INCIDENCE, SURVIVAL AND MORTALITY AMONG WOMEN WITH

EPITHELIAL OVARIAN CANCER BY HISTOTYPE: A POPULATION STUDY IN

BRITISH COLUMBIA, CANADA

by

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Abstract

Objectives. Epithelial Ovarian cancer (EOC) is composed of five distinct histologic subtypes. However, histotype- specific survival and mortality estimates among women with EOC are limited. Also, we lack information on long- term health conditions faced by ovarian cancer survivors. This thesis examined: 1) histotype- specific incidence and survival rates among women with EOC in British Columbia (BC); 2) causes of death among women with EOC by histotype; and, 3) compared these causes of death to age- standardized causes of death in the general population.

Methods. Using population- based administrative datasets, I built two population- based cohorts of all women with EOC diagnosed in BC: 1. women diagnosed between 1980 and 2015(cohort 1) and women diagnosed between 1990 and 2014 (cohort 2). Cohort 1 was used to answer question 1, whereas cohort 2 was used to answer question 2 and 3. For question 2, I compared the causes of death within histotypes, by age at diagnosis, *BRCA* status, and time since diagnosis. For question 3, I calculated all- cause and cause- specific standardized mortality ratios.

Results. Decreasing incidence rates and increasing survival rates were observed among women with EOC in BC. As expected, ovarian cancer was the most common cause of death among these women, which was first surpassed by other causes of deaths at 11 years after diagnosis. When stratified by serous and non- serous EOCs, ovarian cancer was the leading cause of death for 12 years and for 8 years respectively after diagnosis. Of particular interest, the number of deaths from other cancers (breast, colorectal and lung cancer) and external causes (falls) among long- term ovarian cancer survivors (5-9 and 10+ years post diagnosis) were higher than the expected.

Conclusions. Although there was an improvement in the survival over time, ovarian cancer remains the leading cause of death for 11 years following diagnosis of EOC. My findings suggest that long- term survivors (those living 5-9 and 10+ years following diagnosis) are particularly vulnerable to deaths from other cancers and from falls in elderly survivors. Hence, these women may benefit from closer surveillance of other cancers and bone health.

Lay Summary

The most recent survival data in BC dates to 2005 and is in desperate need of updating to understand whether we are making progress in treating ovarian cancer. We now understand that ovarian cancer is not a single disease, but rather 5 distinct diseases, separated according to histotype. Hence, I updated the survival statistics taking histotypes into consideration. I also studied the causes of death among women with ovarian cancer, and among women surviving ovarian cancer for 5-9 years and 10+ years after their diagnosis (long-term survivors). Through this analysis, we were able to illustrate that long-term survivors of ovarian cancer are at higher risk of lung, breast and colorectal cancer and of deaths to falls. This information is important as the end of cancer treatment is not the end of cancer experience, and we must focus on improving the life of ovarian cancer survivors.

Preface

This statement is to certify that the work in this thesis is original. This thesis is manuscript-based and it was proposed, conducted and written by Nimisha Arora. All the research work discussed in this thesis was approved by the University of British Columbia's Behavioural Research Ethics Board: UBC BREB Number: H16-01538.

Chapter 2 is based on work conducted by Nimisha Arora (NA), Aline Talhouk (AT), Jessica N. McAlpine (JM), Michael R. Law (ML), Gillian E. Hanley (GH). NA and GH came up with the study proposal and wrote the manuscript. AT and NA conducted the data analysis. AT and GH assisted NA in the final interpretation of the data. JM, ML contributed to manuscript revision. A version of Chapter 2 will be submitted for journal publication.

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List of abbreviations

Body mass index (BMI)

British Columbia (BC)

Epithelial ovarian cancer (EOC)

Standard deviation (SD)

Standardized mortality ratios (SMR)

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Dedication

This study is wholeheartedly dedicated to my beloved parents, Bharat Kumar Arora and Anita Arora, who have been my ultimate source of unconditional love, support and encouragement. This thesis would not be possible without their valuable presence and constant faith in me.

Mummy and Papa, I am truly proud to be your daughter and I would always appreciate the sacrifices you have made to bless me with the life that I have. Thank you for everything.

Chapter 1: Introduction

1.1   Ovarian Cancer Statistics in Canada

Ovarian cancer is the most lethal cancer of the female reproductive system [1]. While the general population lifetime risk of ovarian cancer is relatively low at 1.4% to 1.7%, it is the seventh most commonly diagnosed cancer [2] and the eighth most common cause of cancer mortality for women worldwide [3]. Within Canada, there were 2,800 new cases of ovarian cancer in Canada in 2017, and 1700 women died of the disease [4], making ovarian cancer the ninth most commonly diagnosed cancer and the fifth most common cause of cancer deaths among Canadian women [5]. There is a crude incidence rate of 17.3 per 10,000 in British Columbia [6]. Although 5-year survival rates have marginally improved over the past decade, survival remains at less than 50% [7].

1.2   Ovarian cancer is not a single disease

Ovaries are composed of three types of cells: germ cells, stromal cells and epithelial cells. Consequently, ovarian cancers are classified into cancers of non-epithelial origin (cancers arising in the germ cells or stromal cells) and epithelial origin (cancers arising in the epithelial cells). Generally, 90% of ovarian cancers are epithelial ovarian cancers (EOCs). In this thesis, I focus only on EOC. In the past, EOC was considered a single disease. However, recent studies have indicated that EOC represents a group of five distinct histologic subtypes [8,9]- high-grade serous cancer, endometrioid ovarian cancer, clear cell ovarian cancer, mucinous ovarian cancer, and low-grade serous cancer. Research has suggested that each of these histotypes have different cellular origins, morphology, and molecular features that dictate clinical behavior, including

treatment response and overall survival. In addition, there are different risk factors associated with the different histotypes of ovarian cancer, and different prevention approaches for each histologic subtype as well [10-14].

The ovary is the most frequent site of the dominant ovarian cancer tumor mass and this led to the focus on cortical inclusion cysts (tubal CICs) within the ovary as the probable source of the disease. Tubal CICs were postulated to arise from transformation of the ovarian surface epithelium trapped within the ovary after ovulation. Our understanding of the fallopian tube's involvement in ovarian cancer changed when examination of the fallopian tubes removed at risk reducing salpingectomy oophorectomy from *BRCA* mutation carriers (women at high risk for ovarian cancer, detailed further below) revealed the presence in the distal fallopian tube (the fimbriae) of tubal malignancies in 2-10% of these high-risk women [15-20]and preinvasive lesions in the fimbriae (serous tubal intraepithelial cancers; STICs) in 1-8% of these women [21-23].

