete the follow-up questionnaires, leaving 96 subjects for analysis. There were no statistically significant differences between participants and non-participants in terms of age at surgery (p=0.29) or BRCA mutation (BRCA1 or BRCA2) (p=0.17).

Characteristics of the 96 participants are described in table 6.1. Ninety-three subjects completed the SF-12® at baseline and follow-up, 89 completed the BSI® 18 and 70 completed the IES. The mean age of all subjects at surgery was 47.7 years and 67.7% of subjects were premenopausal at the time of surgery. Thirty-seven women (38.5%) had a personal history of breast cancer and the average age at surgery for these women was 49.1 years. Twenty-nine (30%) of the women were taking HRT at the time of the follow-up questionnaires.
SF-12® Health Survey: Physical Functioning and Quality of Life

The mean summary scores measuring physical functioning before surgery (physical component score (PCS) 51.97) and after surgery (PCS 50.86) were similar to those of population controls (i.e. were less than 0.5 standard deviations from the population mean of 50). This was also true for women stratified by 1) previous diagnosis of breast cancer, 2) menopausal status at the time of surgery, or 3) current use of HRT at follow-up. The mean change in physical functioning component score for all subjects of -1.11 (95% CI, -2.7-0.47) was not clinically significant (A change in score from before to after surgery of five points for is considered clinically significant).

Women with a previous diagnosis of breast cancer had lower physical functioning scores than women without breast cancer; and women who were not taking HRT at follow-up had lower physical functioning scores than women who were taking HRT (See table 6.2). This was true both before and after surgery. Postmenopausal women also had lower physical functioning scores than premenopausal women before and after surgery but these differences were not significant.

When examining women on an individual basis, 20 of 93 women (21.5%) had a clinically significant worsening of their physical well being (PCS score) while 13 women (14.0%) had a clinically significant improvement in their physical well being (McNemar’s Chi square, p=0.295).

A woman’s reproductive history (specifically age at first birth) was also correlated with her physical functioning. Women who had their first child in their thirties had significantly higher physical functioning scores after surgery (PCS= 54.33) compared with women who had their first child in their twenties (PCS=49.44) (p=0.0009). Age at first birth was correlated with changes in physical functioning during the year following surgery (r=0.43, p=0.0001) and physical functioning after surgery (r=0.38, p=0.0007), but not physical functioning before surgery (r=0.02, p=0.87). Neither level nor amount of physical activity before surgery was correlated with changes in physical functioning after surgery.
SF-12®: Mental Health and Quality of Life

The mean summary scores for mental health functioning before surgery (mental component score (MCS) 47.36) and after surgery (MCS 47.41) were similar to those of population controls (i.e. were less than 0.5 standard deviations from the population mean of 50). This was also true for women stratified by 1) previous diagnosis of breast cancer, 2) menopausal status at the time of surgery, or 3) current use of HRT at follow-up. The mean change in score for all subjects of 0.05 (95% CI, -1.8- 1.9) was not clinically significant. Twenty-one women (22.6%) had a clinically significant worsening of their mental well-being (MCS score) from before to after surgery while 25 (26.9%) women experienced a significant improvement in their mental well being (McNemar’s Chi square test p=0.659).

BSI® 18: General Psychological Distress

Psychological distress was measured in three domains: somatization, depression, and anxiety, with an overall global symptom index score, which incorporates all three domains. Somatization measures distress caused by bodily dysfunction such as faintness, dizziness, weakness, nausea, and numbness or tingling. Psychological distress before prophylactic salpingo-oophorectomy among women in the current study was similar to female population norms (somatization: 49.4, depression: 48.1, anxiety 50.4, and global symptom index: 48.9).[220] (see table 6.3) Of the three domains, there was a significant change in “somatization” (somatization: 52.5, depression: 48.8, and anxiety 49.2, global symptom index: 50.1). After surgery, women experienced an increase in somatization, (mean increase of 4.4 points (p=0.0008)). This increase was significant for premenopausal women (mean T score increase of 4.04 (p=0.0004) but was not significant for post-menopausal women (p=0.50).

Anxiety as measured by the BSI® 18 decreased after surgery for women who were premenopausal at the time of surgery (T score decrease of 2.43, p=0.04). This decrease was not observed among women who were postmenopausal at the time of surgery (p=0.35), however, their anxiety levels were somewhat lower prior to surgery than for premenopausal women (p=0.06).
Mean scores for depression remained unchanged after surgery. The number of women in the clinical range indicating clinically significant distress (Global T score of 63 or greater or scores of 63 or greater for 2 domains) was eight (9.0%) before surgery (two of whom had a prior breast cancer) and six (6.7%) after surgery (two of whom had a prior breast cancer).

**Impact of Events Scale: Worry about Ovarian Cancer**

The Impact of Events Scale measured cancer-specific distress related to being at high risk for ovarian cancer (see table 6.4). The mean intrusion subscale score for ovarian cancer worry before surgery was 8.7 (range 0-33) for all subjects. The mean score for women without breast cancer (7.7, range 0-30) was not significantly different than for women with a previous breast cancer (10.3, range 0-33) (p=0.21). After surgery, the mean score for intrusive thoughts decreased significantly to 3.4 (range 0-25) (p=0.004) for women without breast cancer and similarly to 4.6 (range 0-23) (p=0.002) for subjects with a history of breast cancer. The mean score before surgery for the avoidance subscale was 9.8 (range 0-32) for women without breast cancer and 11.6 (range 0-30) for women with breast cancer. These scores decreased to 5.6 (range 0-28) (p=0.006) for women without breast cancer and to 8.2 (range 0-32) (p=0.06) for subjects with breast cancer. The global scores (intrusion plus avoidance) dropped from a mean of 19.2 (range 0-57) before surgery to 10.4 (range 0-53) after surgery (p<0.0001). Before surgery, 18 of 70 (25.6%) women had a global score ranging from 26-43, indicating a moderate level of cancer specific distress, and six (8.6%) women had scores over 44, indicating severe distress. After surgery this decreased to nine of 70 (12.9%) women and four (5.7%) with scores in the severe range.

**6.6 Discussion**

We studied women with a BRCA mutation who elected to undergo risk-reducing salpingooophorectomy to decrease their risk of ovarian, fallopian tube and breast cancer. Overall, women in our study experienced quality of life comparable to that of the general population before and after prophylactic salpingo-oophorectomy. This observation is consistent with that of other
studies that have reported overall health-related quality of life in women who have undergone prophylactic oophorectomy to be similar to women in the general population and to women having ovarian cancer screening. [167, 169, 174] Two previous studies found that women who underwent prophylactic surgery had poorer functioning (lower scores for some subscales of the SF-36) compared to women who elected to have screening [171] or compared to the general population scores.[169] The latter study also found that women who were younger at the time of surgery (35-44 compared to 45-54 or 55-64) had poorer functioning than the age-matched population. However, these studies did not report the physical and mental component summary scores we report here making comparison difficult. We did not detect significant differences after surgery when comparing women by age (<45, ≥46) for the physical component summary score (mean difference=2.31, 95% CI, -1.55-6.17, p=0.24) or mental component summary score (mean difference=-0.81, 95% CI, -4.99-3.36, p=0.70), however the confidence intervals were wide. Women in our study who were taking HRT at the time of follow-up had better physical functioning than women who were not taking HRT.

We also found that women with a previous diagnosis of breast cancer had poorer functioning (both before and after surgery). This is contrary to Fang et al. who found that women with a previous diagnosis of breast cancer had better physical functioning scores before surgery than women who had not had breast cancer, and similar scores after surgery. [174] The differences in findings may be attributable to the smaller sample size of women with breast cancer in the study by Fang et al.

Approximately 20% of women in our study experienced a decline in physical functioning after surgery. A similar percentage of women experienced a decline in mental functioning. A comparable number of women experienced an increase in functioning in both areas. Interestingly, they were not the same women. In fact, there was a significant negative correlation (r=-0.37, p=0.0003) between changes in physical and mental health. Women who experienced a decline in their physical component scores did not also experience a decline in mental component scores.

Levels of general psychological distress among women in our study as measured by the BSI® were close to published norms for female controls and were considerably lower than mean scores
in all domains reported in an earlier study by our group.[168] Reasons for these differences are not clear but may be due to knowledge of BRCA mutation status. Not all women in the earlier study had had genetic counselling or genetic testing for BRCA1 and BRCA2 and lack of certainty around risk for cancer or greatly elevated perceived risk for cancer after surgery may have contributed to greater distress.

We found that 9% of women in our study were above clinical cut-offs (as defined by the BSI® 18) consistent with the need for clinical counseling before surgery compared to 7% after surgery. This is much lower than the 32% of women above the clinical cut-off described by Metcalfe et al. in a study of women who underwent prophylactic mastectomy in Ontario and lower than found in male and female cancer patients (30%).[221, 225]

Cancer specific distress before surgery was similar to previous reports of both women at increased risk for breast cancer and women at increased risk for ovarian cancer.[226, 227] Women with breast cancer in our study had somewhat higher levels of distress before surgery than women in previous studies [228, 229], possibly due to the timing of the questionnaire in relation to surgery. We found that women who undergo prophylactic salpingo-oophorectomy experience a significant decrease in cancer specific distress after surgery. This finding is consistent with a cross-sectional study by Madalinska et al. who found lower levels of cancer worry among women who had undergone prophylactic surgery compared to women who elected to have screening.[167] Tiller et al. also found that women who underwent prophylactic salpingo-oophorectomy experienced a significant decrease in ovarian cancer distress.[172]

A high proportion of women (34%) experienced moderate to severe ovarian cancer specific distress before surgery. This dropped significantly following surgery however, 18.6% of women experienced significant cancer specific distress after surgery. This is similar to the 20.7% reported by Robson et al. in their retrospective study.[169] Identification of these women and referral for support and counseling may be beneficial.

The strengths of this study include its prospective design and recruitment of women who carry a BRCA mutation from a single centre. All women referred for prophylactic salpingo-oophorectomy were able to access this medical care without cost, therefore the findings may be generalized to populations of varying socioeconomic status. Participants were not asked to report
education, ethnicity or other related factors somewhat limiting our ability to generalize our results to all populations. A possible limitation of our study is the timing of the completion of the questionnaires. Subjects were asked to complete questionnaires during the month prior to their prophylactic surgery; a time when distress related to their risk for ovarian cancer and surgery may have been heightened. In addition, approaching women to participate in this study during the month prior to surgery may have lowered our response rate and as a result may have created selection bias. Distress related to undergoing surgery may have influenced women’s decision to participate or not participate in this study.

This study provides valuable information to women making a decision about prophylactic salpingo-oophorectomy. Women electing to have the procedure may experience few if any health-related quality of life changes and will likely benefit from a decrease in ovarian cancer specific distress. There were significant differences in physical functioning between groups when stratified by breast cancer and by use of HRT. Women with a previous diagnosis of breast cancer and women who were not taking HRT at follow-up experienced poorer functioning both before and after surgery. Distress related to bodily dysfunction increased after surgery in women with and without a previous diagnosis of breast cancer. A subset of women who have undergone prophylactic salpingo-oophorectomy experienced significant cancer specific distress after surgery. Identification of these women is important in order to provide continued counseling and support.
### Table 6.1 Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All subjects</th>
<th>No Previous Breast Cancer</th>
<th>Previous Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=96</td>
<td>n=59</td>
<td>n=37</td>
</tr>
<tr>
<td>Age at surgery, mean (range)</td>
<td>47.7 (37-69)</td>
<td>46.9 (37-69)</td>
<td>49.1 (37-65)</td>
</tr>
<tr>
<td>Months of follow-up: mean (range)</td>
<td>13.7 (10.8-21.8)</td>
<td>13.6 (11.3-21.8)</td>
<td>13.9 (10.8-19.4)</td>
</tr>
<tr>
<td>Age distribution at surgery, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-39</td>
<td>12 (12.5)</td>
<td>7 (11.8)</td>
<td>5 (13.5)</td>
</tr>
<tr>
<td>40-44</td>
<td>27 (28.1)</td>
<td>20 (33.9)</td>
<td>7 (18.9)</td>
</tr>
<tr>
<td>45-49</td>
<td>25 (26.0)</td>
<td>14 (23.7)</td>
<td>11 (29.7)</td>
</tr>
<tr>
<td>50-54</td>
<td>18 (18.8)</td>
<td>13 (22.0)</td>
<td>5 (13.5)</td>
</tr>
<tr>
<td>55-59</td>
<td>6 (6.3)</td>
<td>3 (5.1)</td>
<td>3 (8.1)</td>
</tr>
<tr>
<td>60-69</td>
<td>8 (8.3)</td>
<td>2 (3.4)</td>
<td>6 (16.2)</td>
</tr>
<tr>
<td>Menopausal Status at surgery, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>65 (67.7)</td>
<td>47 (79.7)</td>
<td>18 (48.6)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>31 (32.3)</td>
<td>12 (20.3)</td>
<td>19 (51.4)</td>
</tr>
<tr>
<td>Mutation status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>48 (50.0)</td>
<td>28 (47.5)</td>
<td>20 (54.1)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>48 (50.0)</td>
<td>31 (52.5)</td>
<td>17 (45.9)</td>
</tr>
<tr>
<td>Hormone replacement therapy:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%) Current use at follow-up</td>
<td>29 (30.2)</td>
<td>24 (40.7)</td>
<td>5 (13.5)</td>
</tr>
</tbody>
</table>
Table 6.2 SF-12® Health Survey: Differences between Subgroups Before and After Surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-surgery scores</th>
<th>Post-surgery Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SF-12 Physical Component Score</td>
<td>SF-12 Mental Component Score</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Menopausal status at surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal n=63</td>
<td>53.23</td>
<td>46.28</td>
</tr>
<tr>
<td>Postmenopausal n=30</td>
<td>49.35</td>
<td>49.62</td>
</tr>
<tr>
<td>Personal history of breast cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No n=59</td>
<td>53.65</td>
<td>47.51</td>
</tr>
<tr>
<td>Yes n=34</td>
<td>49.06</td>
<td>47.09</td>
</tr>
<tr>
<td>Current use of HRT at follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No n=65</td>
<td>50.72</td>
<td>47.85</td>
</tr>
<tr>
<td>Yes n=28</td>
<td>54.87</td>
<td>46.22</td>
</tr>
<tr>
<td>Current use of SSRI SNRI at follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No n=80</td>
<td>51.92</td>
<td>48.24</td>
</tr>
<tr>
<td>Yes n=13</td>
<td>52.33</td>
<td>41.94</td>
</tr>
</tbody>
</table>

*Scores based on 1998 population norms with a mean of 50 and a standard deviation of 10
**Lower scores indicate lower functioning
***A change in score of ≥ five points in an individual is considered a clinically significant change
Table 6.3: BSI® 18: Area T Scores using Female Community Norms

<table>
<thead>
<tr>
<th>BSI® 18 Domain</th>
<th>All Subjects</th>
<th>Personal History of Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=89</td>
<td>No n=55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes n=34</td>
</tr>
<tr>
<td>Somatization</td>
<td>Pre-surgery</td>
<td>49.42</td>
</tr>
<tr>
<td>t-score</td>
<td>Post-surgery</td>
<td>52.49</td>
</tr>
<tr>
<td>(mean)</td>
<td>Difference</td>
<td>P=0.0008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P=0.013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P=0.027</td>
</tr>
<tr>
<td>Depression</td>
<td>Pre-surgery</td>
<td>48.09</td>
</tr>
<tr>
<td>t-score</td>
<td>Post-surgery</td>
<td>48.82</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>P=0.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P=0.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P=0.35</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Pre-surgery</td>
<td>50.38</td>
</tr>
<tr>
<td>t-score</td>
<td>Post-surgery</td>
<td>49.17</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>P=0.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P=0.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P=0.91</td>
</tr>
<tr>
<td>Global Score</td>
<td>Pre-surgery</td>
<td>48.85</td>
</tr>
<tr>
<td>t-score</td>
<td>Post-surgery</td>
<td>50.06</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>P=0.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P=0.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P=0.067</td>
</tr>
</tbody>
</table>

*All scores are area T scores have a mean of 50 and a standard deviation of 10

** Higher scores indicate poorer functioning
Table 6.4: Impact of Events Scale: Ovarian Cancer Specific Distress

<table>
<thead>
<tr>
<th>Subscale</th>
<th>All Subjects</th>
<th>Personal History of Breast Cancer*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=70</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mean (range)</td>
<td>No</td>
</tr>
<tr>
<td>Intrusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-surgery</td>
<td>8.7 (0-33)</td>
<td>7.7 (0-30)</td>
</tr>
<tr>
<td>Post-surgery</td>
<td>3.8 (0-25)</td>
<td>3.4 (0-25)</td>
</tr>
<tr>
<td>Difference</td>
<td>P&lt;0.0001</td>
<td>P=0.0042</td>
</tr>
<tr>
<td>Avoidance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-surgery</td>
<td>10.5 (0-32)</td>
<td>9.8 (0-32)</td>
</tr>
<tr>
<td>Post-surgery</td>
<td>6.6 (0-32)</td>
<td>5.6 (0-28)</td>
</tr>
<tr>
<td>Difference</td>
<td>P=0.0009</td>
<td>P=0.006</td>
</tr>
<tr>
<td>Sum Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-surgery</td>
<td>19.2 (0-57)</td>
<td>17.5 (0-57)</td>
</tr>
<tr>
<td>Post-surgery</td>
<td>10.4 (0-53)</td>
<td>8.9 (0-53)</td>
</tr>
<tr>
<td>Difference</td>
<td>P&lt;0.0001</td>
<td>P=0.003</td>
</tr>
</tbody>
</table>

*There were no significant differences in IES scores comparing women with and without breast cancer

**Higher scores indicate greater distress related to being at risk for ovarian cancer

***Sum Scores: 0-8 subclinical, 9-25 mild, 26-43 moderate, ≥44 severe distress
CHAPTER SEVEN

The Impact of Prophylactic Salpingo-oophorectomy on Menopausal Symptoms and Sexual Function in Women who carry a BRCA1 or BRCA2 Mutation

7.1 Abstract

**Objective:** Prophylactic salpingo-oophorectomy is recommended to women who carry a *BRCA1* or *BRCA2* mutation to reduce the risks of breast, ovarian and fallopian tube cancer. We measured the impact of prophylactic salpingo-oophorectomy on menopausal symptoms and sexual functioning in women with a *BRCA* mutation.