The Sectioning and Extensive Examining of the Fimbria (SEE-FIM) protocol was developed to maximize the detection of ovarian cancer precursors or early fallopian tube cancers by sectioning and examining the fallopian tube fimbriae (FTFE) for pathology [24,25]. This protocol has revealed tubal involvement in up to 70% of unselected women diagnosed with ovarian or primary peritoneal High Grade Serous Cancer (HGSC) (with and without *BRCA* mutation), [26-29] including the presence of fimbrial STICs in 40-60% of these women [28]. Importantly, STICs occur extremely rarely in women with benign gynecologic conditions [30].

1.2.1   Histologic subtypes of ovarian cancer

1.2.1.1   High- grade serous ovarian cancers (HGSC)

High-grade serous ovarian cancers are most common form of EOCs, comprising around 70%[31]. Although the pathogenesis is not completely understood, the majority of HSGCs are believed to originate in the fallopian tube [32]. These tumors are commonly diagnosed in older woman [11]. HGSCs usually present in advanced stages with a 5- year overall survival rate of 32% [33]. Women with HGSC initially respond well to cisplatin (first- line chemotherapy), but they eventually develop resistance to chemotherapy, relapse and succumb to their ovarian cancer [34,35].

1.2.1.2   Low- grade serous ovarian cancer (LGSC)

Low- grade serous ovarian cancers are rare, representing only 3-5% of all EOCs [36]. These tumors are commonly diagnosed at younger age compared to HGSC [11], with a 5- year overall survival rate of 84% when detected early [33]. Women diagnosed with LGSC have markedly better survival compared to those diagnosed with HGSC [34].

1.2.1.3   Clear cell ovarian cancer (CCC)

Clear cell carcinomas are the second most common subtype of ovarian cancer, representing 10-26% of all epithelial ovarian cancers[36]. Although the majority of CCCs are detected at early stages with 5- year overall survival rate of 82% [33], they do not respond well to chemotherapy. These cancers have higher rates of relapse than the other histotypes given similar treatment [37]. Some evidence has suggested an association between CCC and endometriosis [35].

1.2.1.4   Endometrioid ovarian cancer (EC)

Representing 7-24% of all EOCs, endometrioid carcinomas are the third most common subtype of ovarian cancer [36]. The majority of EC cases are detected at early stages, thereby presenting favorable clinical outcomes with 5- year overall survival rate of 87% [33]. These tumors are also associated with endometriosis [36].

1.2.1.5   Mucinous ovarian cancer (MC)

Mucinous carcinomas are the least common subtype of ovarian cancer, accounting for 2-6% of all EOCs [32]. Mucinous ovarian cancers are often diagnosed at an early stage with a 5-year overall survival rate of 83% [35]. Like CCC, MC also respond poorly to chemotherapy [37].

1.3   Risk factors

Risk factors for ovarian cancer have been relatively well studied [38-44]. Herein I will describe the incessant ovulation hypothesis and its many associated risk factors for ovarian cancer. I will also outline hereditary risk factors, associations between ovarian cancer and hormone therapy, lifestyle and surgical history.

1.3.1   The 'Incessant ovulation hypothesis' and associated risk factors

One of the earliest hypotheses surrounding the development of ovarian cancer was the 'incessant ovulation hypothesis' [45]. This theory posits that the inflammation in the fimbrial end of the fallopian tube associated with ovulation is believed to promote ovarian carcinogenesis. Epidemiologic studies have consistently observed that decreasing the lifetime number of ovulatory cycles decreases ovarian cancer risk, with multiple studies reporting a reduced risk associated with oral contraceptive use , greater risk reduction with longer duration of oral

contraceptive use, [46,47] and increased protection with increased numbers of pregnancies. The association between increased parity (or pregnancy) with lower ovarian cancer risk is well established [43,44,48]. With each birth, a risk reduction of 20% was observed, particularly for endometrioid and clear- cell EOCs [44]. The protective effect of pregnancy has also been associated with age at pregnancy as well. For instance, risk of ovarian cancer was observed to be higher among women who were pregnant at an older age (~ 35 years) in comparison to women who were pregnant at a younger age (~25 years) [42]; however, age at first pregnancy requires further study as it is unclear whether the relationship is confounded by other factors associated with choosing a later age at first birth. Also, multiparity was also linked with 50% reduced risk of ovarian cancer [43]. Breastfeeding is also linked with reduced risk of ovarian cancer. A reduced risk of 20-25% in developing ovarian cancer among parous women who have breastfed compared to women with the same parity who did not breastfeed has been reported [48], and reduced risk is associated with longer durations of lactation time. However, most studies report that one pregnancy is considerably more protective than a single year of oral contraceptive use[49], making the direct link between pregnancy and number of ovulatory cycles seem overly simplistic and calling into question the validity of the incessant ovulation hypothesis.

Other risk factors posited to result from inflammatory processes include pelvic inflammatory disease and talcum powder use. Pelvic inflammatory disease results in inflammation of ovaries, fallopian tubes and endometrium [50]. Currently, the association between pelvic inflammatory disease and ovarian cancer risk is unclear. However, based on the limited evidence, women with pelvic inflammatory disease are at increased risk of developing ovarian cancer in comparison to those with no history of the disease [42]. Epidemiological studies have suggested an associated between perineal use of talc and ovarian cancer [51,52].

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This association came into the picture in 1960's, when talcum powder may have contained asbestos (a potential carcinogen) [39]. It was believed that the powder particles resulted in inflammation in the ovaries by travelling up to the reproductive system. However, there are conflicting results in the literature regarding the link between talcum powder and ovarian cancer [53,54].

1.3.2   Hereditary risk factors

The most common hereditary cancer syndromes that cause ovarian cancer are hereditary breast-ovarian cancer syndrome and lynch syndrome. Hereditary breast- ovarian cancer syndrome, accounting for 65% - 85% of hereditary ovarian cancers, is caused by inherited mutations in *BRCA*1 and *BRCA*2 genes. Whereas, lynch syndrome is linked with inherited mutation in DNA mismatch repair genes and it is responsible for 10%-15% of the hereditary cases[55].

Women at high- risk of developing ovarian cancer due to their inheritance of germline *BRCA*1 and/or *BRCA*2 mutations have an average lifetime risk for ovarian cancer of between 35-46% and 13-23%, respectively [56-59]. Inherited germline mutations of *BRCA*1 and *BRCA*2 account for approximately 11.7% to 20% of all the invasive ovarian carcinomas [60-63]. Most hereditary ovarian cancers are high- grade serous cancers [48]. Historically women with ovarian cancer were tested for inherited *BRCA* mutations if they had a family history of breast and/or ovarian cancers and/or are of Ash¬kenazi Jewish ethnicity [1,39,42]. We are currently moving into an era of histotype-based referral for hereditary testing as up to 1/5th of women with HGSC will test positive for a *BRCA*1 or *BRCA*2 mutation [64], and many of these women would not have qualified for hereditary cancer testing based on family history criteria [65].