**Methods:** Women who underwent prophylactic salpingo-oophorectomy between October 1, 2002 and June 26, 2008 for a known *BRCA1* or *BRCA2* mutation were invited to participate. Participants completed questionnaires before prophylactic surgery and again one year after surgery. Measures of sexual functioning and menopausal symptoms before and after surgery were compared. Satisfaction with the decision to undergo prophylactic salpingo-oophorectomy was evaluated.

**Results:** 114 women who underwent prophylactic surgery completed questionnaires before and one year after surgery. Subjects who were premenopausal at the time of surgery (n=75) experienced a significant worsening of vasomotor symptoms (hot flashes, night sweats and sweating) and a decline in sexual functioning (desire, pleasure, discomfort and habit). The increase in vasomotor symptoms and the decline in sexual functioning were mitigated by HRT, but symptoms did not return to pre-surgical levels. HRT decreased vaginal dryness and dyspareunia; however, the decrease in sexual pleasure was not alleviated by HRT. Satisfaction with the decision to undergo prophylactic salpingo-oophorectomy was high regardless of increased vasomotor symptoms and decreased sexual function.
**Conclusions:** Women who undergo prophylactic salpingo-oophorectomy prior to menopause experience an increase in vasomotor symptoms and a decrease in sexual functioning. These symptoms are improved by HRT, but not to pre-surgical levels.
7.2 Introduction

Prophylactic salpingo-oophorectomy is recommended to women who carry a BRCA1 or BRCA2 mutation to reduce the risks of breast, ovarian and fallopian tube cancer[98, 99, 101, 116, 230]. Because the risks for these cancers in this population are substantial by the age of 40 [99], many women choose to have preventive surgery prior to menopause. Surgical menopause may impact on several aspects of health and quality of life [167, 188, 189]. Salpingo-oophorectomy performed after menopause may also affect quality of life [231].

Women who experience surgical menopause have a significant decrease in circulating levels of estrogen and testosterone [162, 232]. HRT is an option for BRCA carriers with no personal history of breast cancer, and does not alter the reduction in breast cancer risk associated with salpingo-oophorectomy [233, 234]. HRT reduces symptoms of menopause, such as hot flashes and vaginal dryness [173, 235]. However, the extent to which sexual function is improved with HRT is not clear [236-238].

Several studies have measured menopausal symptoms and sexual functioning in high-risk women after oophorectomy [168, 169, 171, 173]. However, it is optimal to compare vasomotor symptoms and sexual functioning before and after salpingo-oophorectomy. The effectiveness of HRT can also be evaluated. This is the first prospective study to examine the impact of prophylactic salpingo-oophorectomy on menopausal symptoms and sexual functioning among women who carry a BRCA1 or BRCA2 mutation.

7.3 Patients and Methods

Subjects were women who elected to undergo prophylactic salpingo-oophorectomy to reduce the risk of ovarian, fallopian tube and breast cancer due to a mutation in the BRCA1 or BRCA2 gene. Subjects were recruited from the University Health Network in Toronto between October 1, 2002 and June 26, 2008. Women were between 30 and 70 years of age at the time of surgery. Women who had been diagnosed with breast cancer prior to surgery were included. Women diagnosed
with occult cancer at surgery or with breast cancer during the one year follow-up period were excluded. Women were invited to participate by letter, followed by a phone call during the month before surgery. Subjects provided written informed consent and completed three questionnaires (see below). They also answered questions about the frequency and severity of hot flashes and satisfaction with their decision to undergo prophylactic salpingo-oophorectomy. Women who completed the baseline questionnaires were contacted by mail one year after their surgery to complete the questionnaires again. Those who did not respond were contacted by mail or telephone.

**Instruments**

The Medical History Questionnaire for this study included information about reproductive history, history of breast and other cancers, use of HRT and all other medications. The standardized Menopause-Specific Quality of Life questionnaire functions well in differentiating between women according to their quality of life and in measuring changes in their quality of life [239]. The four domains are: vasomotor, psychosocial, physical and sexual. The MENQOL was revised to become the MENQOL-Intervention by including three additional items to the physical domain (increased to 19 items) that may negatively affect quality of life related to HRT and selective estrogen receptor modifiers (i.e. tamoxifen). A summary score was added and the recall period was shortened from one month to one week [240]. For each item, subjects were asked if they were bothered by the symptom, and if yes, how bothered they were using a 7-point Likert scale, from 0 (not bothered) to 6 (extremely bothered). For scoring, the responses were then transferred to an 8-point scale, from 1 (the subject did not experience the symptom) to 8 (the subject was extremely bothered). For each domain, an increase in score indicates a worsening of symptoms and a decrease in score indicates an improvement. The MENQOL-Intervention has a test-retest reliability of 0.73, 0.78, 0.75, and 0.83 for the vasomotor, physical, psychosocial and sexual domains respectively [240]. Women were asked about the frequency of hot flashes on an average day in the previous week and the severity of these hot flashes. Study subjects were asked to categorize their hot flashes as either mild, moderate, severe or very severe [241]. The Sexual Activity Questionnaire evaluates: pleasure (desire, enjoyment and satisfaction), discomfort (vaginal dryness and pain during penetration) and habit (frequency of sexual activity compared to usual) [242]. The pleasure score is the sum of six items, the discomfort score is the sum of two
items and the habit score is derived from one item. A decrease in a score indicates a decline in sexual functioning. Test-retest reliability ($R^2$) ranges from 0.65-0.94 [242]. All subjects were asked to report their level of satisfaction with their decision to have a prophylactic salpingo-oophorectomy on a five point scale from 1 (very dissatisfied) to 5 (extremely satisfied) at follow-up one year after surgery.

7.4 Analysis

The MENQOL-Intervention and the Sexual Activity Questionnaire were scored according to published guidelines, including the imputation of missing scores for the MENQOL-Intervention questionnaire [239, 240]. The statistical package SAS (version 9.1) was used for analysis. Student’s paired t-test was used to evaluate changes in scores from baseline to follow-up for the MENQOL-Intervention Questionnaire and the Sexual Activity Questionnaire. One-way analysis of covariance was used to test for differences in menopausal symptoms and sexual function between groups (i.e. pre vs. postmenopausal, HRT vs. no HRT) controlling for possible confounders (age at surgery, menopausal status at surgery, previous breast cancer and current use of HRT at follow-up). One way analysis of covariance was used to test for differences in changes in scores over time between groups adjusting for possible confounders with the addition of the baseline value as a covariate. Pearson Correlation Coefficients were used to evaluate the relationship between changes in vasomotor symptoms and sexual functioning and satisfaction with the decision to undergo prophylactic salpingo-oophorectomy.

7.5 Results

A total of 213 women underwent prophylactic salpingo-oophorectomy at the University Health Network from October 1, 2002 to June 26, 2008. 209 of 213 were contacted to participate in the study prior to surgery. 144 of 209 (68.9%) women completed the baseline questionnaires prior to surgery. Of the 144 women, 13 (9%) were not eligible; seven of these women were diagnosed with occult cancer at surgery; one woman was diagnosed with colon cancer just prior to prophylactic surgery; one woman died from a previous breast cancer; and four women were
diagnosed with breast cancer during the one year follow-up period. An additional 17 (11.8%) women who completed the baseline questionnaires did not complete the follow-up questionnaires.

Characteristics of the 114 participants are described in table 7.1. Two women did not complete the MENQOL-Intervention and one did not complete the Sexual Activity Questionnaire and they were excluded from the analysis for that questionnaire. Women were considered to be premenopausal if they reported having a menstrual period within the previous year. Five women reported having a hysterectomy prior to salpingo-oophorectomy. Two of these women underwent salpingo-oophorectomy before age 50 and were considered to be premenopausal at time of prophylactic surgery. Women were considered to be current users of HRT (estrogen or estrogen and progesterone) if they reported taking HRT at the time the one year follow-up questionnaires were completed. There were no statistically significant differences between participants and non-participants in terms of age at surgery (p=0.60) or BRCA mutation (BRCA1 or BRCA2) (p=0.17). Seventy-five women were premenopausal at the time of surgery (age 37-53). Of these, 20 (27%) had a previous diagnosis of breast cancer. Twenty-nine of the 75 women (38.7%) reported taking HRT at the time of follow-up (current use). Five of 29 had a previous diagnosis of breast cancer. One of 29 women was using a vaginal estrogen suppository for hormone replacement for local symptom relief. Four (5.3%) women were taking tamoxifen, three (4%) were taking an aromatase inhibitor, and eight (10.6%) were taking a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) at the time of follow-up. Three (4%) women reported current use of testosterone in addition to estrogen or estrogen and progesterone.

Thirty-nine women were postmenopausal prior to surgery (age 37-69), and of these 27 (69.2%) had a previous diagnosis of breast cancer. Four of the 39 women (10.2%) were taking HRT, one of whom had a previous diagnosis of breast cancer. Eighteen of 39 (46.1%) were taking tamoxifen or an aromatase inhibitor, and seven (17.9%) were taking an SSRI or SNRI at the time of follow-up.
Menopausal Symptoms

Results for the Menopause-specific Quality of Life-Intervention (MENQOL-Intervention) Questionnaire are presented in table 7.2. The majority of women who were premenopausal at the time of surgery had a significant worsening of vasomotor symptoms after surgery (hot flashes, night sweats and sweating) (p<0.0001) and a decline in sexual functioning (decrease in sexual desire, vaginal dryness, and avoidance of intimacy) (p<0.0001). Compared to published norms [168, 243], women who were premenopausal at the time of surgery decreased in these domains to levels similar to women who are two to seven years post-menopause (see table 7.3).

Women who were taking HRT had significantly fewer vasomotor symptoms (p=0.0003) and reported better sexual functioning (p=0.015) after surgery than women who were not taking HRT. Both groups experienced a worsening of vasomotor symptoms and a decrease in sexual functioning, compared to pre-surgical levels. The increase in vasomotor symptoms and decline in sexual functioning were significantly greater for those who did not take HRT (p=0.0006 for vasomotor symptoms and p=0.018 for sexual functioning). Women who were postmenopausal at surgery did not experience a worsening of vasomotor symptoms. They did experience a small but statistically significant decrease in sexual functioning indicated by an increase in the sexual domain score (p=0.03).

Both women with and without a history of breast cancer experienced a significant worsening of vasomotor symptoms (p<0.01) and a decrease in sexual function (p<0.05). Premenopausal women with a previous diagnosis of breast cancer had more vasomotor symptoms before surgery than women without breast cancer (p=0.02). This difference did not persist after surgery (p=0.49).

The physical domain of the MENQOL-Intervention questionnaire measured symptoms that included, but were not limited to, difficulty sleeping, muscle aches, physical strength and energy. Premenopausal women who were under 50 at the time of surgery (n=62) and women with a previous diagnosis of breast cancer (n=20) both experienced a small but significant decrease in physical function after surgery (p<0.05). Items used to evaluate psychosocial functioning included questions about satisfaction with personal life, anxiety and nervousness, memory,
depression, and wanting to be alone. For the 15 women who were taking SSRIs or SNRIs at follow-up, psychosocial functioning improved after surgery (p=0.02).

**Hot Flash Frequency and Severity**

Prior to surgery, 23.3% (17/73) of premenopausal women experienced hot flashes. After surgery, this number increased to 73.9% (54/73). Of women who were taking HRT at follow-up, 58.6% (17/29) reported that they experienced hot flashes, compared to 84.1% (37/44) of women who were not taking HRT (p=0.03). Premenopausal women who were taking HRT also reported fewer hot flashes per day than women who were not taking HRT (p=0.004). In terms of hot flash severity, women who were premenopausal at surgery and who reported current use of HRT, stated that on average, 14.6% of their hot flashes were moderate to severe compared to 48.0% for non-HRT users. Prior to surgery, 61.5% of postmenopausal women experienced hot flashes, with 45.8% reported as moderate to severe. One year after surgery, 53.8% of these women experienced hot flashes with 37.2% reported as moderate to severe. Four of 39 women who were postmenopausal at surgery were taking HRT at follow-up.

**Sexual Functioning**

Eighty-three women (73.5%) reported that they were sexually active both before and after surgery. Women were significantly less likely to be sexually active if they had a previous diagnosis of breast cancer (p=0.001). Of the women who were sexually active before surgery, seven (7.6%) women reported that they became sexually inactive after surgery. All seven had partners and reported reasons for inactivity as either they were too tired (five women) and either they had a physical problem (three women) or their partner had a physical problem (two women).

Results of the sexual activity questionnaire are presented in table 7.4. On average, subjects who were premenopausal at surgery experienced a significant decrease in pleasure (p<0.0001), an increase in discomfort (p<0.0001) and a decrease in frequency (p=0.04) (table 7.4). Women who
were postmenopausal at surgery did not experience a significant decrease in the scores for these three factors. Prior to surgery, premenopausal women had better functioning (higher scores) for pleasure (p=0.058) than did postmenopausal women. However, after surgery, pre and postmenopausal women experienced similar levels of pleasure (p=0.48). Comparisons between our results and published norms for pre-and postmenopausal women are shown in table 7.5.

When women who were premenopausal at surgery were subdivided into those who were taking HRT at follow-up and those who were not, both groups experienced a significant decrease in pleasure and an increase in discomfort. At one year post-surgery, premenopausal subjects taking HRT experienced significantly less discomfort than women who did not take HRT (p=0.009), however their pleasure scores were similar (p=0.430).

**Satisfaction with Decision to Have Prophylactic Salpingo-oophorectomy**

The mean satisfaction score for all subjects was 4.55 out of five. Only five women were dissatisfied with their decision to undergo prophylactic surgery (score of 1 or 2). Dissatisfaction was related to onset of menopause for two women, surgical experience for two women and lack of information for one woman. Premenopausal and postmenopausal subjects reported very similar satisfaction scores (4.53 vs. 4.61, p=0.63). There was a significant correlation between increased discomfort (vaginal dryness and pain during penetration) and lower satisfaction with decision to have the surgery among premenopausal women who were not taking HRT (r=0.42, p=0.012). Changes in the physical and psychosocial domain (increase in symptoms) of the MENOL-Intervention Questionnaire were also significantly correlated with lower satisfaction with the decision to have the surgery in this group (r=-0.42, p=0.006 and -0.47, p=0.001). This was not observed among women who were postmenopausal at the time of surgery. There was no significant correlation between decrease in sexual pleasure or increase vasomotor symptoms and satisfaction with the decision to have prophylactic surgery among premenopausal women.
7.6 Discussion

We found that women who were premenopausal at the time of prophylactic oophorectomy experienced a significant increase in hot flashes, night sweats and sweating. Women taking HRT reported fewer moderate to severe hot flashes; however HRT did not entirely relieve vasomotor symptoms. Sixty percent of women taking HRT still experienced hot flashes on a daily basis. A previous cross-sectional study of surgically-induced menopausal women by Madalinska et al. found similar results [173]. Women who took HRT after surgery reported significantly fewer vasomotor symptoms than women who did not take HRT; however, when compared to premenopausal women undergoing screening, the surgically menopausal women who took HRT were more likely to report vasomotor symptoms.

We found that premenopausal women with a previous diagnosis of breast cancer had significantly more vasomotor symptoms before surgery than premenopausal unaffected women. This may be due to effects of breast cancer treatment on ovarian function [244, 245]. A subset of women undergoing chemotherapy may experience temporary amenorrhea and resume menstruation but may still experience vasomotor symptoms.

Women who were premenopausal at surgery experienced a decline in sexual function to levels comparable to that of older, postmenopausal women. This decline in sexual functioning (measured by the MENQOL-Intervention Questionnaire), was present regardless of HRT use. Women who were taking HRT experienced a smaller decline in function over time compared to women who did not take HRT. When pleasure and discomfort were evaluated separately, discomfort was found to be alleviated by HRT to some extent, but HRT did not ameliorate the decrease in sexual pleasure that followed surgical menopause.

Androgens are produced in both the ovaries and the adrenal glands. After oophorectomy, serum levels of androgens decrease by 50% in both premenopausal and postmenopausal women [162, 246] and it has been postulated that the reduction in androgens resulting from bilateral oophorectomy is a factor in sexual dysfunction [247-250]. Testosterone therapy has shown to improve sexual functioning [238, 248, 251, 252]. In the current study three women were taking testosterone. The benefits of testosterone must be considered in light of a possible increase in breast cancer risk, particularly in this population at high risk for breast cancer [230, 253, 254].
Results from studies of testosterone and breast cancer risk are mixed but favour an increased risk for breast cancer with higher levels of endogenous testosterone and with testosterone replacement therapy [253-258].

In the current study, women who were postmenopausal at the time of surgery also experienced a decline in sexual functioning. These findings correspond with retrospective cross-sectional studies of women who reported dyspareunia after surgery and decreased satisfaction with sexual functioning [168, 169]. An earlier study from our group evaluated menopausal symptoms and sexual functioning in a cross-sectional study of women who underwent prophylactic salpingooophorectomy. Despite the fact that 65% of subjects were taking HRT at the time of the study, satisfaction with sexual functioning was compromised in 54% of women [168].