Lynch syndrome is associated with increased risk for non- serous ovarian cancers, particularly endometrioid and clear cell EOCs[55,66,67]. Although Lynch Syndrome is primarily known for its dramatic increase in lifetime risk of colorectal cancer (or Hereditary NonPolyposis Colorectal Cancer, HNPCC), women with Lynch syndrome have an approximately 12% lifetime risk of developing ovarian cancer (compared with 1.4% in the general population) [42]. This syndrome accounts for only 1% of all EOCs [41].

Even after accounting for genetic mutations known to increase risk for ovarian cancer (*BRCA* and Lynch), increased risk remains among women who have first-degree relatives (daughter, sister, mother) with ovarian cancer on either father's or mother's side of their family and are found not to have *BRCA* mutations or Lynch syndrome [39]. The risk gets higher with the increasing number of relatives with ovarian cancer. Family history of other cancers, including breast cancer, uterine cancer, pancreatic and colorectal cancer can also increase risk for ovarian cancer [39,40].

1.3.3 Hormone replacement therapy and associated hormonal therapies risk factors

The use of hormone replacement therapy has been linked with increased risk for ovarian cancer, particularly for serous and endometrioid cancers [43]. Research has suggested that the risk of ovarian cancer is 40% higher among women taking hormone replacement therapy compared with those not taking hormone replacement therapy [38]. Though, this increased risk seems to gradually disappear over time. For example, women who took hormone replacement therapy for 5 years or more are at a significant risk of developing ovarian cancer for at least 5 years since stopping treatment [43,48]. Secondly, the association between infertility (or fertility drugs) and ovarian cancer remains controversial [38,42,43]. Early studies have reported an

increased risk of ovarian cancer with the use of fertility drugs [68,69]. However, majority of recent studies have observed no association [70,71].

1.3.4 Surgical protection risk factors

Previous studies have reported a significant inverse relationship between gynecologic surgeries (Bilateral salpingoooophorectomy, hysterectomy, salphingectomy and tubal ligation) and risk of ovarian cancer. Among high-risk women (*BRCA* mutation carriers), a risk reduction of at least 90% is achieved by bilateral prophylactic salpingoooophorectomy (a surgery involving removal of both fallopian tubes and ovaries) [50]. Surgical removal of fallopian tubes hinders the cancer initiation, specifically for high- grade serous EOCs which originates from the distal end of fallopian tube and block the transport of potentially cancerous cells to ovaries or peritoneal cavity[72].

Tubal ligation (a form of permanent sterilization that generally cauterizes fallopian tubes) has been shown to decrease ovarian cancer risk by 29% overall, but there are differences in this effect across subtype [73,74]. In the detailed analysis of primary individual data from studies in the Ovarian Cancer Association Consortium (OCAC), the greatest risk reduction was found in endometrioid EOCs (52%), followed by clear cell EOCs (48%), and there was a 20% reduction in risk of high grade serous carcinomas [74]. Surgical ligation is hypothesized to have a greater protective effect against endometrioid and clear EOCs (endometriosis- associated ovarian cancers) due to the blockage of retrograde menstruation flow (transport of endometrial cells to peritoneal cavity and on to ovary through the fallopian tubes) [74].

Another recent meta-analysis of published results reported similar findings [73], and a case-control study by the Hereditary Ovarian Cancer Clinical Study Group reported that tubal

ligation decreased the risk of ovarian cancer by 60% in *BRCA*1 or *BRCA*2 mutation carriers. Results by histologic subtype were not reported [75].

There are also encouraging data on a small number of excisional tubal surgery cases (defined as complete salpingectomy, distal fimbriectomy or partial salpingectomy). Researchers from the Rochester epidemiology project reported a 64% reduction in the risk of ovarian cancer after excisional tubal sterilization compared with those without sterilization or with non-excisional tubal sterilization (Odds ratio, OR =0.36; 95% confidence interval, 95%CI= 0.13, 1.02) [76]. Danish researchers using a national database, reported that bilateral salpingectomy (removal of both the fallopian tubes while sparing the ovaries) reduced risk for ovarian cancer by 42% (OR=0.58; 95% CI= 0.36, 0.95) [77]. Most recently, a retrospective population-based study using Swedish health registers reported that bilateral salpingectomy was associated with a 65% reduction in risk (Hazard ratio, HR=0.65, 95% CI= 0.52, 0.81) [78]. This Swedish study reported that other surgeries such as hysterectomy (removal of uterus), and hysterectomy with bilateral salpingectomy, were also associated with statistically significant reductions in ovarian cancer risk (HR = 0.79, 95% CI= 0.70, 0.80; HR= 0.06, 95% CI= 0.03, 0.12 respectively). A recent meta-analysis, including the three studies described above, concluded that there was a significant decrease in the risk of ovarian cancer occurrence in patients who underwent bilateral salpingectomy relative to controls (OR=0.51; 95% CI 0.35, 0.75) [79].

1.3.4.1 Current surgical approaches in practice

The standard of care is bilateral salpingo- oophorectomy among women with *BRCA1* or *BRCA2* mutations. This surgical approach, involving removal of both the ovaries and fallopian tubes, is associated with a 80% to 90% reduction in ovarian cancer risk [18,19,25]. However, it is not recommended in the general population due the fact that it puts women into surgical

menopause, increasing their risk for osteoporosis, coronary heart disease and stroke [80]. Given the health risks associated with bilateral salpingo- oophorectomy and given our understanding of the fallopian tube as the sources of origin for most HGSCs, bilateral salpingectomy has been proposed a prevention strategy in the general population.

Recommendations for opportunistic salpingectomy were made by the Ovarian Cancer Research team (OVCARE) in British Columbia in 2010, similar recommendation from the Society of Gynecologic Oncology of Canada [81], and later by the Society of Gynecologic Oncology [82]. More recently the American College of Obstetricians and Gynecologists and the Society of Obstetricians and Gynecologists of Canada have supported the recommendation [83,84]. It has been advocated to consider: 1) performing bilateral salpingectomy at the time of hysterectomy; 2) performing bilateral salpingectomy instead of tubal ligation for permanent contraception- commonly referred to as opportunistic salpingectomy. OVCARE reported encouraging results on the safety of opportunistic salpingectomy; no additional risks associated with this treatment procedure [85]. However, long- term studies are needed to evaluate the effectiveness of opportunistic salpingectomy among women in the general population.