In studies to date, HRT after prophylactic salpingo-oophorectomy has not been associated with an increase in breast cancer risk in BRCA1 and BRCA2 carriers [233, 234]. Our findings suggest that HRT provides significant relief of hot flashes, night sweats and sweating after surgical menopause. It also provides some relief from sexual discomfort.

Fang et al. have published a prospective study, which compared women undergoing prophylactic surgery for family history or BRCA mutation to those who elected serial screening [174]. They reported that quality of life deficits that were present at one month post surgery were no longer apparent at six and 12 months post-surgery, with the exception of bodily pain. Women in the surgery group experienced greater pain at 12 month post-surgery. A retrospective study by Fry et al. also found no significant differences in sexual functioning between women who elected prophylactic surgery and those who elected to have screening [171]. It is possible that smaller sample sizes or differing characteristics of the women in these two studies compared with ours account for the differences in our findings.

The impact of increased menopausal symptoms and decreased sexual function can be understood through women’s satisfaction with their decision to undergo prophylactic salpingooophorectomy. Women in this study reported a high level of satisfaction. An increase in sexual discomfort, and in physical symptoms (difficulty sleeping, muscle aches, decrease in physical strength and energy) and psychosocial symptoms (dissatisfaction with personal life, anxiety and nervousness, poor memory, depression, and wanting to be alone) were related to satisfaction in
our study among women who were premenopausal at surgery and who were not taking HRT at follow-up. Of note, satisfaction was not altered by increased vasomotor symptoms or decreased sexual pleasure.

Our study is limited by the small sample size. Subjects in our study were not randomized to HRT and as a result may be subject to confounding by indication. Women who elected to take HRT may have experienced more vasomotor symptoms or sexual discomfort due to vaginal dryness. In addition, the majority of subjects in this study underwent hysterectomy at the time of salpingo-oophorectomy so we cannot distinguish the effects of hysterectomy independent of oophorectomy.

The strengths of this study include its prospective design and recruitment of women who carry a \textit{BRCA} mutation from a single centre. To date, there has been very little prospective data regarding changes in quality of life related to sexual functioning and vasomotor symptoms in women who elect to undergo prophylactic salpingo-oophorectomy. These women are unique given the young age at salpingo-oophorectomy and concomitant factors such as risk of breast cancer or history of breast cancer. Our study finds that women who are premenopausal at the time of surgery experience an increase in vasomotor symptoms and a decline in sexual functioning from baseline to one-year following surgery that are somewhat but not fully mitigated by HRT. Women who experience a decline in sexual pleasure do not derive a significant benefit from traditional HRT. This study provides information for women who are considering prophylactic surgery about what they may experience in the year following surgery and the possible benefits HRT may provide. It is important for clinicians and their patients to weigh the possible costs of surgery, such as symptoms related to hormone deprivation, in light of the substantial benefits derived from surgery (decrease in cancer risk). Larger long-term prospective studies are needed to develop a greater understanding of the long-term effects of prophylactic salpingo-oophorectomy.
Table 7.1 Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All subjects n=114</th>
<th>Premenopausal at surgery n=75</th>
<th>Postmenopausal at surgery n=39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at surgery, mean (range)</td>
<td>47.5 (35-69)</td>
<td>44.7 (35-53)</td>
<td>52.7 (37-69)</td>
</tr>
<tr>
<td>Procedure, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSO only</td>
<td>5 (4.4)</td>
<td>2 (2.7)</td>
<td>3 (7.7)</td>
</tr>
<tr>
<td>BSO, prior TAH</td>
<td>5 (4.4)</td>
<td>2 (2.7)</td>
<td>3 (7.7)</td>
</tr>
<tr>
<td>TAH BSO</td>
<td>104 (91.2)</td>
<td>71 (94.7)</td>
<td>33 (84.6)</td>
</tr>
<tr>
<td>Months of follow-up: mean (range)</td>
<td>13.6 (10.8-21.8)</td>
<td>13.7 (10.9-21.8)</td>
<td>13.4 (10.8-19.3)</td>
</tr>
<tr>
<td>Age distribution at surgery, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-39</td>
<td>16 (14.0)</td>
<td>14 (18.7)</td>
<td>2 (5.1)</td>
</tr>
<tr>
<td>40-44</td>
<td>31 (28.0)</td>
<td>24 (33.3)</td>
<td>7 (17.9)</td>
</tr>
<tr>
<td>45-49</td>
<td>31 (25.4)</td>
<td>27 (33.3)</td>
<td>4 (10.3)</td>
</tr>
<tr>
<td>50-54</td>
<td>20 (18.4)</td>
<td>10 (14.7)</td>
<td>10 (25.6)</td>
</tr>
<tr>
<td>55-59</td>
<td>7 (6.1)</td>
<td>0</td>
<td>7 (17.9)</td>
</tr>
<tr>
<td>60-69</td>
<td>9 (7.9)</td>
<td>0</td>
<td>9 (23.1)</td>
</tr>
<tr>
<td>Mutation status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>58 (50.8)</td>
<td>41 (54.7)</td>
<td>17 (43.6)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>56 (49.1)</td>
<td>34 (45.3)</td>
<td>22 (56.4)</td>
</tr>
<tr>
<td>Height (inches) mean (range)</td>
<td>64.2 (56-70)</td>
<td>64.1 (56-70)</td>
<td>64.2 (60-69)</td>
</tr>
<tr>
<td>Weight at time of surgery (lbs) mean (range)</td>
<td>148.6 (95-245)</td>
<td>145.8 (104-245)</td>
<td>154.1 (95-210)</td>
</tr>
<tr>
<td>BMI at time of surgery, mean (range)</td>
<td>25.5 (17.3-43.4)</td>
<td>25.1 (17.8-43.4)</td>
<td>26.2 (17.3-38.4)</td>
</tr>
<tr>
<td>Previous breast cancer, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>47 (41.2)</td>
<td>20 (26.6)</td>
<td>27 (69.2)</td>
</tr>
<tr>
<td>No</td>
<td>67 (58.7)</td>
<td>55 (73.3)</td>
<td>12 (30.7)</td>
</tr>
<tr>
<td>Hormone replacement therapy: n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current use at follow-up</td>
<td>33 (28.9)</td>
<td>29 (38.7)</td>
<td>4 (10.3)</td>
</tr>
</tbody>
</table>
Table 7.2 Menopausal Symptoms Before and After Salpingo-oophorectomy Stratified by Menopausal Status and Use of Hormone Replacement Therapy

<table>
<thead>
<tr>
<th>Domain</th>
<th>Menopausal status</th>
<th>Premenopausal Women: Current HRT use at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Premenopausal (n=73)</td>
</tr>
<tr>
<td>Vasomotor</td>
<td>Baseline</td>
<td>1.92</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>3.39</td>
</tr>
<tr>
<td></td>
<td>Change</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>Baseline</td>
<td>2.70</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>2.83</td>
</tr>
<tr>
<td></td>
<td>Change</td>
<td>p=0.45</td>
</tr>
<tr>
<td>Physical</td>
<td>Baseline</td>
<td>2.29</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>2.51</td>
</tr>
<tr>
<td></td>
<td>Change</td>
<td>p=0.07</td>
</tr>
<tr>
<td>Sexual</td>
<td>Baseline</td>
<td>2.03</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>3.52</td>
</tr>
<tr>
<td></td>
<td>Change</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

An increase in a score indicates an increase in symptoms where 1=no symptoms and 8=extremely bothered by symptoms

*Analyses adjusted for age at surgery, previous breast cancer and use of HRT at follow-up

**Analyses adjusted for age at surgery and previous breast cancer

†Adjusted for baseline value in addition to other variables
Table 7.3 Menopause-specific Quality of Life-Intervention Questionnaire

<table>
<thead>
<tr>
<th>Domain</th>
<th>Pre-surgery*</th>
<th>Post-surgery*</th>
<th>Hilditch et al.[243]</th>
<th>Elit et al.[168]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor</td>
<td>1.92</td>
<td>3.39</td>
<td>3.14</td>
<td>2.8</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>2.70</td>
<td>2.84</td>
<td>2.72</td>
<td>3.3</td>
</tr>
<tr>
<td>Physical</td>
<td>2.29</td>
<td>2.51</td>
<td>2.45</td>
<td>3.3</td>
</tr>
<tr>
<td>Sexual</td>
<td>2.02</td>
<td>3.52</td>
<td>2.32</td>
<td>3.6</td>
</tr>
</tbody>
</table>

An increase in score indicates an increase in symptoms

*Mean scores for subjects in the current study who were premenopausal at the time of surgery
# Table 7.4 Sexual Functioning Before and After Salpingo-oophorectomy Stratified by Menopausal Status and Use of Hormone Replacement Therapy

<table>
<thead>
<tr>
<th></th>
<th>Menopausal Status at surgery</th>
<th>Premenopausal Women: Current HRT use at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Premenopausal (N=61)</td>
<td>Post-menopausal (N=22)</td>
</tr>
<tr>
<td><strong>Age at surgery</strong></td>
<td>43.9</td>
<td>52.8</td>
</tr>
<tr>
<td><strong>Pleasure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>13.48</td>
<td>10.55</td>
</tr>
<tr>
<td>Follow-up</td>
<td>11.35</td>
<td>9.90</td>
</tr>
<tr>
<td>Change</td>
<td>p&lt;0.0001</td>
<td>p=0.50</td>
</tr>
<tr>
<td><strong>Discomfort</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.77</td>
<td>3.41</td>
</tr>
<tr>
<td>Follow-up</td>
<td>3.51</td>
<td>2.67</td>
</tr>
<tr>
<td>Change</td>
<td>p&lt;0.0001</td>
<td>p=0.14</td>
</tr>
<tr>
<td><strong>Habit</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.85</td>
<td>0.77</td>
</tr>
<tr>
<td>Follow-up</td>
<td>0.62</td>
<td>0.55</td>
</tr>
<tr>
<td>Change</td>
<td>p=0.04</td>
<td>p=0.20</td>
</tr>
</tbody>
</table>

A decrease in a score indicates a decline in function: Pleasure (range 0-18), Discomfort (range 0-6), Habit (range 0-3).

*Analyses adjusted for age at surgery, previous breast cancer and use of HRT at follow-up

**Analyses adjusted for age at surgery and previous breast cancer

†Adjusted for baseline value in addition to other variables
Table 7.5 Sexual Activity Questionnaire: Comparison of pre- and post-surgery scores with published norms

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Premenopausal*</th>
<th>Premenopausal Atkins et al.[259]</th>
<th>Postmenopausal*</th>
<th>Postmenopausal Atkins et al.[259]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Post-surgery 11.35</td>
<td></td>
<td>Post-surgery 9.90</td>
<td></td>
</tr>
<tr>
<td>Discomfort (range 0-6)</td>
<td>Pre-surgery 4.77</td>
<td>5.23</td>
<td>Pre-surgery 3.41</td>
<td>4.18</td>
</tr>
<tr>
<td></td>
<td>Post-surgery 3.51</td>
<td></td>
<td>Post-surgery 2.67</td>
<td></td>
</tr>
<tr>
<td>Habit (range 0-3)</td>
<td>Pre-surgery 0.85</td>
<td>1.31</td>
<td>Pre-surgery 0.77</td>
<td>1.31</td>
</tr>
<tr>
<td></td>
<td>Post-surgery 0.62</td>
<td></td>
<td>Post-surgery 0.55</td>
<td></td>
</tr>
</tbody>
</table>

Lower scores indicate lower functioning.

*Mean scores for subjects in the current study

**Premenopausal norms from Atkins et al.:** Mean scores for premenopausal women were derived from a combined sample of healthy women at risk for breast cancer and healthy women at population risk for breast cancer.

**Postmenopausal norms from Atkins et al.:** Mean scores for postmenopausal women were derived from a combined sample of women undergoing ovarian cancer screening, women with ovarian cancer and women at risk for breast cancer.
8 CHAPTER EIGHT

General Discussion

8.1 Summary of results

The goal of this thesis was to evaluate the impact of salpingo-oophorectomy in women who carry a BRCA1 or BRCA2 mutation. Overall, our findings of the actual reduction in cancer risk, the perceived reduction in cancer risk, the impact on quality of life and satisfaction with the decision to have surgery were favorable.

We estimated the penetrance of ovarian cancer in women with ovaries intact to be 62% to age 75 for BRCA1 and 18% for BRCA2.[99] Prophylactic salpingo-oophorectomy reduced the risk for ovarian and fallopian tube cancer by 80% (HR, 0.20; 95% CI, 0.07-0.58; p=0.003).[99] The observed incidence of primary peritoneal cancer after salpingo-oophorectomy in women who carried a BRCA1 or BRCA2 mutation combined was 217 per 100,000 per year or 4.3% risk at 20 years following the surgery.[99]

Women in our study perceived a significant reduction in risk of both breast and ovarian cancer as a result of surgery.[170] We found that women who carried a BRCA1 or BRCA2 mutation accurately perceived their risk of breast cancer both before and after prophylactic salpingo-oophorectomy. On average, both BRCA1 and BRCA2 carriers understood that salpingo-oophorectomy reduced the risk for breast cancer if performed before menopause. Ovarian cancer risk prior to surgery was somewhat overestimated, particularly by women who carried a BRCA2 mutation. The risk for ovarian cancer after surgery was also overestimated, but to a lesser extent.

Physical and mental health functioning did not change significantly after surgery and was comparable to the general population both before and after surgery. Women with a previous diagnosis of breast cancer and women who were not taking HRT at follow-up had poorer physical functioning both before and after surgery; prior diagnosis of breast cancer did not
predict a greater decrease in physical functioning. Reproductive history appeared to be related to changes in physical functioning. Age at first birth was significantly correlated with changes in physical functioning (r=0.43, p=0.0001). Women who had their first birth in their thirties had significantly better physical functioning after surgery than women who had their first birth in their twenties. Neither level nor amount of physical activity before surgery was correlated with changes in physical functioning after surgery.

General psychological distress was similar to general population levels both before and after surgery. Women who were premenopausal at the time of surgery did experience an increase in distress related to symptoms such as faintness, dizziness, weakness, nausea and numbness or tingling after surgery. Of note, anxiety decreased significantly after surgery in these same women. Levels of depression were unchanged after surgery. Overall, worry about being at risk for ovarian cancer decreased significantly after surgery. However, almost 20% of women continued to experience significant cancer worry after prophylactic salpingo-oophorectomy.

The majority of women who were premenopausal at the time of salpingo-oophorectomy experienced a significant increase in vasomotor symptoms (hot flashes, night sweats and sweating) after surgery. While HRT did not completely alleviate these symptoms, women who were taking HRT at one year following surgery had significantly fewer vasomotor symptoms than women who were not taking HRT. Women who were taking HRT also reported fewer moderate to severe hot flashes (15%) than women who were not taking HRT (48%).

Sexual functioning declined in women who were premenopausal at the time of surgery with a decrease in sexual pleasure, an increase in sexual discomfort, and a decrease in frequency. Women who reported taking HRT at one year following surgery experienced significantly less sexual discomfort than women who were not taking HRT. However, their sexual pleasure was similar i.e. HRT did not alter the decrease in sexual pleasure. There was a statistically significant decrease in sexual functioning among women who were postmenopausal at the time of surgery. While this is consistent with previous studies, the relative decrease we observed was small and it is possible it is not a clinically significant change.

Despite the changes in menopausal symptoms and sexual functioning, women reported high levels of satisfaction with their decision to have prophylactic salpingo-oophorectomy. There was
a significant correlation between the increase in sexual discomfort and decreased satisfaction with the decision to have the surgery among women who were premenopausal at the time of surgery and who were not taking HRT at follow-up ($r=0.42$, $p=0.01$). There was no correlation between the decrease in sexual pleasure or the increase in vasomotor symptoms and satisfaction with the decision to have prophylactic salpingo-oophorectomy among premenopausal women.

### 8.2 Clinical implications

Our study of the reduction in risk associated with prophylactic salpingo-oophorectomy supports the recommendation for this surgery in women who carry a *BRCA1* or *BRCA2* mutation. Based on the age distribution of ovarian and fallopian tube cancers diagnosed in our cohort (both in women with ovaries and fallopian tubes intact and women diagnosed at prophylactic surgery), we show that *BRCA1* carriers should proceed to surgery close to age 35 or after childbearing is complete to maximize the reduction in cancer risk, while women who carry a *BRCA2* mutation may delay the procedure until age 40 or closer to menopause. Women should be made aware that the risk of primary peritoneal cancer after surgery is approximately 0.2% per year. As yet, there is no useful screening tool or proven intervention for primary peritoneal cancer after prophylactic salpingo-oophorectomy.

Our findings are consistent with the literature demonstrating that the fallopian tube is a component of the hereditary breast and ovarian cancer syndrome. Based on the gaps in the current literature, it is likely premature to state definitively whether or not hysterectomy should be included at the time of salpingo-oophorectomy in *BRCA1* and *BRCA2* carriers. Among the seven women who were diagnosed with primary peritoneal cancer after prophylactic surgery in our prospective cohort, three women underwent both hysterectomy and salpingo-oophorectomy compared to four with salpingo-oophorectomy alone. While there are no case reports of primary peritoneal cancers that originated in the intramural portion of the fallopian tube remaining after salpingo-oophorectomy, diagnosing the exact origin of primary peritoneal cancers after salpingo-oophorectomy is likely impossible. Controlled studies comparing the rate of primary peritoneal cancer among women who do and do not retain their uterus after salpingo-oophorectomy are required.
As expected, we found that women who were premenopausal at the time of surgery experienced a significant worsening of hot flashes, night sweats, sweating, vaginal dryness and dyspareunia and that HRT significantly reduced these symptoms. It is important that women considering prophylactic salpingo-oophorectomy are made aware of the option of HRT in mitigating these symptoms after surgery.