1.3.5   Lifestyle risk factors

The association between diet and ovarian cancer risk is highly inconsistent, ranging from positive to no effect of dietary factors on the risk of ovarian cancer. Based on a relatively limited literature, dietary factors such as vegetables, whole- grain food and low-fat milk are believed to reduce the risk of the disease [86], whereas, high intake of saturated fats increases the risk of ovarian cancer [87]. Studies report inconclusive effects of meat, tea, coffee, and Vitamin D consumption on ovarian cancer [50]. Consistent with diet- specific findings, the association

between exercise and ovarian cancer risk are also not firmly established. However, the most active women are observed to have 20% lower risk of ovarian cancer in comparison to the least active women [50]. Another study reported reduced risk among women performing recreational biking and walking compared with women who did not exercise [43].

Smoking was not considered a risk factor for ovarian cancer until the association was studied separately for histotypes [88,89]. A metanalysis involving 51 epidemiological studies reported 50% increase in ovarian cancer risk among women who smoke with mucinous EOCs compared to never smokers [89]. This finding supported a hypothesis that mucinous EOCs resemble mucinous gastrointestinal cancers, which have also been associated with smoking [50].

Some studies have reported (modest) increases in risk of ovarian cancer among obese women [42,48]. For instance, premenopausal women with BMI greater than 30 are at higher risk of developing ovarian cancer (adjusted OR = 2.19; 95% CI 1.19-4.04) in comparison with premenopausal women with BMI less than 25 [90]; however, BMI is not currently considered an important risk factor for ovarian cancer.

1.3.6   Other factors

There is an increased risk of developing ovarian cancer, particularly clear- cell EOCs and endometrioid EOCs, among women with endometriosis (a condition where a uterine tissue from grows outside the uterus). In a meta-analysis of 15 cohort and 20 case- control studies, the relative risks of developing clear cell and endometrioid EOCs among self reported endometrioid cases (reported history of endometrioid) were 2.606 and 1.759 respectively [91].

Table 1: Risk factors associated with increased or decreased risk for EOCs

Decreased EOC risk	Oral contraceptive use Gynecologic surgeries Breast feeding Diet Exercise Increased parity
Increased EOC risk	Mutated *BRCA* genes Lynch Syndrome Family history of ovarian cancer Endometriosis Personal history of cancer Hormonal replacement therapy Infertility and fertility treatment Pelvic inflammatory disease Perineal Use of talcum powder (or talc) Smoking Obesity

1.4   Presentation

Ovarian cancer is often diagnosed at advanced stages (Stage III and IV), primarily because symptoms are not common in the early stages (Stage I and II), and when they do occur, the symptoms may be general and non-specific such as bloating, urinary frequency, loss of appetite, back pain [92]. Hence, ovarian cancer is often referred to as the silent disease. Approximately 60% of cases are detected at advanced stages, when cancer has spread beyond the ovary to distant lymph nodes or other organs [36]. Since the survival rate is correlated with the stage at diagnosis, women with ovarian cancer diagnosed in late stages have a significantly lower 5- year survival rate (17% to 28%) [1] than women diagnosed in early stages (92%) [1,93]. However, detecting ovarian cancer early remains very difficult, as despite the tremendous international effort [94-97], no effective screening methods are currently available [98].

1.5   Screening: Secondary Prevention of Ovarian Cancer

Cancer screening is defined as the detection of cancer at an earlier and more curable stage, using a test or a combination of tests, on an asymptomatic population [99]. The objectives of a cancer-screening program are reducing the number of deaths from the disease in a population, followed by increasing the life expectancy of cancer patients [100]. Hence screening programs are widely applied only when they result in a significant reduction in mortality from the disease in question.

Below I am reviewing 3 major ovarian cancer screening trials. These studies evaluated the efficacy of screening by determining whether they result in meaningful reductions in mortality and result in a significantly earlier detection in the cancer (measure by stage). A brief review of this research is relevant to understand why survival rates have been slow to improve in this disease.

1.5.1   Large prospective trials of Ovarian Cancer Screening

1.5.1.1   The Prostate, Lung, Colorectal and Ovarian Cancer Screening (PLCO)

The PLCO trial was a randomized controlled trial conducted in the USA [94]. It included 78,216 women aged 55 to 74, of which 39,105 received annual screening (intervention group) and 39,111 received usual care (control group). The annual screening was performed, using CA-125 level measurements (CA-125) and transvaginal sonography (TVS). The intervention group received annual screening with CA-125 and TVS for 4 years, followed by CA-125 only for the next 2 years while the control group received usual medical care, which consisted of no screening for ovarian cancer. Participants were followed for a median of 12.4 years. Ovarian cancer was diagnosed in 176 women (0.45%) in the control group and 212 women (0.54%) in the

intervention group. Among screen-detected cases, 77% of cases were detected at the advanced stages. Thus no mortality reduction was observed with the application of annual screening, and this method of screening for ovarian cancer was concluded to be ineffective.

1.5.2   The Japanese Multicentral Screening

The Schizuoka Cohort Study of Ovarian Cancer Screening (SCOCS) was performed in Japan [96]. The study was a randomised controlled trial, including 82, 487 low-risk post menopausal women. Of 82, 487 participants, 41,688 received annual screening (intervention group) and 40,799 did not (control group). Corresponding to PLCO trial, this study performed annual screening using CA-125 and TVS.

In the intervention group, 27 women (0.06%) were diagnosed of ovarian cancer, with relatively good sensitivity (77.1%) and specificity (99.9%). Among screen-detected cases, 17 (63%) were Stage I, 1 (4%) were Stage II, 7 (26%) were Stage III, and 2 (7%) were Stage IV. Thus over 2/3rds of cases were detected at the early stages, but this rise in the detection of early-stage ovarian cancer was not significant, and ovarian cancer mortality in the intervention and control groups was not reported, and thus we cannot conclude that screening reduced mortality.

1.5.3   The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)

The UKCTOCS is the largest screening trial to date [95]. It was a RCT of 202,638 women, including control group (n= 101,359); multimodal screening group (n= 50,640) and ultrasound screening group (n = 50,639). The multimodal screening (or MMS) group underwent annual screening, using CA-125 level with TVS as a second line test. A major step that differentiates this trial from other studies is "Risk of Ovarian Cancer (ROCA)" algorithm. The patented algorithm was used to interpret CA-125 levels in the MMS group, instead of using a fixed cut off

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value. The ROCA algorithm calculates a woman's level of risk based on her CA-125 levels and changes in these values over time combined with known risk factors [101]. The ultrasound screening (USS) group underwent screening by TVS alone, and the control group received usual care (consisting of no screening for ovarian cancer).

Participants were followed for 11.1 years. Of 202,638 women, ovarian cancer was diagnosed in 1282 women: 630 (0.6%) in the control group, 338 (0.7%) in the MMS group and 314 (0.6%) in the USS group [102]. Over the first 14 years of the study, an average mortality reduction of 15% (8% for years 0-7; 23% for years 7-14) was reported in the MMS group versus control group and 11% (2% for years 0-7; 21% for years 7-14) in the USS group versus control group. However, a significant mortality reduction of 28% was observed with the MMS group in years 7 to 14 years, when prevalent cases were excluded. False-positive surgeries were performed in 14 and 50 per 10,000 screen detected cases in the MMS and TVS groups, respectively.

Among women in the MMS group, a greater number of cancers were detected at an early stage in comparison to the control group. However, 641 patients need to be screened annually using the MMS method for 14 years to prevent one cancer death, raising questions about the cost-effectiveness of this method. Recent cost-effectiveness studies suggest that the cost of the ROCA algorithm will be critical to determining cost-effectiveness [103,104], along with ensuring that mortality reductions do reach significance following further follow up in the MMS group.

In conclusion, despite rigorous research on ovarian cancer screening, none of these trials has observed a significant reduction in either ovarian cancer- specific or all cause mortality. While the results from the UKCTOCS are promising and we await further follow-up to

determine whether the mortality reduction will become statistically significant, until such evidence is available, ovarian cancer screening cannot be recommended in the general population. Even if the UKCTOCs trial shows a modest reduction in mortality among the MMS group, rigorous cost-effectiveness analyses would need to be done accounting for the price of the ROCA algorithm before recommendations for screening among the general population would be made. However, it is possible that women who are at higher risk for ovarian cancer, including *BRCA* and Lynch mutation carriers, could benefit from screening. Some experts have already recommended that *BRCA* mutation carriers who have not yet undergone bilateral salpingo-oophorectomy be screened with TVS, CA-125, and/or pelvic exam every six months beginning at one of the following scenarios: between 30 and 35 years of age; 35 years of age; 5 to 10 years before the onset of first ovarian case in their family [105].

1.6 Current Diagnostic Evaluation for ovarian cancer

The first step in the diagnostic evaluation for ovarian cancer is the assessment of symptoms (abdominal pain, bloating, frequent urination etc) and risk factors. If the symptoms indicate ovarian cancer, a complete physical examination is conducted to investigate abdominal and pelvic masses. Women with abnormal masses (or suspected ovarian cancer) are evaluated by TVS and CA-125 biomarker test. If these women are suspected to have ovarian cancer based on these examinations, they should be referred to a gynaecologic oncologist who could conduct biopsy to confirm the presence of cancer (Appendix A) [1].

1.7 Ovarian cancer treatment

Approximately 75% of affected women present at an advanced stage (Stage III and Stage IV), requiring platinum-based chemotherapy and optimal cytoreductive surgery. Owing to major advances in these standard treatment strategies (the addition of paclitaxel to platinum in the late 1990s, *BRCA1* and *BRCA2* testing with prophylactic surgery, use of intraperitoneal chemotherapy, anti-angiogenic therapies, and polyADP-ribose polymerase (PARP) inhibitors)[106], a few studies have suggested an improvement in 5- year survival [7]. However, cancer in at least 90% of women with diagnosed with (high-grade serous) ovarian cancer reoccurs, alongside resistance to chemotherapy [107] and most women succumb to the disease [108].

Presently, the standard of care for EOC involves surgical debulking and platinum-based chemotherapy. The order in which these two treatments are administered depends on several factors, including distribution of disease, health/nutritional status of the patient including frailty/age, tumor grade, histotype and molecular features (reflecting chemosensitivity).

1.7.1 Surgery for ovarian cancer

If removal of all tumor burden is deemed achievable, surgery is often the preferred first step. Ovarian cancer is a surgically staged disease with the best outcomes observed in women who undergo surgery by a gynecologic oncologist [109]. Surgery is performed to assess the spread of cancer (**staging**) and to remove as much tumor as possible (**optimal cytoreduction**). Surgery for ovarian cancer should be performed by a gynaecologist oncologist [110,111].

1.7.1.1 Staging Epithelial ovarian cancer

Staging determines where the cancer has spread from its origin (stage) and provides tumor for pathology interpretation (grade, histotype) to direct treatment. Staging consists of thorough

examination of the pelvis and abdomen. Peritoneal washings or removal of ascites is performed, followed by hysterectomy (removal of uterus), salpingectomy (removal of the fallopian tubes), oophorectomy (removal of the ovary), bilateral oophorectomy (removal of both the ovaries), omentectomy (removal of the omentum, the layer of fatty tissue covering abdominal intestines) and/or removal of lymph nodes. In the vast majority of cases, a hysterectomy with bilateral salpingo-oophorectomy is performed.

1.7.2 Chemotherapy for ovarian cancer

Chemotherapy is a systemic therapy, where drugs are administered into the bloodstream to kill cancer cells through out the body. In simpler terms, systemic chemotherapy treats the entire body and not just the organ(s) affected by the cancer. Chemotherapy can be given after the surgery to remove remaining cancer cells (adjuvant chemotherapy) or before the surgery to reduce the tumor size (neoadjuvant chemotherapy). Adjuvant chemotherapy is specifically administered to the cases, where cancer has spread beyond the ovaries [1]. Neoadjuvant chemotherapy is meant for the advanced staged cases, when a patient is unable to tolerate surgery. Chemotherapy for ovarian cancer uses a combination of a platinum drug (carboplatin or cisplatin) and a taxane drug (paclitaxel/taxol or docetaxel). The most commonly used combination is carboplatin with taxol. Typically, the drugs are administered intravenously every 3 to 4 weeks [112].

For adjuvant chemotherapy, chemotherapy can be primarily performed in two ways: g Intravenous (IV) chemotherapy (injecting drugs into a vein), and intraperitoneal (IP) chemotherapy (injecting drugs into abdominal cavity using a thin tube). Of note, IP chemotherapy is generally administered as a combination of IV and IP chemotherapy [113].

1.7.2.1   Intraperitoneal chemotherapy

Intraperitoneal chemotherapy involves direct delivery of chemotherapy drugs to the peritoneal cavity. This rationale is supported by preclinical and pharmacokinetic data. For instance, there was a 20- fold and 1000-fold greater concertation in the abdominal cavity with IP administration in comparison to IV administration [114]. IP chemotherapy is most suitable for optimally cytoreduced cases as direct penetration of this therapy is evident for tumors less than 3mm [113].