There is a concern that HRT could be dangerous for women who carry a BRCA mutation and who have had a diagnosis of breast cancer. A randomized trial by the HABITS Study Group found an increased risk of new breast cancer events (primarily local recurrence and contralateral breast cancer) in women who took hormone replacement after their diagnosis of breast cancer (HR=2.4, 95% CI=1.3-4.2). Therefore HRT is not recommended after a diagnosis of breast cancer. As a result, women with a previous diagnosis of breast cancer have limited options for the management of vasomotor and sexual symptoms related to menopause. This is of particular concern for women who proceed to prophylactic salpingo-oophorectomy for a BRCA mutation, as a substantial proportion will have had a prior breast cancer diagnosis.

The importance of breast cancer prevention in this population should be stressed, not only an end in itself, but to ensure that HRT remains a viable option after oophorectomy, particularly for women who are proceeding to surgery in their late thirties and forties when still premenopausal. Studies to date have shown that HRT does not increase the risk for breast cancer after salpingo-oophorectomy. HRT appears to offer quality of life benefits after salpingo-oophorectomy, and also offers some protection from other effects of oophorectomy such as decreases in bone and cardiac health, as demonstrated in studies of women in the general population.

According to our findings, women should be counselled that HRT may not alleviate decreases in sexual functioning after salpingo-oophorectomy, such as decline in sexual pleasure. Alternatives to manage these changes should be openly discussed both before and after prophylactic salpingo-oophorectomy. The role of testosterone in sexual function after salpingo-oophorectomy, and the safety of testosterone use in BRCA carriers should be the subject of future studies.

Some women overestimate their risks for ovarian cancer both before and after salpingo-oophorectomy. In addition, a significant proportion of women who undergo prophylactic
salpingo-oophorectomy continue to experience significant cancer worry after the surgery. Identification of these women is important and will allow for further genetic counselling and support, and possibly referral for psychological counselling. These findings point to the possible role of a screening measure to be administered during the genetic counseling process and/or after prophylactic salpingo-oophorectomy to identify women who may need additional counseling and support.

While the effects of the surgery on quality of life during the first year after surgery appear to be manageable given the high level of satisfaction reported by women after the procedure, the overall long term health costs of the surgery, particularly in premenopausal women who carry a BRCA mutation, are not fully known. This should be part of the discussion when counseling women about the decision to undergo the surgery.

Together these studies provide women with more information about the effects of prophylactic surgery in relation to menopausal status, choice in relation to HRT, and personal history of breast cancer. The balance of the benefits and negative effects of surgery appear to be dependent on many factors and this balance will likely vary significantly from person to person. These findings point to the need for individualized medical care and counselling for women electing to undergo salpingo-oophorectomy. This will be discussed further in Future Directions (section 8.4).

### 8.3 Strengths and Limitations

The first objective was to determine the reduction in ovarian and fallopian tube cancer risk associated with prophylactic salpingo-oophorectomy and the subsequent risk of primary peritoneal cancer after salpingo-oophorectomy. Strengths of this study include its size, prospective design and inclusion of participants from a large number of centres in many countries. Therefore, results of this study may be generalized to a broad population.

The true rate of primary peritoneal cancer after prophylactic salpingo-oophorectomy is most accurately evaluated in a prospective study limited to women who underwent this surgery with current standards for complete pathologic examination i.e. serial sectioning of both fallopian tubes and ovarian tissue. Current studies, including our study presented here include some
women who underwent salpingo-oophorectomy before the importance of thorough pathologic examination of the ovary and fallopian tubes was recognized.

Women who were diagnosed with occult ovarian or fallopian tube cancer at the time of salpingo-oophorectomy were excluded from the analysis. Including them may have overestimated cancer risks as the time to diagnosis of clinically apparent cancer from occult cancer is not known. Women diagnosed with occult cancer at the time of salpingo-oophorectomy may not have presented with ovarian or fallopian tube cancer during the follow-up period. Conversely, it is also possible that the risk for ovarian and fallopian tube cancer may have been underestimated by excluding these cancers from the analysis.

It was not possible to obtain follow-up of all subjects in the international cohort of women with a \textit{BRCA} mutation evaluating the reduction in risk associated with prophylactic salpingo-oophorectomy. This may have created bias as women who were diagnosed with cancer may have been preferentially reported. It is also possible that subjects who were deceased from ovarian, fallopian tube or peritoneal cancer may have been less likely to be included in the analysis and excluded as lost to follow-up. We excluded centres without sufficient follow-up from the study, in order to reduce this possible bias.

We estimated the residual risk for primary peritoneal cancer after prophylactic salpingo-oophorectomy to be 4.3% at 20 years among women who carry a \textit{BRCA1} or \textit{BRCA2} mutation.[99] This figure is based on the diagnosis of seven primary peritoneal cancers after salpingo-oophorectomy among 1045 women followed for a mean of 3.5 years (3221 person years; observed incidence 217 per 100,000 per year). The 20 year cumulative risk estimate of 4.3%, is based on the observed annual incidence ($1-((1-0.00217)^{20})=0.0425$). Reporting this cumulative risk makes the assumption that the annual risk of primary peritoneal cancer after salpingo-oophorectomy is constant and does not increase or decrease with age or other factors over this period of time.

The second objective was to determine the perception of risk for the development of breast and ovarian cancer before and after prophylactic salpingo-oophorectomy. Our study was retrospective, therefore we were not able to ask women prior to surgery what they perceived their risk of breast and ovarian cancer to be. Women were asked to report this after surgery, which
may have introduced recall bias. We did not evaluate perception of risk among women who elected to undergo screening instead of surgery. Women who elect to proceed to prophylactic surgery likely perceived their risks for cancer to be higher than women who delay surgery or continue with screening, this may have contributed to the high perception of ovarian cancer risk in the group we studied.

The optimal method to investigate the impact of salpingo-oophorectomy on perception of risk and all aspects of health would be the randomization of women to screening or prophylactic surgery. The findings for the two groups would be compared and contrasted as in a randomized controlled trial. This is clearly not ethically possible given the lack of evidence to support screening for ovarian and fallopian tube cancer and the evidence in support of salpingo-oophorectomy.

The third and fourth objectives were to assess changes in health-related quality of life, cancer worry and psychological distress. We used standardized questionnaires to evaluate changes in health-related quality of life, cancer worry and psychological distress after prophylactic salpingo-oophorectomy. These questionnaires were completed by participants within the month prior to surgery and, as a result, levels of distress may have been elevated due to the impending surgery. This may have overestimated the decrease in worry and distress in relation to prophylactic salpingo-oophorectomy.

The fifth objective was to assess changes in menopausal symptoms and sexual functioning after prophylactic salpingo-oophorectomy. The sixth objective was to evaluate satisfaction with the decision to undergo the surgery. We studied these outcomes during the one year period following surgery. This follow-up period is relatively short and a longer follow-up period is necessary to determine if symptoms of surgical menopause linger longer than symptoms in women who experience natural menopause. The same is true for changes in sexual functioning, cancer worry, general psychological distress and satisfaction.

The majority of women in these studies of menopausal symptoms, sexual functioning and quality of life had a hysterectomy at the time of salpingo-oophorectomy. The results presented provide information regarding the impact of surgical menopause in addition to hysterectomy. We were not able to evaluate the differing effects of hormone replacement regimens (estrogen plus...
progesterone versus estrogen alone). In addition, our studies did not include a control group, with hysterectomy alone or screening without surgery. The most informative comparison group to evaluate changes in sexual functioning may have been women who had hysterectomy but did not undergo salpingo-oophorectomy to tease out the relative contribution, if any, of hysterectomy on sexual functioning. Studies have been published on sexual functioning after hysterectomy, however, the majority of these studies were reporting functioning in women who had hysterectomy for complaints such as bleeding or other gynecologic problems.[261, 262]

We determined that participants in our study of the impact of menopausal symptoms and sexual function were highly satisfied with their decision to undergo salpingo-oophorectomy. While the response rate was quite high with 69% of women participating prior to surgery and a retention rate of 87% at one year follow-up, approximately 58% of eligible women participated by completing both baseline and follow-up questionnaires. It is possible that the women who participated in our study are not representative of all women electing to undergo this preventive surgery. There are three subsets of women: all women who carry a BRCA mutation, all women who carry a BRCA mutation and who elect to undergo prophylactic salpingo-oophorectomy and finally women who carry a BRCA mutation, elect to undergo the surgery and who participated in our study. Surveying only the last group may have created a selection bias. Women who were satisfied with their decision to undergo prophylactic salpingo-oophorectomy may have been more likely to participate, skewing our results in favour of high levels of satisfaction with the procedure.

Objectives two to six were achieved with a cohort of women recruited at a single centre in Ontario, a province with free universal health care. This is a unique and valuable population as women are able to avail themselves to medical care without cost. Prophylactic salpingo-oophorectomy is available to all women who are referred to this centre and who are found to carry a BRCA mutation reducing selection bias based on socioeconomic status. In addition, women who carry a BRCA mutation are referred from a broad geographical area in the province to this centre with a specialization in prophylactic surgery, increasing the representativeness of the sample of women surveyed. Both of these factors contribute to the generalizability of our results. We did not request specific information regarding education, ethnicity or other factors
that may be related to the decision to undergo salpingo-oophorectomy and are therefore not able to comment on the generalizability related to each of these specific factors.

8.4 Future Directions

In the absence of alternatives to prophylactic salpingo-oophorectomy, a more thorough understanding of the long-term impact of the surgery is essential.

1. Risk factors for primary peritoneal cancer after salpingo-oophorectomy.
We are continuing to develop the international prospective cohort of women who carry a BRCA mutation. This will allow for increasingly accurate measurements of the risk for primary peritoneal cancer after salpingo-oophorectomy as the size of the cohort and the length of follow-up increases. The subset of women who underwent salpingo-oophorectomy with optimal pathologic examination will be the most informative cohort to determine the risk of primary peritoneal cancer. Further analysis of risk factors such as parity, breast feeding, the oral contraceptive pill and HRT, and their association with the development of primary peritoneal cancer will also be possible.

2. Evaluation of the long term impact of salpingo-oophorectomy on menopausal symptoms and sexual functioning.
Our studies evaluating the impact of salpingo-oophorectomy on menopausal symptoms and sexual functioning during the year following surgery likely evaluated the most acute period for these changes. These symptoms must be evaluated in long term prospective studies. We are currently completing follow-up to three years post surgery in the same cohort with additional follow-up after that. The possible role of testosterone in the treatment of changes in sexual functioning and its safety in women who carry a BRCA mutation should be evaluated.

3. Long term impact of salpingo-oophorectomy on bone and cardiac health.
To date, there is no literature examining the short or long-term effect of prophylactic salpingo-oophorectomy on bone density and cardiac health in women who carry a BRCA1 or BRCA2 mutation. While there have been studies of women who underwent oophorectomy before menopause for indications other than cancer prevention, the age at oophorectomy may be later in
these women than in women who carry a \textit{BRCA1} or \textit{BRCA2} mutation. It is also possible that the physiology of bone and cardiac health is different in women who carry a \textit{BRCA} mutation than for women who do not. If this is true, the long term health implications may be very different from what has been observed in the literature to date. We are currently designing a multi-centre long-term follow-up study to examine the short and long-term effects of prophylactic salpingo-oophorectomy on bone health, cardiac health and overall health in women who carry a \textit{BRCA} mutation.

\textbf{4. Integrated multidisciplinary care of women who undergo salpingo-oophorectomy for a \textit{BRCA} mutation.}

Our studies highlight the number of factors that play a role in each woman’s experience of salpingo-oophorectomy. We have also identified the many varied needs of women after the procedure such as management of vasomotor symptoms, counselling about HRT, counseling and management of changes in sexual functioning, and psychological support for cancer worry and psychological distress after the surgery. These needs also include medical care such as monitoring overall health including bone density, particularly for women who are premenopausal at the time of surgery.

While many centres that perform prophylactic salpingo-oophorectomy likely follow their patients after surgery, it is unlikely that these women are offered the tools and support to deal with the effects of salpingo-oophorectomy, in addition to their experience of being at high risk for cancer. In the era of personalized medicine, a model of integrated multidisciplinary clinical care of women who elect to undergo prophylactic salpingo-oophorectomy is appropriate and necessary. In this model, a woman who elects to undergo salpingo-oophorectomy would be cared for by a multidisciplinary team at a single centre before and after the surgery including genetic counsellors, gynecologic oncologists or gynecologists, psychologists, and additional specialists for management of vasomotor symptoms, sexual health, bone health and possibly cardiac health.
8.5 Conclusions

Prophylactic salpingo-oophorectomy is effective in reducing the risk of ovarian and fallopian tube cancer and in women who carry a \textit{BRCA1} or \textit{BRCA2} mutation. The impact of this surgery on health and quality of life are considerable and are dependent on many factors which include but are not limited to menopausal status at the time of surgery, personal history of breast cancer, and choice regarding HRT. We found that despite the effects of the surgery, women were satisfied with their decision to undergo prophylactic salpingo-oophorectomy.

The recommendation for salpingo-oophorectomy at 35 or after childbearing is complete in women who carry a \textit{BRCA} mutation should be presented with information about what may be expected after the surgery, in addition to the reduction in cancer risk afforded by the surgery. The tools and guidance needed to manage the effects of the surgery should also be made available. The studies presented here begin to answer these questions and also highlight the need for future studies to further understand the experiences of women who undergo the procedure in addition to the possible long-term health effects.

In order to reduce the burden of ovarian and fallopian tube cancer in women with a \textit{BRCA1} or \textit{BRCA2} mutation through risk-reducing salpingo-oophorectomy, the procedure has to be viewed as an acceptable option by both clinicians and women who carry a mutation. Based on our studies and the literature to date, the benefits in terms of reduction in cancer risk and cancer worry in women who carry a \textit{BRCA} mutation are likely greater than the costs. Further research is necessary to make this absolute determination. It is essential that women who carry a \textit{BRCA1} or \textit{BRCA2} mutation are counselled with all information possible so that they may make this judgment for themselves.
References


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Appendices

1. Introductory letter, Prophylactic Salpingo-oophorectomy Study
2. Information sheet, Prophylactic Salpingo-oophorectomy Study
3. Consent form, Prophylactic Salpingo-oophorectomy Study
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12. Baseline Questionnaire, International Risk Factor Study
13. Follow-up Questionnaire, International Risk Factor Study
Appendix 1: Introductory letter, Prophylactic Salpingo-oophorectomy Study

Ms. Jane Doe
123 Bell Street
Toronto, ON
XXX XXX

January 1, 2006

Dear Ms. Doe:

We are writing to ask you to participate in a clinical study that will provide us with more information about how to best care for women with a hereditary predisposition to ovarian cancer. Many women who have a hereditary predisposition to ovarian cancer are choosing to have surgery (prophylactic oophorectomy) to prevent the development of it. It is our understanding that you are planning to have a prophylactic oophorectomy. Many women like yourself have approached us with detailed questions relating to patients’ satisfaction with preventive surgery, possible side effects, and the extent of risk reduction of cancer associated with the surgery.

In order to evaluate this procedure, we are conducting a research study of women who are electing to have a preventative oophorectomy, and we are inviting you to participate. The purpose of this study is to measure the risk reduction of cancer associated with prophylactic oophorectomy, to document the symptoms experienced as a result of surgery, to measure women’s personal satisfaction with their decision to have preventive surgery, and to assess quality of life after surgery. The enclosed information sheet describes the study in further detail and as you will see, the study will involve completing questionnaires and allowing the researchers to contact you for follow-up information in the future. The study will be of several years duration.

All information in this study will be treated in a strictly confidential manner. No information from this study will become part of your medical records.

If you are interested in learning more about this study or are interested in participating, or if you have any questions or concerns that will help you to decide, please do not hesitate to call Amy Finch at (416) 351-3800 ext. 2751. If we do not hear from you, Amy will contact you shortly to discuss your participation.

Thank you.

Sincerely,

Barry Rosen, MD, FRCSC   Joan Murphy, MD, FRCSC
Director Familial Breast and Ovarian Cancer Clinic   Head, Division of Gyn/Oncology
Appendix 2: Information sheet, Prophylactic Salpingo-oophorectomy Study

Study of Preventive Oophorectomy in High Risk Women

INFORMATION SHEET

Investigators:  Dr. Barry Rosen, MD, FRCSC
University Health Network

Dr. Joan Murphy, MD, FRCSC
University Health Network

Dr. Steven Narod, MD, FRCPC
Women’s College Hospital

PURPOSE OF RESEARCH:

You are asked to participate in a research project because of your decision to have a preventative oophorectomy (removal of ovaries for prevention of cancer). The purpose of this study is to measure the level of risk reduction of cancer associated with prophylactic oophorectomy, the symptoms experienced as a result of surgery, personal satisfaction with decision to have preventive surgery, and to assess quality of life and sexuality after surgery. The information gained from this study will be useful for women who are considering having preventive surgery in the future.

Your participation in this study is voluntary, and if you agree to participate you may withdraw your consent and discontinue your participation from the study at any time. Your medical care will not be affected if you leave the study. You may choose to participate in some parts of this research study, and not in others.

PROCEDURE:

Prior to surgery you will be asked to complete six questionnaires, to undergo a bone density assessment, and to provide a blood sample. The questionnaires are titled: 1) Medical History 2) Menopause and Quality of Life 3) Sexual Activity Questionnaire 4) Impact of Event Scale 5) Medical Outcome Short-Form Survey and 6) Brief Symptom Inventory. The estimated time to complete all questionnaires is 28-35 minutes. The blood will be used to assess menopausal status and to evaluate ovarian tumour markers. The surgical specimens will be examined at the hospital where you have your surgery, and then further investigated at Women’s College Hospital by a pathologist who is involved with this research study. Following surgery you will be asked to complete several follow-up questionnaires, which include questions relating to medical outcomes, quality of life, sexual functioning, your satisfaction with your decision to have surgery and your experience of menopausal symptoms. You will be asked to sign a consent for the review of your medical records. This study will be continuing for the next 10 years, and you will be asked to allow the researchers to contact you every 2 years by telephone for follow-up information. You may discontinue at any time.
RISKS:

There are no known risks associated with participating in this study.