Three large chemotherapy trials for ovarian cancer have suggested improved survival for IP administration over IV administration among optimally debulked Stage III patients [115-117]. The most recent of these trials i.e. GOG-172 study compared IV cisplatin-paclitaxel (IV arm) and a course combining IV paclitaxel and IP cisplatin-paclitaxel (IV/IP arm)[115]. This trial observed a median overall survival of 65 months in the IV/IP arm in comparison to 49.7 months in the IV arm. Overall, a significant improvement in survival was noted (i.e median overall survival difference of 16 months) after IP administration compared with that after conventional IV chemotherapy.

Although IP chemotherapy showcased survival advantage over IV chemotherapy, it is associated with toxic effects such as metabolic toxicity, myelotoxicity, gastro- intestinal toxicity, neurologic toxicity and worse quality of life [118]. Hence, a significant proportion of patients were not able to complete the treatment in the IV/IP arm. For instance, in GOG-162 study, only 42% patients completed all cycles of the IV/IP arm compared to 83% in the IV arm. Likely owing to this increased toxicity, the use of IP chemotherapy has been slow in gaining acceptance in clinical practice [119].

1.7.3   Radiation therapy

Radiation is rarely used in treating ovarian cancer. However, it can be considered for certain histotypes of ovarian cancer, primarily clear cell, endometrioid, and mucinous EOCs [120].

1.7.4   Molecular targeted therapy

Molecular targeted therapy acts on specific molecules within the cancer cells disrupting signals necessary for the cancer cells to grow or divide. Herein I have focused on: 1. Anti-angiogenic therapy and 2. PARP (Polyadenosine diphosphate ribose polymerase) inhibitors. Other therapies involve targeting the epidermal growth factor receptor, the folate receptor alpha, the WEE1 tyrosine kinase, the PI3 K/AKT and RAS/RAF/MEK pathways [7,106]. I have focused on the anti-angiogenic therapy and the PARP inhibitors as there is the most evidence for increased survival with these targeted therapies [7,107,108].

1.7.4.1   Anti- angiogenic therapy

Tumor angiogenesis is a key component in sustaining cancer. In the process, normal cells are stimulated by tumor cells to produce key mediators [121], also termed as angiogenic molecules such as the vascular endothelial growth factor (VEGF). As a result, new blood vessels are produced, which facilitate growth, metastasis, and survival of tumor cells. Moreover, VEGF is observed to be over-expressed in ovarian cancers and is associated with cancer progression and poor prognosis [7]. To disrupt tumor angiogenesis, anti- angiogenic agents are required which basically prevent the interaction between VEGF ligand and its receptors. Presently, bevacizumab (a monoclonal antibody) is the most studied anti-angiogenic agent in EOC. However, it is associated with several toxicities, including hypertension, and bowel perforation.

There are also patients who are resistant to therapy, and there is a high cost for bevacizumab treatment ($79,086 CAD for 1.1 quality-adjusted life-year) [7,108,122].

1.7.4.2   PARP inhibitors

A single cell can experience at least 10,000 injuries in its DNA on a regular basis, resulting from environmental factors (UV light) or normal DNA replication [123]. The resulting DNA damage is mediated by key DNA- repair pathways such as homologous recombination (HR), and non-homologous end joining (NHEJ) [110]. The HR pathway is responsible for repairing double stranded DNA breaks, whereas NHEJ (or PARP) pathway is responsible for repairing single stranded DNA breaks. These pathways are controlled by two sets of genes, *BRCA*1 and *BRCA*2. Mutations in *BRCA* genes are a major risk factor in developing ovarian cancer. The HR pathway of DNA repair is disrupted in these mutated deficient cells. Consequently, these cells must depend solely on the PARP pathway for cell survival [106]. This biological mechanism was used to propose the idea of "synthetic lethality". The PARP pathway, the only DNA repair pathway in *BRCA*1 and/or *BRCA*2 deficient cells, is targeted by PARP inhibitors. Inhibition of the PARP pathway leads to the accumulation of DNA damage (single- strand and double strand DNA breaks) and thereby cell death. Once both the repair pathways have non-functioning proteins, the cancerous cells cannot survive [123]. Olaparib is the most studied PARP inhibitor in ovarian cancer. Since normal cells can repair DNA damage using both the DNA repairing mechanisms, the cells are not susceptible to the synthetic lethality. Under the condition of PARP inhibition, the normal cells can still be repaired by the HR pathway [107].Hence, the introduction of PARP inhibitors was a milestone strategy in treating ovarian cancer among women with *BRCA* mutations, while sparing normal cells.

Previous literature has reported improved survival among ovarian cancer patients treated with olaparib. A randomised trial of 265 women with *BRCA* mutation and recurrent high- grade serous cancer received either olaparib (treatment group) or placebo (control group) as maintenance therapy following their platinum-based chemotherapy. Among women treated with olaparib, the progression free survival was 8.4 months compared to 4.8 months in the control group [124]. Another analysis studying the effects of Olaparib on progression free survival among women with relapsed serous ovarian cancer by *BRCA* mutation status reported similar results. In this study, 51% of women were *BRCA* mutation carriers. Of these women with *BRCA* mutation, the median progression free survival was 11.2 months for women treated with olaparib, whereas the median progression free survival was 4.3 months for women treated with placebo. While overall survival did not differ significantly between the groups (with and without *BRCA* mutation), women with relapsed serous ovarian cancer and a *BRCA* mutation were most likely to benefit from olaparib treatment [125].

1.8   Survival statistics for ovarian cancer

1.8.1   Increased survival among women with ovarian cancer

Partly owing to some of these innovative therapies, improving treatment and post-operative care, some limited evidence has suggested that 2- and 5- year survival rates of women diagnosed with ovarian cancer have been increasing temporally [5,126,127]. In 2011, a population-based Canadian study compared relative survival ratios over the period of 1992-2005 among women with EOC by age, histology of tumor and geographic regions of residence. This study was based on the hypothesis that the survival among women with ovarian cancer has increased over time. 7771 women were included in the study after being diagnosed with epithelial ovarian cancer in

Canada over the period of 1992 and 2005. Of which, 4104 died by the end of 2006. The relative survival curves were plotted by age at diagnosis (<40, 40-49, 50-59, 60-69, 70-79, >= 80 years), histology of tumor (serous, mucinous, endometroid, clear cell, transitional cell), and geographical location (Ontario, British Columbia, Eastern Canada, Central- West and Northern Canada). Relative survival ratio by age group decreased with increasing age. Moreover, the survival curves of the oldest group were constant 5 years post diagnosis, indicating no excess mortality rate compared to undiagnosed women in the same age group. Their histology-specific results indicated that women with serous cancers had the lowest 2- and 5-year survival rates followed by women with mucinous cancers. Relative survival by geographical location showed the highest survival for Ontario, followed by British Columbia. Also, trends in 2- and 5- year relative survival rates were evaluated for all age groups, based on year of diagnosis. The resulting upward trends supported the hypothesis that there have been modest improvements in survival among women with EOC between 1992 and 2005. This improvement was attributed to improvement in diagnostic methods (down staging), treatment therapies (IP chemotherapy), and post- operative care.