BENEFITS:

The information gathered from this research study may be beneficial to you as well as other women who are considering having preventive surgery done. If you request, you will be given up to date information about the risks of cancer associated with a family history and will be provided with information about the nearest genetic counseling center. Information will be available regarding the management of menopausal symptoms if requested.

CONFIDENTIALITY:

Medical and all other information produced by this study will be strictly confidential and will be subject to the privacy regulations of the University of Toronto. This information will not become part of your personal medical record and no information will be released to any other person than you without your consent.

REQUEST FOR FURTHER INFORMATION:

Dr. S. Narod and Ms. Amy Finch will be available to answer any questions about the study at (416) 351-3800 Ext 2751. The Research Ethics Board Coordinator at the University Health Network is also available to answer any questions at (416) 946-2388.
Appendix 3: Consent Form, Prophylactic Salpingo-oophorectomy Study

Study of Preventive Oophorectomy in High Risk Women

SUBJECT CONSENT FORM

Investigators: Dr. Barry Rosen, MD, FRCSC
University Health Network

Dr. Joan Murphy, MD, FRCSC
University Health Network

Dr. Steven Narod, MD, FRCPC
Women’s College Hospital

PURPOSE OF RESEARCH:

You have been asked to participate in a research project because of your decision to have a preventive oophorectomy (removal of ovaries for prevention of cancer). The purpose of this study is to measure the level of risk reduction of cancer associated with prophylactic oophorectomy, the symptoms experienced as a result of surgery, personal satisfaction with decision to have preventive surgery, and to assess quality of life and sexual functioning after surgery. The information gained from this study will be useful for women who are considering having preventive surgery in the future.

Your participation in this study is voluntary, and if you agree to participate, you may withdraw your consent and discontinue your participation from the study at any time. Your medical care will not be affected if you leave the study. You may decide to participate in some parts of this research study, but not in all.

PROCEDURE:

Prior to surgery you will be asked to complete six brief questionnaires, to undergo a bone density assessment, and to have an ovarian ultrasound, and to provide a blood sample. The questionnaires are titled: 1) Medical History 2) Menopause and Quality of Life 3) Sexual Activity Questionnaire 4) Impact of Event Scale 5) Medical Outcome Short-Form Survey and 6) Brief Symptom Inventory. The estimated time to complete all questionnaires is 28-35 minutes. The blood will be used to assess menopausal status and to evaluate ovarian tumour markers. Your surgical specimens will be examined at the hospital where you have your surgery, and then further investigated at Women’s College Hospital by a pathologist who is involved with this research study. Following surgery you will be asked to complete several follow-up questionnaires, which include questions relating to medical outcomes, quality of life, sexual functioning, your satisfaction with your decision to have surgery and your experience of menopausal symptoms. Your medical chart will be reviewed for research purposes. You will be asked to sign a separate consent form to allow us to receive information from other hospitals. This study will be continuing for the next 10 years, and you will be asked to allow the researchers to contact you every 2 years by telephone for follow-up information. You may discontinue at any time.

RISKS:
There are no known risks associated with participating in this study.

**BENEFITS:**

The information gathered from this research study may be beneficial to you as well as other women who are considering having preventive surgery. If you request, you will be given up to date information about the risks of cancer associated with a family history and will be provided with information about the nearest genetic counselling center. Information will be available regarding the management of menopausal symptoms if requested.

**CONFIDENTIALITY:**

Medical and all other information produced by this study will be strictly confidential and will be subject to the privacy regulations of the University Health Network. This information will not become part of your personal medical record and no information will be released to any other person than you without your consent.

**QUESTIONS:**

If you have any questions about your rights as a research participant, please call Dr. R. Heslegrave, Chair of the University Health Network Research Ethics Board at (416) 340-4557. This person is not involved with the research project in any way and calling him will not affect your participation in the study.

**REQUEST FOR FURTHER INFORMATION:**

Dr. Narod, or the research coordinator, Ms. Amy Finch will be available to answer any questions about the study at (416) 351-3800 Ext. 2751.

**CONFIRMATION OF PARTICIPATION:**

____________________  ________________________  ____________________
Participant Name    Signature    Date

I have explained to ___________________________ the purpose of this research, the procedures required, and the possible risks and benefits of the study.

____________________  ________________________  ____________________
Investigator Name  Signature    Date

In the future, do you wish to be **contacted by email** regarding future aspects of this research study?

____________________  ________________________
Signature    email address
Appendix 4: Medical History Questionnaire, Prophylactic Salpingo-oophorectomy Study

Study of Preventive Oophorectomy in High Risk Women

QUESTIONNAIRE:
Medical History

Investigators:
Barry Rosen
Joan Murphy
Steven Narod

Today’s Date: ____________

Study ID#: ________________
Thank you for taking the time to complete this questionnaire. The questions that are asked in this questionnaire relate to your medical history.

1. **Height and Weight**

   i) What is your current height? _______ feet _______ inches

   ii) What is your current weight _______ pounds

2. **Reproductive history**

   i) Total number of children __________

   ii) Age at first birth __________ years

   iii) Age at last birth __________ years

   iv) Have you ever had a tubal ligation?

      No _____ Yes _____ If yes, age __________

   v) Have you ever used birth control pills?

      No _____

      Yes _____ → please complete for each time you used the pill

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<tr>
<th>Starting year</th>
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3. Menopause

i) Do you currently have menstrual periods? i.e. have you had a menstrual period within the past year?
   No _____  Yes _____

ii) Have your periods stopped completely?
    No _____  Yes _____

iii) Have you ever had a hysterectomy (uterus removed)?
     No _____
     Yes _____ → at what age? ______ years

iv) How old were you when your periods stopped completely?
    _____ years old  OR  ______ not stopped yet

v) What was the reason your periods stopped? (check one)
   _____ Natural menopause (change of life)
   _____ Because of hysterectomy (uterus removed/ovaries not removed)
   _____ Took medication that stopped periods (e.g. chemotherapy)
   _____ Other, specify: ___________________________________________

vi) Have you had other surgery on your reproductive organs?
    No ______
    Yes ______ → describe operation____________________________
                    Year of operation__________
4. Breast and other cancers

i) Have you ever been diagnosed with breast cancer?
   No ______
   Yes ______ → Year of diagnosis ______

ii) Have you ever been diagnosed with another form of cancer?
   No ______
   Yes ______ → Type of cancer _______________________
                   Age of diagnosis_____________________

5. Physical activity

i) Over the past year, how would you describe your level of recreational physical activity?
   Little ______
   Moderate ______
   Strenuous ______

ii) On average, how many hours per week over the past year did you partake of moderate to strenuous physical activity?
   Less than one hour per week ______
   One to three hours per week ______
   Three to five hours per week ______
   Five or more hours per week_______

iii) What is your current occupation?_________________________
     Would you describe this as:
     Little or no physical activity? ______
     Moderate physical activity? ______
     Considerable physical activity? ______
6. Coffee, smoking, alcohol

i) Over the past year, on an average day how many cups of coffee did you drink?
   Caffeinated _______ cups
   Decaffeinated _______ cups

ii) Over the past year, on an average day, how many cigarettes did you smoke
    None ______
    1 to 5 ______
    5 to 10 ______
    10-20 ______
    more than twenty ______

iii) Over the past year, on an average week, how many alcoholic beverages did you consume?
    0-3 ______
    4-9 ______
    10-20 ______
    20 or more ______
7. Medications

Did you consume any of the following medications over the past week or year?

(check where applicable)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Past Week</th>
<th>Past Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vitamins and Minerals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium:</td>
<td></td>
<td></td>
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<tr>
<td>Apo-cal</td>
<td></td>
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</tr>
<tr>
<td>Actical</td>
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<tr>
<td>Calcite</td>
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<tr>
<td>Caltrate</td>
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<tr>
<td>Diovol</td>
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<td>Os-cal</td>
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<td>Tums</td>
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<tr>
<td>Viactiv</td>
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<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td></td>
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<tr>
<td>Calcium and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D:</td>
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<tr>
<td>Cal-Mag</td>
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<tr>
<td>Caltrate+D</td>
<td></td>
<td></td>
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<tr>
<td>Caltrate Plus</td>
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</tr>
<tr>
<td>Cholecalciferol</td>
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<tr>
<td>Calcitriol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rocaltrol</td>
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<td></td>
</tr>
<tr>
<td><strong>Multivitamins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(many brands)</td>
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<td></td>
</tr>
<tr>
<td><strong>Drugs for Osteoporosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clodronate</td>
<td>Bonefos</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ostac</td>
<td></td>
</tr>
<tr>
<td>Alendronate</td>
<td>Fosamax</td>
<td></td>
</tr>
<tr>
<td>Pamidronate</td>
<td>Aredia</td>
<td></td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Evista</td>
<td></td>
</tr>
<tr>
<td>Risodronate</td>
<td>Actonel</td>
<td></td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Calcimar</td>
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<tr>
<td></td>
<td>Caltine</td>
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<td></td>
<td>Miacalcin</td>
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<tr>
<td>Etidronate</td>
<td>Didronel</td>
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<td></td>
<td>Didoocal</td>
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<tr>
<td><strong>Other osteoporosis drug:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Name</strong></td>
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</table>
## Medication

<table>
<thead>
<tr>
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<th>Past Week</th>
<th>Past Year</th>
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### Anti-inflammatory drugs

<table>
<thead>
<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
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<tr>
<td>Tylenol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Celebrex</td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Voltaren</td>
<td></td>
</tr>
<tr>
<td>Oxaprozin</td>
<td>Daypro</td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Indocid</td>
<td></td>
</tr>
<tr>
<td>Piroxicam</td>
<td>Feldene</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fexicam</td>
<td>Novo-Pirocam</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Naprosyn</td>
<td>Novo-Naprox</td>
</tr>
<tr>
<td></td>
<td>Anaprox</td>
<td>Novo-Naprox</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Advil</td>
<td>Motrin</td>
</tr>
<tr>
<td></td>
<td>Novo-Profen</td>
<td></td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>Vioxx</td>
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</table>

Other anti-inflammatory drugs:

Name

### Drugs for hot flashes

<table>
<thead>
<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Effexor</td>
<td></td>
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<tr>
<td>Prozac</td>
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<tr>
<td>Paxil</td>
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<tr>
<td>Luvox</td>
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<tr>
<td>Celexa</td>
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<tr>
<td>Zoloft</td>
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<tr>
<td>Serzone</td>
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<tr>
<td>Trazorel</td>
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<tr>
<td>Wellbutrin</td>
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<tr>
<td>Clonidine</td>
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</table>

Other drugs for Hot Flashes:

Name

### Drugs for High Blood Pressure

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<thead>
<tr>
<th>Name:</th>
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Name:
<table>
<thead>
<tr>
<th>Medication</th>
<th>Past Week</th>
<th>Past Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs for High Cholesterol</strong></td>
<td></td>
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<tr>
<td>Name:</td>
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<tr>
<th>Medication</th>
<th>Past Week</th>
<th>Past Year</th>
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<tbody>
<tr>
<td><strong>Drugs for Diabetes</strong></td>
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<td>Name:</td>
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<tr>
<th>Medication</th>
<th>Past Week</th>
<th>Past Year</th>
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<tbody>
<tr>
<td><strong>Steroids</strong></td>
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<tr>
<td>Inhaled steroids:</td>
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<tr>
<td>Name</td>
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<tr>
<td>Oral steroids:</td>
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<tr>
<td>Name</td>
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</table>

<table>
<thead>
<tr>
<th>Medication</th>
<th>Past Week</th>
<th>Past Year</th>
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</thead>
<tbody>
<tr>
<td><strong>Drugs to Prevent Breast Cancer</strong></td>
<td></td>
<td></td>
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<tr>
<td>Tamoxifen</td>
<td></td>
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<tr>
<td>Nolvadex</td>
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<tr>
<td>Apo-Tamox</td>
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<tr>
<td>Tamofen</td>
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<tr>
<td>Raloxifene</td>
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<td>Evista</td>
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<tr>
<td>Other:</td>
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<tr>
<td>Name</td>
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<table>
<thead>
<tr>
<th>Medication</th>
<th>Past Week</th>
<th>Past Year</th>
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</thead>
<tbody>
<tr>
<td><strong>Drugs to Treat Breast Cancer</strong></td>
<td></td>
<td></td>
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<tr>
<td>Tamoxifen</td>
<td></td>
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<tr>
<td>Megace</td>
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<tr>
<td>Arimidex</td>
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<tr>
<td>Zolodex</td>
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<tr>
<td>Lupron</td>
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<td>Other:</td>
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<tr>
<td>Name</td>
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</tr>
<tr>
<td>Medication</td>
<td>Past Week</td>
<td>Past Year</td>
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</tr>
<tr>
<td><strong>Hormone replacement therapy</strong></td>
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<tr>
<td><strong>A: Pills</strong></td>
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<tr>
<td>Estrogen</td>
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<tr>
<td>Demulen</td>
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<tr>
<td>Estrace</td>
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<td>Ogen</td>
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<tr>
<td>Progesterone</td>
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<tr>
<td>Novo-Medrone</td>
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<tr>
<td>Prometrium</td>
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<tr>
<td>Combination</td>
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<tr>
<td>Estrogen</td>
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<tr>
<td>and Progesterone</td>
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<td></td>
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<tr>
<td>Tricyclen</td>
<td></td>
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<tr>
<td>Triquilin</td>
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<tr>
<td>Testosterone</td>
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<tr>
<td>DHEA</td>
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<tr>
<td>Other Pills:</td>
<td></td>
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<tr>
<td>Name</td>
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<tr>
<td><strong>B: Skin Patches or Creams</strong></td>
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<tr>
<td>Climara</td>
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<td></td>
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<tr>
<td>Estraderm</td>
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<td>Estrigel</td>
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<td>Oesclim</td>
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<tr>
<td>Vivelle</td>
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<tr>
<td>Estracomb</td>
<td></td>
<td></td>
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<tr>
<td>Estalis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>C: Vaginal Suppositories</strong></td>
<td></td>
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<tr>
<td>Estriing</td>
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<td></td>
</tr>
<tr>
<td>Oestrilin</td>
<td></td>
<td></td>
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<tr>
<td>Premarin</td>
<td></td>
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<tr>
<td><strong>D: Injections</strong></td>
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<tr>
<td>Delestrogen,</td>
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</tr>
<tr>
<td>Depo-Estradiol</td>
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<tr>
<td>Climacteron</td>
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<td></td>
</tr>
<tr>
<td>Depoprovera</td>
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</tbody>
</table>
### Other Drugs Not Listed Above

<table>
<thead>
<tr>
<th>Name:</th>
<th>Past Week</th>
<th>Past Year</th>
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<tbody>
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</table>

### Herbal Remedies

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<tr>
<th>Medication</th>
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<th>Past Year</th>
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</thead>
<tbody>
<tr>
<td>Black cohosh</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dong Quai</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red clover</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soybeans (soya)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evening Primrose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flaxseed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green tea</td>
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<td></td>
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<tr>
<td>Saw Palmetto</td>
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</tr>
<tr>
<td>St Johns Wort</td>
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<td></td>
</tr>
<tr>
<td>Wild Yam</td>
<td></td>
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</tr>
<tr>
<td>Other:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 8. Other medical conditions

In the past year/ever have you been treated for any of the following?

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Past year</th>
<th>Ever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>______</td>
<td>______</td>
</tr>
<tr>
<td>Bladder infection</td>
<td>______</td>
<td>______</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>______</td>
<td>______</td>
</tr>
</tbody>
</table>
9. Other surgery

Have you had any of these surgeries?

i) Bladder operation
   
   No ________  Yes ________ →  Year:__________

ii) Gall bladder removal
   
   No ________  Yes ________ →  Year:__________

iii) Appendix removal
   
   No ________  Yes ________ →  Year:__________

iv) Caesarean Section
   
   No ________  Yes ________ →  Year:__________

v) Prophylactic Mastectomy
   
   No ________  Yes ________ →  Year:__________

vi) Breast Resconstruction
   
   No ________  Yes ________ →  Year:__________

Thank you for filling out this questionnaire and for helping with this study. In the future we may recontact you by mail, telephone or e-mail.

Telephone number:  Day_________________________
                      Evening______________________

Email address: _______________________________________

In addition, in case we are unable to make contact with you, could you provide us with the names and addresses of two next of kin (preferably your children, spouse or sister) that we may contact

Name  Relationship  Telephone  Address

1.  

2.
Appendix 5: Menopause and Quality of Life-Intervention Questionnaire, Prophylactic Salpingo-oophorectomy Study

Study of Oophorectomy
In High Risk Women

QUESTIONNAIRE:
Menopause and Quality of Life

Investigators:
Dr. Barry Rosen
Dr. Joan Murphy
Dr. Steven Narod

Today’s Date: ___________________
Study ID#: ___________________
Thank you for taking the time to complete this questionnaire. There are three separate sections that ask questions about quality of life, genitourinary symptoms, and hot flashes. It is important that you respond to each question to ensure that we receive complete information about your experience with menopause. Thank you.

**PART I (Quality of Life):**

For each of the following items, indicate whether you have experienced the problem in the PAST WEEK. If you have, rate how much you have been bothered by the problem.

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<thead>
<tr>
<th></th>
<th>Not at all Bothered</th>
<th>Extremely Bothered</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1 2 3 4 5 6</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Item</th>
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<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hot flushes or flashes</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2. Night Sweats</td>
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<td></td>
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<tr>
<td>3. Sweating</td>
<td></td>
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</tr>
<tr>
<td>4. Dissatisfaction with my personal life</td>
<td></td>
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<tr>
<td>5. Feeling anxious or nervous</td>
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<td>6. Poor memory</td>
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<tr>
<td>7. Accomplishing less than I used to</td>
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<td>8. Feeling depressed, down or blue</td>
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<td>9. Being impatient with other people</td>
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<tr>
<td>10. Feelings or wanting to be alone</td>
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</tr>
<tr>
<td>11. Flatulence (wind) or gas pains</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not at all Bothered</td>
<td>Extremely Bothered</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>----------------------</td>
<td>---------------------</td>
<td>-------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>Aching in muscles and joints</td>
<td>NO</td>
<td>YES 0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13.</td>
<td>Feeling tired or worn out</td>
<td>NO</td>
<td>YES 0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.</td>
<td>Difficulty sleeping</td>
<td>NO</td>
<td>YES 0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15.</td>
<td>Aches in back of neck or head</td>
<td>NO</td>
<td>YES 0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.</td>
<td>Decrease in physical strength</td>
<td>NO</td>
<td>YES 0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17.</td>
<td>Decrease in stamina</td>
<td>NO</td>
<td>YES 0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.</td>
<td>Lack of energy</td>
<td>NO</td>
<td>YES 0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19.</td>
<td>Dry skin</td>
<td>NO</td>
<td>YES 0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20.</td>
<td>Weight gain</td>
<td>NO</td>
<td>YES 0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21.</td>
<td>Increased facial hair</td>
<td>NO</td>
<td>YES 0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22.</td>
<td>Changes in appearance, texture or tone of my skin</td>
<td>NO</td>
<td>YES 0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23.</td>
<td>Feeling bloated</td>
<td>NO</td>
<td>YES 0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24.</td>
<td>Low backache</td>
<td>NO</td>
<td>YES 0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25.</td>
<td>Frequent urination</td>
<td>NO</td>
<td>YES 0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26.</td>
<td>Involuntary urination when laughing or coughing</td>
<td>NO</td>
<td>YES 0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PART II (Genitourinary Symptoms):

Do you experience, and, if so, how much are you bothered by: Not at all Slightly Moderately Greatly

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Greatly</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Frequent urination</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>2. Urine leakage related to the feeling of urgency</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>3. Urine leakage related to physical activity, coughing, or sneezing</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>4. Small amounts of urine leakage (drops)</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>5. Difficulty emptying your Bladder</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>6. Pain or discomfort in the lower abdominal or genital area</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>
Has urine leakage and/or prolapse affected your:

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Greatly</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ability to do household chores</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>2. Physical recreation such as walking, swimming, or other exercise</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>3. Entertainment activities (movies, concerts, etc.)</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>4. Ability to travel by car or bus more than 30 minutes from your home</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>5. Participation in social activities outside your home</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>6. Emotional health (nervousness, depression, etc.)</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>7. Feeling frustrated</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
</tbody>
</table>

PART IV (Hot Flashes):

1. On an average day in the last week, how often did you experience hot flashes?
   ☐ 0 times per day
   ☐ 1-4 times per day
   ☐ 5-8 times per day
   ☐ 9-12 times per day
   ☐ 13-16 times per day
   ☐ greater than 16 times per day

2. Please see the list of definitions of severity of hot flashes on the next page. If on the previous question you indicated that you experience at least one hot flash per day, what percentage of your hot flashes are (should add up to 100%):

   Mild _____ %
   Moderate _____ %
   Severe _____ %
   Very severe _____ %

= 100%
PATIENT INFORMATION SHEET
HOT FLASH DEFINITIONS FOR THE FEMALE PATIENT

Please refer to these examples of hot flashes that have been given by cancer survivors in previous studies when describing their hot flash severity. One or more of these descriptions may help to categorize your hot flash as mild, moderate, severe, or very severe.

**MILD**

Duration: Lasting less than 5 minutes  
Physical symptoms: Warmth, felt uncomfortable, red face  
Emotional symptoms: Not expected  
Action needed: Usually no action taken

**MODERATE**

Duration: Lasting up to 15 minutes  
Physical symptoms: Head, neck, ears, or whole body felt warm; tense, tight muscles; clammy (wet skin); a change in heart rate or rhythm (heart speeds up or changes beat); some sweating; dry mouth  
Emotional symptoms: Felt irritated, felt agitated (restless), felt as though energy was drained out, felt embarrassed when having a hot flash in front of others, felt tired, felt annoyed  
Action needed: Needed to use a fan, awakened sometimes at night, needed to uncover, took off layers of clothing, drank water, opened the windows even when cold outside, wore lighter clothing

**SEVERE**

Duration: Lasting up to 20 minutes  
Physical symptoms: Warmth, sometimes described as a raging furnace or burning up; a change in heart rate or rhythm (heart speeds up or changes beat); felt faint; headache; severe sweating; weakness, a pricking, stinging sensation over skin; chest heaviness  
Emotional symptoms: Embarrassment, anxiety, feelings of having a panic attack  
Action needed: Needed to stop what was being done at that time, usually awakened at night and removed covers, needed to remove clothes, opened windows, kept the house a cooler temperature, frequently used fans

**VERY SEVERE**

Duration: Lasting up to 45 minutes  
Physical symptoms: Boiling heat, rolling sweat, difficulty breathing, felt faint, felt dizzy, feel and/or legs cramping, a change in the heart rate or rhythm (heart speeds up or changes beat), felt slightly sick to stomach  
Emotional symptoms: Felt distressed, had the urge to escape, had difficulty functioning  
Action needed: Awakened frequently at night, needed to change sheets and pajamas, needed to take a cold shower, needed to hold ice on skin
Appendix 6: Sexual Activity Questionnaire, Prophylactic Salpingo-oophorectomy Study

Appendix 11: SEXUAL ACTIVITY QUESTIONNAIRE
(© Fallowfield)

Occasionally, around the time of the menopause, some women notice hormonal changes which may affect their sexual relationships. Although the following questions are sensitive and personal, they are important in determining how hormonal treatment affects this part of your life. Please be assured that your responses to these questions will remain confidential.

Section I

1. Are you currently married or having an intimate relationship with someone?  
   Yes ☐ No ☐

2. Have you changed your sexual partner in the last 6 months?  
   Yes ☐ No ☐

3. Do you engage in sexual activity with anyone at the moment?  
   Yes ☐ No ☐

If 'Yes' please go to next page If 'No' please answer remaining questions on this page

Section II

I answered 'No' to question 3. I am not sexually active at the moment because  
(Please tick as many of these items as apply)

a) I do not have a partner at the moment ☐
b) I am too tired ☐
c) My partner is too tired ☐
d) I am not interested in sex ☐
e) My partner is not interested in sex ☐
f) I have a physical problem which makes sexual relations difficult or uncomfortable ☐
g) My partner has a physical problem which makes sexual relations difficult or uncomfortable ☐
h) Other reasons (please describe) ☐
Please complete this section if you are sexually active (i.e. you answered ‘Yes’ to question 3).

Please read each of the following questions carefully and tick the box that best indicates your sexual feelings and experiences during the past month.

Section III

During the past month:

1. Was ‘having sex’ an important part of your life this month?
   - very much: 3
   - somewhat: 2
   - a little: 1
   - not at all: 0

2. Did you enjoy sexual activity this month?
   - very much: 3
   - somewhat: 2
   - a little: 1
   - not at all: 0

3. In general, were you too tired to have sex?
   - very much: 0
   - somewhat: 1
   - a little: 2
   - not at all: 3

4. Did you desire to have sex with your partner(s) this month?
   - very much: 3
   - somewhat: 2
   - a little: 1
   - not at all: 0

5. During sexual relations, how frequently did you notice dryness of your vagina this month?
   - very much: 0
   - somewhat: 1
   - a little: 2
   - not at all: 3

6. Did you feel pain or discomfort during penetration this month?
   - very much: 0
   - somewhat: 1
   - a little: 2
   - not at all: 3

7. In general, did you feel satisfied after sexual activity this month?
   - very much: 3
   - somewhat: 2
   - a little: 1
   - not at all: 0

8. How often did you engage in sexual activity this month?
   - 5 times or more: 3
   - 3-4 times: 2
   - 1-2 times: 1
   - not at all: 0

9. How did this frequency of sexual activity compare with what is usual for you?
   - much more: 3
   - somewhat more: 2
   - about the same: 1
   - less than usual: 0

10. Were you satisfied with the frequency of sexual activity this month?
    - very much: 3
    - somewhat: 2
    - a little: 1
    - not at all: 0

Any other comments?

Thank you very much for answering these questions.
Appendix 7: Impact of Events Scale (IES)

Study ID#:____________________      Date: ____________________

IMPACT OF EVENT SCALE

EVENT:      Being at high risk for ovarian cancer

Directions: Below is a list of comments made by people about stressful life events and the context surrounding them. Read each item and decide how frequently each item was true for you DURING THE PAST 7 DAYS for the event described above.

<table>
<thead>
<tr>
<th></th>
<th>NOT AT ALL</th>
<th>RARELY</th>
<th>SOME-TIMES</th>
<th>OFTEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I thought about it when I didn’t mean to.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. I avoided letting myself get upset when I thought about it or was reminded about it.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. I tried to remove it from memory.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. I had trouble falling asleep or staying asleep, because of pictures or thoughts that came into my mind.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. I had waves of strong feelings about it.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. I had dreams about it.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. I stayed away from reminders of it.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. I felt as if it hadn’t happened or wasn’t real.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. I tried not to talk about it.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Pictures about it popped into my mind.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Other things kept making me think about it.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. I was aware that I still had a lot of feelings about it, but I didn’t deal with them.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. I tried not to think about it.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Any reminder brought back feelings about it.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. My feelings about it were kind of numb.</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 8: Basic Symptom Inventory (BSI® 18)

**BSI-18**

**Study ID#:_______________**

**Date:_______________**

INSTRUCTIONS: Below is a list of problems people sometimes have. Please read each one carefully, and circle the number that best describes HOW MUCH THAT PROBLEM HAS DISTRESSED OR BOTHERED YOU DURING THE PAST 7 DAYS INCLUDING TODAY. Please circle only one number for each problem and do not skip any items. If you change your mind, erase your first mark carefully.

<table>
<thead>
<tr>
<th>Problem</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nervousness or shakiness inside</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Faintness or Dizziness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Thoughts of ending your life</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Pains in head or chest</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Suddenly scared for no reason</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. Feeling blue</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Nausea or upset stomach</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Feeling tense or keyed up</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. Feeling no interest in things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. Trouble getting your breath</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. Spells of terror or panic</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. Feeling hopeless about the future</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. Hot or cold spells</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. Feeling so restless you couldn’t sit</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15. Feelings of worthlessness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16. Numbness or tingling in parts of your body</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>17. Feeling fearfu</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. Feeling lonely</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Appendix 9: SF-12 Health-Related Quality of Life Questionnaire (SF-12® Health Survey)

SF-12® Health Survey  
Study ID#: ____________________________  
Date: ________________________________

This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities.

Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Very Good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
</tbody>
</table>

The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

2. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

<table>
<thead>
<tr>
<th>Yes, limited a lot</th>
<th>Yes, limited a little</th>
<th>No, not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
</tbody>
</table>

3. Climbing several flights of stairs

   | o | o | o |

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

4. Accomplished less than you would like

   | o | o |

5. Were limited in the kind of work or other activities

   | o | o |

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

6. Accomplished less than you would like

   | o | o |

7. Didn't do work activities as carefully

   | o | o |

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
</tbody>
</table>
These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>A good bit of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Have you felt calm and peaceful?</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>10. Did you have a lot of energy?</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>11. Have you felt downhearted and blue?</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
</tbody>
</table>

12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
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Study of Preventive Oophorectomy
In High Risk Women

QUESTIONNAIRE:
Satisfaction Following
Prophylactic Oophorectomy

Study ID#: __________

Date Completed: ___________________
(month) (day) (year)
Thank you for taking the time to complete this questionnaire. As has previously been explained, we are interested in your experience following a preventive oophorectomy. Please feel free to share your thoughts in the margins.

SATISFACTION

1. How satisfied are you with your decision to have a prophylactic oophorectomy?

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<tbody>
<tr>
<td>(very dissatisfied)</td>
<td>(neither satisfied or dissatisfied)</td>
<td>(extremely satisfied)</td>
<td></td>
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</table>

2. If you feel any amount of dissatisfaction with your decision to have preventive surgery, please list the reasons.
   i) _______________________________________
   ii) _______________________________________
   iii) _______________________________________

3. Would you recommend this surgery to other women who have an increased risk of developing breast or ovarian cancer?

   NO → Reason _______________________________________
   _______________________________________

   YES → Reason _______________________________________
   _______________________________________

4. Do you still worry about developing ovarian cancer?

   □ NEVER (feel confident I won’t develop ovarian cancer)
   □ SOMEBEYES (the thought still crosses my mind occasionally)
   □ ALWAYS (I think about developing ovarian cancer every day)
   □ OTHER: _______________________________________

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5. Please describe your worry about developing ovarian cancer since you had the prophylactic oophorectomy?

☐ DECREASED WORRY

☐ INCREASED WORRY

☐ SAME AMOUNT OF WORRY

6. Was there information that you needed or would have liked at the time of surgery that you didn’t receive?

NO

YES → Please describe: ______________________________

__________________________________________

7. Did you experience any complications following your preventive ovarian surgery?

NO

YES → Please describe: ______________________________

__________________________________________

**OVARIAN CANCER**

6. What do you think your risk was of developing ovarian cancer before your oophorectomy (in percentage)? Example: if you think that you had a 20% chance of developing ovarian cancer before your surgery, place a mark at 20.

7. What do you think your risk of developing ovarian cancer is now, after you have had your surgery (in percentage)? Example: if you feel that you have a 20% risk of developing ovarian cancer, place a mark at 20.
11. What do you think your risk was of developing breast cancer before your oophorectomy (in percentage)? Example: if you think that you had a 20% chance of developing breast cancer before your surgery, place a mark at 20.

0  20  40  60  80  100

12. What do you think your risk of developing breast cancer is now, after you have had your surgery (in percentage)? Example: if you feel that you have a 20% risk of developing breast cancer, place a mark at 20.

0  20  40  60  80  100

Thank you for your participation and interest in this research study.
Appendix 11: Consent Form, International Risk Factor Study

CONSENT FORM

for

Risk factor analysis of hereditary breast and ovarian cancer

PRINCIPAL INVESTIGATOR:  Dr. Steven Narod
SITE:  Women’s College Research Institute

CO-INVESTIGATOR:  
SITE:  

PURPOSE OF RESEARCH:
I understand that I have been asked to participate in a research project of familial cancer. The purpose of this study is to identify hormonal, reproductive and lifestyle factors that are associated with the risk of developing breast and ovarian cancer among women at high risk.

PROCEDURE:
I understand that if I agree to participate I will be asked to complete a baseline questionnaire asking about my medical history, my family history of cancer and factors related to my lifestyle. I understand that members of the research team may also contact me by telephone every two years for follow-up to this questionnaire as part of their ongoing research.

I understand that my participation is voluntary and if I agree to participate I may withdraw my consent and discontinue my participation at any time. I understand that my participation will not affect my choice of, or access to, treatment or screening. I understand that my participation may be terminated with or without my consent.

CONFIDENTIALITY:
I understand that medical and all other information produced by this study will be strictly confidential and will be held securely at and will be subject to the confidentiality and privacy regulations of Sunnybrook and Women’s College Health Sciences Centre and the University of Toronto. This information will not become part of my personal medical record. This information will be available to the study research team, and not released to any other party, except upon my expressed written consent. Information regarding my medical history or test results will not be disclosed to any other member of my family. Information pertaining to the medical history or test results of my relatives will not be disclosed to me.

BENEFITS:
Genetic counselling will be available to me and members of my family. The research team will be available to provide the most current information regarding genetic risk assessment and will provide referral to screening centres for cancer if requested. I understand that I may have access to any information regarding my personal risk of developing cancer upon my request.

I understand that there is no compensation available for my participation in this research study. I understand that representatives of the National Cancer Institute of Canada, (the research granting agency) may inspect the research records.
**RISKS:**
There are no risks for participating in this study.

**REQUEST FOR MORE INFORMATION:**
I understand that I may ask more questions about the study. Dr. Narod is available to answer my questions and concerns (Tel. (1)-416-351-3765).

**CONFIRMATION OF PARTICIPATION:**
I confirm that the purpose of the research, the study procedures that I will undergo, as well as benefits that I may experience have been explained to me in sufficient detail.

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care.

I give permission to Dr. Narod and the study team to contact me by telephone if additional information is needed.

(Please initial)  YES______   Telephone ________________________
NO _____

__________________________________________  __________________________
Participant’s Signature          Date

I have explained to _____________________________ the purpose of this research, the procedures required and the possible risks and benefits of the study.

__________________________________________  __________________________
Investigator’s Signature          Date
RESEARCH QUESTIONNAIRE FOR
A STUDY OF BREAST AND OVARIAN CANCER
IN HIGH RISK FAMILIES

This questionnaire is part of a research study to improve our understanding of the prevention and treatment of hereditary breast and ovarian cancers.

Name: ____________________________

Date of Birth: ___/___/___  Age: ___

Date Completed: ___/___/___

This questionnaire is part of a research study to improve our understanding of the prevention and treatment of hereditary breast and ovarian cancers.

Name: ____________________________

Date of Birth: ___/___/___  Age: ___

Date Completed: ___/___/___
SECTION I – Fertility History
We would like you to describe your pregnancy history, as this has been found to affect the risk of cancer in some women.