A similar study was conducted by Statistics Canada, evaluating relative survival estimates for women with ovarian cancer between the ages 15 and 99. A steady decrease in five- year survival was observed for all age groups between 2006 and 2008. However, age standardized survival estimates at 1, 3 and 5 years post diagnosis depicted significant improvement in survival for women diagnosed between 2006 and 2008 in comparison to women diagnosed between 1992 and1994 [5].

As these studies reflect a limited amount of evidence indicating a potential improvement in survival among women with EOC, but all use data that are at least 10 years old, it is important to

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update our knowledge on 1- year, 3-year, and 5-year survival curves among women diagnosed with EOC in BC. Given that a fewer studies have examined histology-specific survival rates, more evidence regarding histologic survival is also needed to better inform women with EOC and clinicians.

1.9   Survivorship

The Institute of Medicine (IOM) defines cancer survivorship as a different dimension of cancer research and notes that survivorship has received less attention in education, research, advocacy, and clinical practice. Improving our understanding of the post- treatment medical needs (psychosocial, or health outcomes) will assist affected individuals and their health care providers in implementing suitable interventions to maximize survivors long-term health [36].

Gynaecological cancer survivors are expected to experience adverse health issues post treatment. These issues include general medical problems and potential side-effects of treatment, which can negatively impact their quality of life [128]. With respect to ovarian cancer, most of the published research has focused on psychological concerns [129-132], including emotional distress (anxiety, depression) and fear of recurrence, as well as pain, fatigue, sexual dysfunction, and cognitive dysfunction. Some of the most commonly reported medical conditions include bowel obstruction, bladder dysfunction, gastro-intestinal side effects, and peripheral neuropathy [128,129]. However, there is a lack of research into the long-term health consequences of ovarian cancer survivors. The survivorship findings of other, better studied, cancers (e.g. breast and prostate) are unlikely expected to apply to ovarian cancer survivors [130]. Hence, long-term health consequences among ovarian cancer survivors must be investigated to facilitate timely intervention.

1.9.1 Using underlying causes of death to better understand long-term health consequences among women with ovarian cancer

Some preliminary research has suggested that women diagnosed with EOC typically die of cancer-related causes within five years of diagnosis [133].The risk, however, decreases with time and women become vulnerable to death from other causes. However, other leading causes of death among women surviving their ovarian cancer have received very little attention to date, and no extensive research has been done on causes of death among Canadian women surviving their ovarian cancer for greater than 5 years. Understanding whether ovarian cancer survivors are at increased risk of dying from certain causes compared to the age- standardized general population (women who have never had ovarian cancer) will shed light on key areas of ovarian cancer survivorship research that need to be explored in the future. In particular, it could improve our understanding of the health consequences faced by ovarian cancer survivors.

1.10 Purpose

We expect that women with ovarian cancer in British Columbia (BC) are also surviving longer following a diagnosis and treatment for ovarian cancer; however, BC survival rates need to be updated as the most recent reported survival curves are from 1992 to 2005. These numbers suggest improvements in 2- year and 5- year relative survival rates over the period of 1992 to 2005, across all the age groups[126] . Existing epidemiological studies fail to incorporate our modern understanding of various ovarian cancer histologic subtypes. In other words, these survival rates also need to reflect our most current understanding of the disease, and thus survival rates should be reported considering histologic subtype. Given the evidence that survival is increasing following ovarian cancer, there is an urgent need to better understand the health

outcomes of ovarian cancer survivors, an area that has been largely ignored in research to date likely due to the paucity of survivors. There is a reason to be concerned about long-term health consequences in ovarian cancer survivors, particularly in relation to their causes of death. Therefore, this proposal seeks to examine temporal and histologic subtype trends and survival rates following an ovarian cancer diagnosis in British Columbia and to study major causes of death among ovarian cancer survivors.

1.11   Study objectives and research questions

The overarching aim of my research is to improve our knowledge of ovarian cancer survivorship. To achieve this aim, I will ask the following research questions:

1) Have incidence rates and survival rates (1- year, 3- year and 5- year overall and disease specific survival) of ovarian cancer changed significantly in British Columbia between 1980 and 2015?

2) Among women with ovarian cancer what are the most common causes of death, and when do other causes of death surpass ovarian cancer as the leading cause of death? Does this differ by histologic subtype?

3) Among women with ovarian cancer, and among women surviving their ovarian cancer for 5-9 or 10+ years, what are the most common causes of death and how do they compare to causes of death among and age-standardized population of women who have never been diagnosed with ovarian cancer?

1.12 Thesis roadmap

This thesis consists of five chapters. Chapter 2 outlines the trends in incidence rates and survival rates (1- year, 3- year and 5- years overall and disease specific survival rates) for women with ovarian cancer diagnosed between 1980 and 2015. Chapter 3 reports the causes of death among women with ovarian cancer in British Columbia diagnosed between 1990 and 2014 by histotype, age at diagnosis and *BRCA* status, and examines how many years women need to survive before other causes of death surpass ovarian cancer as the leading cause of death. Chapter 4 evaluates age- specific and cause- specific standardized mortality ratios (SMR), by comparing the causes of deaths in women with ovarian cancer (including women surviving ovarian cancer for 5-9 and 10+ years post diagnosis) with the causes of death in the general population. Finally, Chapter 5 summarizes the findings, discusses the implications, the strengths and limitations of this dissertation, and suggests potential areas of future research in ovarian cancer.

Chapter 2: Recent trends in ovarian Cancer incidence and survival in British Columbia by histotype.

2.1 Introduction

Ovarian cancer is the deadliest gynecologic cancer. It is commonly diagnosed in women aged between 55 and 64 years [1]. Despite a low lifetime risk of developing ovarian cancer in the general population (1.4%) [134], it is the fifth most common cause of cancer death among women. Early detection of ovarian cancer is hindered by its non- specific symptoms. Hence, the majority of women are diagnosed at the advanced stages (Stage III and IV) with a 5- year survival rate of less than 50%. Furthermore, no screening methods for ovarian cancer have yet demonstrated a significant reduction in disease specific or all- cause mortality [94-97].