1. Have you ever been pregnant?
   □ No  →  Go to question 6.
   □ Yes

2. Please consider all pregnancies, in order, from first to last. Give year of pregnancy. Place an ‘X’ in the appropriate column for the outcome of each pregnancy. For live-born children try to recall for how long you breast-fed each child and indicate months of breast-feeding in the right column (if not breast-fed, enter ‘0’).

<table>
<thead>
<tr>
<th>PREGNANCY OUTCOMES</th>
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<tbody>
<tr>
<td>#</td>
</tr>
<tr>
<td>1</td>
</tr>
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<td>8</td>
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<tr>
<td>9</td>
</tr>
</tbody>
</table>
   *(for twins, enter ‘T’ at the corresponding cell)*

3. How many of these pregnancies were caesarean sections? _________
   Circle which pregnancies (1-9 in chart above):  1  2  3  4  5  6  7  8  9

4. Did you ever have difficulty breast-feeding?
   □ No
   □ Yes  →  Reason: __ poor milk production       __ pain
            __ premature infant       __ mastitis (breast inflammation)
            __ other (please specify): __________________________
   Circle which child (1-9 in chart above) you experienced this with:
   1  2  3  4  5  6  7  8  9

5. Have you ever taken medication to stop milk production?
6. How old were you when you had your first menstrual period? _____ YEARS OLD

7. How would you describe your menstrual cycle? By regular we mean that the start of your period was predictable within 5 days. (Please check one)
   - My periods are/were always regular.
   - My periods are/were usually regular.
   - My periods are/were never regular.

8. How many days apart are your menstrual periods? That is, from the start of one period to the start of the next period. For example, many women have cycles of 28-32 days. (Please check one)
   - 28 days
   - 29 days
   - 30 days
   - 31 days
   - 32 days
   - Other → _______ days

9. Do you currently have menstrual periods? That is, have you had a menstrual period within the last year? Please answer “Yes” if you are currently pregnant or breast-feeding.
   - No
   - Yes

10. Have your periods stopped completely?
    - No → Go to question 13.
    - Yes

11. How old were you when your periods stopped completely? _____ YEARS OLD

12. What was the reason your periods stopped? (Select one only)
    - Natural Menopause (change of life)
    - Hysterectomy (uterus removed/ovaries not removed)
    - Uterus and ovaries removed
    - Oopherectomy (ovaries removed/uterus not removed)
    - Medication / Chemotherapy
    - Other (please specify): ________________________________

13. Have you ever seen a doctor for a problem of difficulty in getting pregnant or in carrying a pregnancy, such as several miscarriages?
14. Have you ever taken medication to increase your chances of becoming pregnant?
   □ No   → Go to question 16.
   □ Yes  → What reason did the doctor give to explain why you had trouble getting or staying pregnant? (Please check all that apply.)
   __ no problem was found __ problem with cervix
   __ problem with ovaries __ partner has fertility problem
   __ problem with fallopian tubes __ endometriosis
   __ other (please specify):___________________

   Name of medication(s): ___________________________________
   For how many months did you take this medication? _____ months
   What years did you take this medication? ______, ______

15. Have you ever received fertility treatment such as in vitro fertilization/Embryo Transfer (IVF/ET) to help you get pregnant?
   □ No   → Go to question 16.
   □ Yes  → What type of treatment did you receive? ______________________________

16a. Have you ever used birth control pills, Norplant (implants), or Depo-Provera (injections) to prevent pregnancy or for any other reason?
   □ No   → Go to question 17.
   □ Yes  → Can you describe the times?

<table>
<thead>
<tr>
<th>Name of Medication</th>
<th>Starting Year</th>
<th>Ending Year</th>
<th>Length of time used</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pills</td>
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<td>Implants</td>
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<td></td>
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<td></td>
<td>Injections</td>
<td></td>
</tr>
</tbody>
</table>

16b. Are you currently using birth control pills, Depo-Provera or Norplant?
   □ No
   □ Yes

17a. Have you ever taken hormone replacement therapy for menopause (i.e. estrogen, progesterone)?
   □ No   → Go to question 18.
   □ Yes  → Complete table below:
<table>
<thead>
<tr>
<th></th>
<th>Name of Hormone</th>
<th>Starting Year</th>
<th>Ending Year</th>
<th>Length of time used (Years)</th>
<th>Method</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pills, Skin Patches, Vaginal Suppositories</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pills, Skin Patches, Vaginal Suppositories</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pills, Skin Patches, Vaginal Suppositories</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pills, Skin Patches, Vaginal Suppositories</td>
</tr>
</tbody>
</table>

17b. Are you currently taking hormone replacement therapy?
- No
- Yes → Name of hormone: ______________ dose? ______________

SECTION II – Breast Cancer Diagnosis

18. Have you ever been diagnosed with breast cancer?
- No → Go to question 32 (Section III).
- Yes → Year of diagnosis: _________

Check one → I have had cancer in
- [ ] one breast
- [ ] both breasts

We would like to discuss your first diagnosis.
What year was it? _________ Month (if known)? _________
Which breast? [ ] Left [ ] Right

Type of Cancer (check one):
- [ ] It was an invasive cancer.
- [ ] It was a non-invasive cancer (early stage breast cancer).
  → Was it Ductal Carcinoma In-situ (DCIS)? [ ] Yes [ ] No
  → Was it Lobular Carcinoma In-situ (LCIS)? [ ] Yes [ ] No
- [ ] It was both invasive and non-invasive.
- [ ] I’m not sure.

Treatment
Did you have surgery for the first breast cancer?
- No
- Yes → Year of surgery: _________

What type of surgery did you have?
Check one → ___ Lumpectomy (tumour removed, breast remains)

___ Mastectomy (one breast removed)

___ Bilateral mastectomy (both breasts removed)

Detection

How was the lump first detected?

Check one → ___ Only by mammography screening

___ Did you feel a lump?

___ Did the doctor feel a lump?

___ MRI screening

___ Other: ______________________

19. Did you receive chemotherapy for the first breast cancer?

☐ No

☐ Yes

20. Did you receive radiation therapy for the first breast cancer?

☐ No

☐ Yes

21. Did you receive Tamoxifen (Nolvadex) for the first breast cancer?

☐ No

☐ Yes → Number of pills per day: __________

From: _________ (year) to _________ (year)

22. Did you receive any other drugs for the first breast cancer?

☐ No

☐ Yes → Which drug? ☐ Femara (letrozole)

☐ Aromasin (exemstane)

☐ Arimidex (anastrazole)

☐ Other: ______________________

Number of pills per day: __________

From: _________ (year) to _________ (year)

23. Have you had a recurrence of your first breast cancer?

☐ No

☐ Yes → Date: __ __ / __ __ / __ __ __ __ (mm / dd / yyyy)

Site of recurrence: __________________________________________

24. Have you had further surgery in the affected breast (such as complete mastectomy or reconstruction)?

☐ No

☐ Yes → Date: __ __ / __ __ / __ __ __ __ (mm / dd / yyyy)

Type of surgery: __________________________________________
25. We would like to discuss your **second** diagnosis (This does NOT include a recurrence, i.e. a cancer in the same breast as the previous breast cancer).

What year was it? _________  Month (if known)?  _________

Which breast?  □  Left  □  Right

**Type of Cancer (check all that apply):**

- It was an invasive cancer.
- It was a non-invasive cancer (early stage breast cancer).
  →  Was it Ductal Carcinoma In-situ (DCIS)?  □  Yes  □  No
  →  Was it Lobular Carcinoma In-situ (LCIS)?  □  Yes  □  No
- It was both invasive and non-invasive.
- I’m not sure.

**Treatment**

Did you have surgery for the **second** breast cancer?

- □  No
- □  Yes  →  Year of surgery: _________
  What type of surgery did you have?
  Check one  →  ___ Lumpectomy (tumour removed, breast remains)
  ___ Mastectomy  (one breast removed)
  ___ Bilateral mastectomy  (both breasts removed)

**Detection**

How was the lump first detected?

Check one  →  ___ Only by mammography screening
  Did you feel a lump?
  ___ Did the doctor feel a lump?
  ___ MRI screening
  ___ Other: _______________

26. Did you receive chemotherapy for the second breast cancer?

- □  No
- □  Yes

27. Did you receive radiation therapy for the second breast cancer?

- □  No
- □  Yes

28. Did you receive Tamoxifen (Nolvadex) for the second breast cancer?

- □  No
- □  Yes  →  Number of pills per day: _________
  From: _________ (year) to _________ (year)
29. Did you receive any other drugs for the second breast cancer?
   □ No □ Yes → Which drug? □ Femara (letrozole) □ Aromasin (exemstane) □ Arimidex (anastrozole) □ Other: ______________________
   Number of pills per day: __________
   From: _________ (year) to _________ (year)

30. Have you had a recurrence of your second breast cancer?
   □ No □ Yes → Date: __ __ / __ __ / __ __ __ __ (mm / dd / yyyy)
   Site of recurrence: __________________________________________

31. Have you had further surgery in the affected breast (such as complete mastectomy or reconstruction)?
   □ No □ Yes → Date: __ __ / __ __ / __ __ __ __ (mm / dd / yyyy)
   Type of surgery: __________________________

SECTION III – Breast Cancer Screening/Prevention

32. Have you ever taken any drugs for the prevention of breast cancer (i.e. drugs taken before any diagnosis of breast cancer)?
   □ No □ I’m not sure □ Yes → Name of Drug: ___ Tamoxifen (Nolvadex) ___ Raloxifene (Evista)
    ___ Aromasin (Exemestane) ___ Femara (Letrozole)
    ___ Arimidex (Anastrozole) ___ Other (please name): ______________________
   Number of pills per day: __________________________
   Date started: __ __ / __ __ __ __ (mm / yyyy) to __ __ / __ __ __ __ (mm / yyyy)

33. Have you ever participated in a clinical trial for the prevention of breast cancer?
   □ No □ Yes → Which one? ___ Tamoxifen Trial (Tamoxifen vs. placebo)
    ___ STAR Trial (Tamoxifen vs. Raloxifene)
    ___ Other: __________________________
    ___ Unknown
   Do you know which drug you took? □ Yes □ No
   If yes, which one? __________________________
34. Do you have or have you had breast implants or breast reconstruction?
   - No
   - Yes → What type?  ___ Saline  ___ Silicone
     ___ TRAM-flap  ___ Other: ________________________

35. Have you undergone surgery at any time in order to prevent breast cancer (e.g. preventive removal of the breasts)?  
   **NOTE:** The surgery is only preventive if you’ve never previously been diagnosed with cancer in that breast.
   - No
   - Yes → What year? _________
     Which breast? ___ Left  ___ Right  ___ Both
     Procedure: ___ Total mastectomy (nipple and areola removed)
     ___ Subcutaneous mastectomy (nipple and areola preserved)

36. Have you ever had a breast biopsy?
   - No
   - Yes → Number of biopsies: _________
     Month/Year of last biopsy: _______/___________
     What was the result of the biopsy? (Check all that apply)
     __ normal  __ DCIS  __ atypical hyperplasia
     __ cancer  __ LCIS  __ fibroadenoma
     __ other (please specify): ______________________________

37. Approximately how many mammograms have you had in your lifetime?
   I have had ______ mammograms. If you do not recall the exact number, please provide a range.
   Age at first mammogram? _________ years old.
   Age at last mammogram? _________ years old.

38. Have you ever had any abnormalities detected by mammogram?
   - No
   - Yes → Please describe the abnormality: ______________________________
     Month/Year of abnormality: _______/___________

39. Have you ever had MRI screening of your breasts?
   - No
   - Yes → What year? _________
SECTION IV – Ovarian Cancer

40. Have you ever had ovarian cancer?
   □ No → Go to question 45 (Section V).
   □ Yes → Year of diagnosis: __________

41. Did you have surgery for your ovarian cancer?
   □ No
   □ Yes → Check one → ___ One ovary was removed
            ___ Both ovaries were removed

42. Did you receive chemotherapy for your ovarian cancer?
   □ No
   □ Yes

43. Did you receive radiation therapy for your ovarian cancer?
   □ No
   □ Yes

44. Have you had a recurrence of your ovarian cancer?
   □ No
   □ Yes → Date: ___ / ___ / ___ ___ (mm / dd / yyyy)
            Site of recurrence: _________________________

SECTION V – Reproductive/ Abdominal Surgeries

45. Have you had one or both of your ovaries removed (oophorectomy) for reasons other than ovarian cancer? (e.g. preventative measures, fibroids, cyst, scar tissue, or pain)
   □ No
   □ Yes → Year of surgery: __________
            Reason for the surgery: _____________________________
            Number of ovaries removed: ___ One ___ Two

46. Have you ever had a tubal ligation (fallopian tubes tied)?
   □ No
   □ Yes → Year: __________

47. Have you had surgery performed on your reproductive organs: including ovaries, fallopian tubes, or uterus? (e.g. hysterectomy, cervix removed, myomectomy, D & C)
   □ No
   □ Yes → Year: __________
            What operation was performed? _____________________________
            Reason for the surgery: _____________________________
48. Have you ever had another operation on your abdomen? (e.g. gall bladder, appendix, laparoscopy, hernia, etc)

☐ No
☐ Yes →

1. Type of surgery: ____________________________ Year: _________
2. Type of surgery: ____________________________ Year: _________
3. Type of surgery: ____________________________ Year: _________

SECTION VI – Personal Information

Today’s Date: ____________________________
Month – Day – Year

Date of Birth: ____________________________
Month – Day – Year

Place of Birth: ____________________________
City Province/State

Current Residence: ____________________________
City Province/State

Ethnic Background: ____________________________

49a. What is the major ancestry of your father? (Please circle one option.)

African or African American (country of origin: ________)

Ashkenazi Jewish

Asian/Pacific Islander (country of origin: ________)

Dutch

English

European Bloc countries

French Canadian

German

Hispanic (country of origin: ________________)

Irish

Italian

Native American (Amer. Indian)

Polish/Slavic/Eastern

Russian

Scandinavian (Swedish/Finnish/
Norwegian/Dane)

Scot-Irish or Scottish

Sephardic Jewish

Other (specify: _____________)

Unknown
49b. What is the major ancestry of your mother? *(Please circle one option.)*

- African or African American (country of origin: ________)
- Ashkenazi Jewish
- Asian/Pacific Islander (country of origin: ________)
- Dutch
- English
- European Bloc countries
- French Canadian
- German
- Hispanic (country of origin: _____________)
- Irish
- Italian
- Native American (Amer. Indian)
- Polish/Slavic/Eastern
- Russian
- Scandinavian (Swedish/Finnish/Norwegian/Dane)
- Scot-Irish or Scottish
- Sephardic Jewish
- Other (specify: _____________)
- Unknown

50. What is your: current weight? _______ pounds
current height? ______ feet _____ inches

Think back to when you were 18 years old, about the time you graduated from high school.
How much did you weigh then? ______ pounds
at age 30? ______ pounds
at age 40? ______ pounds

What is the most you have ever weighed (exclude pregnancy)? ______ pounds

How old were you when you weighed the most? ______ years old

51. Do you know how much you weighed when you were born?
- No
- Yes → _____ pounds _____ ounces OR ______ grams

52. What is your mother’s year of birth? _____________

53. What is your birth order (i.e. first-born, second-born, third-born etc.)? _____________

54. Were you part of a multiple birth (i.e. twin, triplet)?
- No
- Yes → *(Please check one)*
  - ___ twin → Are you an identical twin?  Yes    No
  - ___ triplet
  - ___ other (please specify): __________
SECTION VII – Lifestyle

55. Have you ever smoked cigarettes regularly?
   ☐ No
   ☐ Yes →  From: __________ (age first started) to __________ (age last used)
   On average, how many packs do/did you smoke per week? __________
   Do you still smoke?    ☐ Yes    ☐ No

56. Do you or did you ever drink coffee regularly?
   ☐ No
   ☐ Yes →  From: __________ (age first started) to __________ (age last used)
   On average, how many cups do/did you drink a day?
   Caffeinated: _____cups    Decaffeinated: _____cups    Total: _____cups
   Do you still drink coffee?    ☐ Yes    ☐ No

57. Do you drink alcoholic beverages?
   ☐ No
   ☐ Yes →  On average, how many alcoholic drinks do/did you have a week?
   ____0-3 ____4-9 ____10-20 ____20 or more
   →  What age did you start drinking alcoholic drinks? ________ years

58. Have you ever been a regular user of talcum powder?
   ☐ No
   ☐ Yes →  Did you apply it directly to the vaginal area?    ☐ Yes    ☐ No
   Did you apply it to sanitary napkins?    ☐ Yes    ☐ No
   Other use of talcum powder? (describe) __________________________
   What age did you start using talcum powder? ____________ years old
SECTION VIII – Other Illnesses

59. Are you taking or have you taken any medications (prescriptions or over-the-counter) on a regular basis?

☐ No
☐ Yes → Complete:

1. Drug: ________________________________
   From: _______ (year) to _______ (year)
   Reason: _______________________________________

2. Drug: ________________________________
   From: _______ (year) to _______ (year)
   Reason: _______________________________________

3. Drug: ________________________________
   From: _______ (year) to _______ (year)
   Reason: _______________________________________

60. Do you have or have you had any of the following?

Hay Fever    ☐ Yes    ☐ No
Asthma       ☐ Yes    ☐ No
Eczema        ☐ Yes    ☐ No

61. Have you been diagnosed with any cancer other than breast or ovarian?

☐ No
☐ Yes → What type? _______________________ Year of Diagnosis? __________

62. Please describe briefly any medical problems that you have had in the past, especially those that may have required hospitalization.

_____________________________________________________________________
_____________________________________________________________________
Thank you for taking the time to complete this questionnaire. Should the need arise, may we call you again?

☐ No
☐ Yes → Telephone number __________________________

In the case that we are unable to reach you at this number, please provide a telephone number of a relative that we can call to obtain your new contact information:

Name: ____________________________     Relationship: __________________

Telephone number: _____________________________
FOR OFFICE USE (to be completed by Genetic Counsellor):

Participating centre: ____________________________

Contact person: ____________________________

Interviewer (if by phone): ____________________________

Family Number: __________

Individual Identification No: __________

Date questionnaire sent: __________
    Month – Day – Year

Date questionnaire received: __________
    Month – Day – Year

Information received by mail _______ or by telephone _______ or in clinic _______

<table>
<thead>
<tr>
<th>Genetic Test Result Disclosed to Patient?</th>
<th>☐ Yes</th>
<th>☐ No</th>
</tr>
</thead>
</table>
| Date Test Result Disclosed:              | __________
    Month – Day – Year |
| Mutation: BRCA___: ____________________________ | Exon___ |
Appendix 13: Follow-up Questionnaire, International Risk Factor Study

FOLLOW-UP QUESTIONNAIRE FOR

A STUDY OF BREAST AND OVARIAN CANCER
IN HIGH RISK FAMILIES

Date Completed: _________________________________ (mm / dd / yyyy)
Name: ________________________________________________
Date of Birth: _________________________________ (mm / dd / yyyy)
Fam/Ind#: ________________________________________________
Telephone #: ________________________________________________
Date of Previous Questionnaire: _________________________________ (mm / dd / yyyy)
Centre: ________________________________________________
SECTION I - REPRODUCTIVE UPDATE

1. Have you had any pregnancies since ___ / ____ / ____ (mm / yyyy) (including still born, miscarriage, abortion)?
   □  No
   □  Yes → Year of pregnancy: ___ / __ / ___ Date of birth: ___ / ___ / ____ (mm/dd/yyyy)
   Pregnancy outcome (please check one):
   ___ Liveborn ___ Stillborn ___ Abortion
   ___ Miscarriage ___ Other: ______________________________

2. Have you ever had any difficulty breastfeeding?
   □  I have never breastfed
   □  No
   □  Yes → Reason: ______________________________

3. Are you still having menstrual periods?
   □  Yes
   □  No → At what age did they stop? ______________
   Reason they stopped? (Please check one)
   ___ Ovaries removed (uterus remained) ___ Medication/Chemotherapy
   ___ Uterus removed (ovaries remained) ___ Natural Menopause
   ___ Both uterus and ovaries removed ___ Other ____________________

4. Have you ever taken birth control medication?
   □  No
   □  Yes → (i) From: ___ / ___ / ___ to ___ / ___ / ___ (year)
   Length of time used: _________ years _________ months
   Name of medication: ___________________________________
   Method (please check one): ___ Pill ___ Injection
   ___ Implant ___ Other __________________

   (ii) From: ___ / ___ / ___ to ___ / ___ / ___ (year)
   Length of time used: _________ years _________ months
   Name of medication: ___________________________________
   Method (please check one): ___ Pill ___ Injection
   ___ Implant ___ Other __________________

Are you still using birth control medication? □ Yes □ No
5. Have you ever taken hormone replacement therapy (HRT)?
   □ No
   □ Yes ⇒ (i) From: __ ______ to __ ______ (year)
            Length of time used: ____________ years ___________ months
            Name of medication: ___________________________________
            Dose (mg/day): ___________________________
            Method (please check one): ___ Pills      ___ Cream       ___ Gel ___ Patch
            ___ Vaginal Suppositories ___ Other _______

   (ii) From: __ ______ to __ ______ (year)
            Length of time used: ____________ years ___________ months
            Name of medication: ___________________________________
            Dose (mg/day): ___________________________
            Method (please check one): ___ Pills      ___ Cream       ___ Gel ___ Patch
            ___ Vaginal Suppositories ___ Other _______

   Are you still using HRT?  □ Yes  □ No

SECTION II - LIFESTYLE

6. Have you ever smoked cigarettes?
   □ No
   □ Yes ⇒ From: ________ (age first started) to ________ (age last used)
            On average, how many packs do/did you smoke per week?
            _______________

            Do you still smoke?  □ Yes  □ No

7. Have you ever drank coffee?
   □ No
   □ Yes ⇒ From: ________ (age first started) to ________ (age last used)
            On average, how many cups do/did you drink a day?
            Caffeinated: ______cups  Decaffeinated: _____cups
            Total: ______cups

            Do you still drink coffee?  □ Yes  □ No
8. Have you ever drank alcohol?
   □ No
   □ Yes → From: __________ (age first started) to __________ (age last used)
   On average, how many alcoholic drinks do/did you have per week?
   
   *(Please check one)*
   
   ____ 0-3  ____ 4-9  ____ 10-20  ____ 20 or more
   
   What type of alcoholic beverages do/did you drink? *(Check all that apply)*
   ____ beer  ____ wine  ____ hard liquor

9. What is your current weight: ____________ pounds  or  ____________ kgs

10. What is your highest level of education? *(please check one)*
   
   ____ No Schooling
   ____ Attended elementary school  ____ Graduated from elementary school
   ____ Attended high school  ____ Graduated from high school
   ____ Attended college/university  ____ Graduated from college/university
   ____ Attended graduate school  ____ Graduated from graduate school

**SECTION III – MEDICAL HISTORY**

11. Have you had any surgery since ___ / ________ (mm / yyyy)?
   
   □ No
   □ Yes  *(Complete table below)*

<table>
<thead>
<tr>
<th>Date of Surgery</th>
<th>Type of Surgery</th>
<th>Reason for Surgery</th>
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12. Have you taken any regular prescription medications since ____ / ______ (mm / yyyy)?

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<th>No</th>
<th>Yes</th>
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(Complete table below)

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<thead>
<tr>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Drug 3</th>
<th>Drug</th>
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<tbody>
<tr>
<td>Name of Drug</td>
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<td>Date Started</td>
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<tr>
<td>Date Ended</td>
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<tr>
<td>Reason</td>
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13. Do you take dietary supplements or vitamins (i.e. multi-vitamins, calcium supplement etc.)?

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<th>No</th>
<th>Yes</th>
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→ ___ Multi-vitamins for ______ years ______ months
→ ___ Supplements (including herbal supplements)
→ Type (e.g. Evening Primose Oil, calcium etc):

1. ________________ for ______ years ______ months
2. ________________ for ______ years ______ months
3. ________________ for ______ years ______ months

14. Do you have any other medical conditions?

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<th>No</th>
<th>Yes</th>
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→ Describe: ___________________________________________

15. Have you received your genetic test results?

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<th>No</th>
<th>Yes</th>
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→ Date you received your results: __ __ / __ __ / __ __ __ __ (mm / dd / yyyy)

SECTION IV – BREAST CANCER SCREENING/PREVENTION

16. Have you ever had a mammogram?

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<th>No</th>
<th>Yes</th>
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→ Age at first mammogram: ___________

→ How many mammograms have you had? ___________

→ Were there any abnormalities detected by mammogram? Yes No

If yes, please describe: ___________________________________________

→ Year of abnormality: __ __ __ __

→ What year was your last mammogram done? __ __ __ __
17. Have you ever had MRI screening of your breasts?

☐ No
☐ Yes → Age at first MRI: _______

How many MRIs have you had? _________________

Where were they done: ___________________________________

Were there any abnormalities detected by MRI? ☐ Yes ☐ No

If yes, please describe: ___________________________________

Year of abnormality: __ __ __ __

What year was your last MRI done? __ __ __ __

18. Have you ever had a breast biopsy (this includes needle and core biopsies)?

☐ No
☐ Yes → Number of biopsies: _______________

Date of first biopsy: ___ / ___ / _____ (mm / dd / yyyy)

Date of last biopsy: ___ / ___ / _____ (mm / dd / yyyy)

Result of biopsies: ___________________________________

19. Have you undergone preventive removal of your breasts?

☐ No
☐ Yes → Date: ___ / ___ / ______ (mm / dd / yyyy)

Which breast was removed? ____ Left ____ Right ____ Both

Procedure: ___ Subcutaneous Mastectomy (nipple and areola preserved)

___ Total Mastectomy (nipple and areola removed)

___ Other: _____________________________________________

20. Have you ever had breast implants or breast reconstruction?

☐ No
☐ Yes → Type: ___ Saline ___ Silicone ___ TRAM-flap

___ Other: _____________________________________________

Year of surgery: __ __ __ __

21. Have you ever taken any drugs for the prevention of breast cancer (i.e. drugs taken before any diagnosis of breast cancer)?

☐ No
☐ Yes → Name of Drug: ___ Tamoxifen (Nolvadex) ___ Raloxifene (Evista)

___ Aromasin (Exemestane) ___ Femara (Letrozole)

___ Arimidex (Anastrozole) ___ Other (please name):

Dosage (mg/day): ____________________
22. Have you ever participated in a clinical trial for the prevention of breast cancer?
   - [ ] No
   - [ ] Yes → Which one?  
     - [ ] Tamoxifen Trial (Tamoxifen vs. placebo)
     - [ ] STAR Trial (Tamoxifen vs. Raloxifene)
     - [ ] Other: __________________________
     - [ ] Unknown
   Do you know which drug you took?  
     - [ ] Yes  
     - [ ] No  
     If yes, which one? __________________________

SECTION V – OVARIAN CANCER SCREENING/PREVENTION

23. Have you ever had a trans-vaginal ultrasound (internal ultrasound done through the vagina)?
   - [ ] No
   - [ ] Yes → Age at first ultrasound: __________________________
   Number of ultrasounds: __________________________
   Abnormalities detected by ultrasound:  
     - [ ] Yes  
     - [ ] No  
   If Yes: Describe: __________________________
   Year of last trans-vaginal ultrasound: __ __ __ __

24. Have you ever had a blood test for CA125 (marker for ovarian cancer)?
   - [ ] No
   - [ ] Yes → Age at first CA125: __________________________
   Date of last CA125: __ __ / __ __ / __ __ __ __ (mm / dd / yyyy)
   Abnormalities detected:  
     - [ ] No  
     - [ ] Elevated  
     - [ ] Don’t Know
   Year of abnormality: __ __ __ __

25. Have you had your ovaries removed for reasons other than ovarian cancer?
   - [ ] No
   - [ ] Yes → Year: __ __ __ __  
     Number removed:  
       - [ ] 1  
       - [ ] 2  
   Year: __ __ __ __  
     (if ovaries removed in two separate surgeries)
   Reason:  
     - [ ] Abnormal CA125 test
     - [ ] Preventative
     - [ ] Cyst  
     - [ ] Other __________________________
Did you have breast cancer at the time of or prior to the date of the last questionnaire?

☐ NO  →  Go to Question 29 (Section VII).
☐ YES  →  Please complete this section.

Year of previous cancer: ___ / ___ / ___ (mm / yyyy)
Side: ___ Left  ___ Right  ___ Both
Type (check all that apply): ___ Invasive
___ Non-invasive → ___ Ductal Carcinoma In-situ (DCIS)
___ Lobular Carcinoma In-situ (LCIS)
Treatment: ___ Surgery: ____________  ____ Radiation
___ Chemotherapy   ____ Hormone Therapy

26. Have you ever taken any drugs for the treatment (and to prevent a recurrence) of your breast cancer?

☐ No  
☐ Yes  →  Name of Drug: ___ Tamoxifen (Nolvadex) ___ Raloxifene (Evista)
___ Aromasin (Exemestane) ___ Femara (Letrozole)
___ Arimidex (Anastrozole) ___ Other: ____________
Dosage (mg/day): __________________
Date started: ___ / ___ / ___ (mm / yyyy) to ___ / ___ / ___ (mm / yyyy)

27. Have you had a breast cancer recurrence?

☐ No  
☐ Yes  →  Date: ___ / ___ / ___ / ___ (mm / dd / yyyy)
Site: __________________________________________
Mode of detection: ___ Mammogram   ___ X-ray   ___ Doctor
___ Self-exam   ___ Other: ______________________
Treatment: __________________________________________

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28. Have you had any further surgery on the affected breast(s)?
   □ No
   □ Yes → Type of surgery: _____ **Lumpectomy** (part of breast removed)
   Which breast? ___ Left  ___ Right  ___ Both
   Date of lumpectomy:  ____/____/____ (mm/dd/yyyy)

   _____ **Mastectomy** (whole breast removed)
   Which breast? ___ Left  ___ Right  ___ Both
   Date of mastectomy:  ____/____/____ (mm/dd/yyyy)

   _____ **Reconstruction**
   Which breast? ___ Left  ___ Right  ___ Both
   Date of reconstruction:  ____/____/____ (mm/dd/yyyy)

**SECTION VII – OVARIAN CANCER (PREVIOUS DIAGNOSIS)**

Did you have ovarian cancer at the time of or prior to the date of the last questionnaire?
   □ NO → Go to Question 31 (Section VIII).
   □ YES → Please complete this section.
   Year of previous cancer:  ____/____/____ (mm/yyyy)

29. Have you had an ovarian cancer recurrence?
   □ No
   □ Yes → Date:  ____/____/____ (mm/dd/yyyy)
   Site: _____________________________________________
   Mode of detection:  ___ CA125 test  ___ Trans-vaginal ultrasound
   ___ Doctor  ___ Other ____________________________
   Treatment: __________________________________________________________________________

30. Do you still have your ovaries?
   □ No
   □ Yes → How many?  □ 1  □ 2

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SECTION VIII – NEW BREAST CANCER DIAGNOSIS

31. Have you been diagnosed with breast cancer since ___ / _______ (mm / yyyy)?
   □ No → Go to Question 33 (Section IX).
   □ Yes → Date of diagnosis: ___ / ___ / _______ (mm / dd / yyyy)
   Which breast? ___ Left ___ Right ___ Both

Type of Cancer (check all that apply):
   □ It was an invasive cancer.
   □ It was a non-invasive cancer (early stage breast cancer).
      → Was it Ductal Carcinoma In-situ (DCIS)?
         □ Yes □ No
      → Was it Lobular Carcinoma In-situ (LCIS)?
         □ Yes □ No
   □ I’m not sure.

Treatment: (i) Surgery? □ Yes □ No
   If Yes: _____ Mastectomy (whole breast removed)
   Which breast? ___ Left ___ Right ___ Both
   Date of mastectomy: ___ / ___ / _______ (mm / dd / yyyy)
   _____ Lumpectomy (part of breast removed)
   Which breast? ___ Left ___ Right ___ Both
   Date of lumpectomy: ___ / ___ / _______ (mm / dd / yyyy)
   _____ Axillary Node Dissection (lymph nodes removed)
   Number removed: _____
   Were any found to have cancer? □ Yes □ No
   How many? _____

(ii) Chemotherapy? □ Yes □ No
   If yes, name of drug: ____________________

(iii) Radiation therapy? □ Yes □ No

(iv) Other treatment drugs (e.g. Tamoxifen, Femara, etc.)?
   □ Yes □ No
   If yes, name of drug: ___________________ Dosage (mg/day): _______
   Date started: ___ / ___ ______ to ___ / ___ ______ (mm / yyyy)
   Name of hospital: _____________ City: __________________________
   How was the cancer first detected? ______________________________
If a lump was felt, was a mammogram done to confirm the cancer?

☐ Yes  ☐ No

If yes, was an abnormality detected?

☐ Yes  ☐ No

32. Have you had a breast cancer recurrence?

☐ No  
☐ Yes → Date: __ __ / __ __ / __ __ __ __ (mm / dd / yyyy)

Site of recurrence: ____________________________
Treatment: ____________________________

SECTION IX – NEW OVARIAN CANCER DIAGNOSIS

33. Have you been diagnosed with ovarian cancer since ____ / ________ (mm / yyyy)?

☐ No  → Go to Question 35 (Section X).
☐ Yes → Date of diagnosis: __ __ / __ __ / __ __ __ __ (mm / dd / yyyy)

Treatment:
(i) Ovaries removed?  ☐ Yes  ☐ No
If Yes: How many?  1  2
Date of surgery: __ __ / __ __ / __ __ __ __ (mm / dd / yyyy)

(ii) Chemotherapy?  ☐ Yes  ☐ No
If Yes: Name of drug: ____________________________

(iii) Radiation therapy?  ☐ Yes  ☐ No
Name of hospital: ____________________________ City: ____________________________
How was the cancer first detected? ____________________________
Was a trans-vaginal ultrasound done?  ☐ Yes  ☐ No
If yes, were any abnormalities detected?  ☐ Yes  ☐ No
Was a CA125 test done?  ☐ Yes  ☐ No
If yes, were any abnormalities detected?  ☐ Yes  ☐ No

34. Have you had an ovarian cancer recurrence?

☐ No  
☐ Yes → Date: __ __ / __ __ / __ __ __ __ (mm / dd / yyyy)

Site of recurrence: ____________________________
Treatment: ____________________________
SECTION X – OTHER CANCERS

35. Have you been diagnosed with any cancer other than ovarian or breast?

- [ ] No
- [x] Yes → Date of diagnosis: ___ / ___ / _____ (mm / dd / yyyy)
  Type: ___________________________________
  Treatment: __________________________________

SECTION XI – PEDIGREE UPDATE

36. Have there been any new cancers diagnosed in your family since ____ / _____ (mm / yyyy)?

- [ ] No
- [x] Yes  (Complete table below)

<table>
<thead>
<tr>
<th>Name</th>
<th>Relationship</th>
<th>Type of Cancer</th>
<th>Year of Diagnosis</th>
<th>Age at Diagnosis</th>
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37. Have there been any births or deaths in your family since ____ / _____ (mm / yyyy)?

- [ ] No
- [x] Yes  (Complete table below)

<table>
<thead>
<tr>
<th>Name</th>
<th>Relationship</th>
<th>Date of Birth</th>
<th>Date of Death</th>
<th>Cause of Death</th>
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Thank you very much for taking the time to complete this questionnaire.

Should the need arise, may we contact you again?  □ No  □ Yes

Telephone number: ________________  Alternate contact: ________________