In recent years, advances in treatment and management of women with ovarian cancer have suggested potentially improved survival rates [7]. Prior studies have shown that women with advanced ovarian cancer, receiving appropriate treatment (optimal surgical debulking surgery and/or standard of care chemotherapy), have better survival than those not receiving this treatment [135,136]. Research from the Netherlands has revealed increases in survival rates between 1989 and 2009 that appear directly connected to higher rates of optimal treatment (as defined above) [137]. While little recent Canadian research is available, a population-based Canada-wide study, showed a significant improvement in the trends of 2- and 5- year relative survival for all the age groups, over the period of 1992-2005 [126]. Statistics Canada also reported a significant increase in the age standardized survival at 1,3, 5 and 10 years post diagnosis between the early 1990's and 2006 to 2008 [5].

Our understanding of the histologic diversity in epithelial ovarian cancer, accounting for 90% of all ovarian malignancies, has also changed [138]. We now understand that epithelial ovarian cancer comprises five distinct histologic subtypes: high grade serous cancer (HGSC), low grade serous cancer(LGSC), endometrioid cancer, clear cell cancer and mucinous cancer [37]. These subtypes differ in their cells of origin, molecular features, clinical features (risk factors, prognosis, treatment response) and survival [11-13]. A retrospective study evaluating differences in survival outcomes between high- grade serous cancers and low- grade serous cancers reported that women with high- grade serous cancers had less than half the median survival of women with low- grade serous cancers [34]. Recently, the CONCORD programme, a large international study, has compared survival among women with ovarian cancer by histotype. The study observed that the survival rates among women with high-grade serous cancers were lowest [13].

Survival statistics are commonly used to assess the progress against cancer, and thus should be regularly updated. For ovarian cancer, histotype- specific survival estimates would provide information for patients and clinicians to inform prognosis and direct treatment/management. Beginning to consider histotype-specific survival rates will be part of our progress toward a histotype-specific approach to ovarian cancer treatment and management wherein referral for hereditary cancer testing, surgical approaches, adjuvant treatment and survivorship plans will all be informed by the histologic subtype of ovarian cancer. In the present study, I examined age-standardized trends in the incidence and in the overall survival and disease- specific survival rates (1- year, 3- year and 5- year survival rates) of different EOC histotypes in British Columbia, between 1980 and 2015.

2.2   Methods

2.2.1   Data sources

I used data from the population-based BC Cancer Registry [139]. The BC Cancer Registry receives notifications of cancer from many sources including pathology, cytology, other labs, death certificates, and admissions to cancer centers operated by the BC Cancer Agency. The Registry contains personal and demographic information, information about the specific cancer diagnosis, as well as mortality information received from the BC Vital Statistics Agency [140].

I accessed information on all women diagnosed with ovarian cancer between 1980 and 2015 in British Columbia. My dataset included detailed information such as date of diagnosis, age at diagnosis, death status, last appointment date, date of death, and cancer histotype.

2.2.2   Study cohort

My study population consisted of all patients diagnosed with ovarian cancer in British Columbia between 1980 and 2015. The International Statistical Classification of Diseases and Related Health problems: tenth revision (ICD-10) was used to identify women with ovarian cancer with the code C48.1(peritoneum, specified parts), C48.2 (peritoneum, non- specified parts), C56.0 (ovary), and C57. 0 (fallopian tube) in the Canadian cancer registry. I then used the ICD-O morphology codes to identify the histologic subtype of cancer. Informed by the WHO criteria, I worked with an anatomical pathologist who is an expert in ovarian cancer, Dr. Anthony Karnezis to assign the ICD-O morphology codes to their relevant histotype.

The initial stage of this review ensured that only epithelial tumors were included, and thus codes were reviewed with an eye to removing all women with non-epithelial tumors from our study cohort. Once we had developed a list of codes that pertained only to EOCs, the codes were next classified according their malignant versus benign versus borderline status. All women with

non-malignant EOCs were excluded at this stage (i.e. patients with benign and borderline epithelial tumors were excluded). Using his knowledge of the pathology, the remaining codes (those for malignant EOCs) were stratified into serous, mucinous, endometrioid, and clear cell and 'others and unspecified' epithelial ovarian cancers based on the descriptions provided for each code (see Table 1 for further details).

Our final breakdown of the ICD-O morphology into relevant histotypes was then compared with other published lists and differences were considered and discussed [33], and Dr. Karnezis had the final say as to classification. The codes do not distinguish by grade, thus high-grade and low-grade serous cancers are grouped together. Mixed carcinoma, malignant Brenner tumors, and other unspecified epithelial tumors (codes that were too general to enable histotype-specific classification) labelled as 'others and unspecified' histologic subtype were presented separately so as not to contaminate the histotype-specific analysis.

Table 1: ICD- 10 codes for classifying EOC histotypes

Histotype	ICD-O codes
Serous	
	84603 Papillary serous cystadenocarcinoma (C56.9)
	84413 Serous cystadenocarcinoma, NOS (C56.9)
	84613 Serous surface papillary carcinoma
	82603 Papillary adenocarcinoma, NOS
	80203 Carcinoma, undifferentiated, NOS
	84403 Cystadenocarcinoma, NOS
	80503 Papillary carcinoma, NOS
	84503 Papillary cystadenocarcinoma, NOS (C56.9)
	81203 Transitional cell carcinoma, NOS
	80213 Carcinoma, anaplastic, NOS
	80223 Pleomorphic carcinoma
	81303 Papillary transitional cell carcinoma (C67.0)
Mucinous	
	84803 Mucinous adenocarcinoma
	84703 Mucinous cystadenocarcinoma, NOS (C56.9)
	84713 Papillary mucinous cystadenocarcinoma (C56.9)

	84813	Mucin-producing adenocarcinoma
	84711	Papillary mucinous cystadenocarcinoma, borderline (C56.9)
	84823	Mucinous adenocarcinoma, endocervical type
Endometrioid		
	83803	Endometrioid adenocarcinoma, NOS
	85603	Adenosquamous carcinoma
	85703	Adenocarcinoma with squamous metaplasia
	83813	Endometrioid adenofibroma, malignant
	83823	Endometrioid adenocarcinoma, secretory variant
Clear cell		
	83103	Clear cell adenocarcinoma, NOS
	91103	Mesonephroma, malignant
	83133	Clear cell adenocarcinofibroma (C56.9)
	82903	Oxyphilic adenocarcinoma
	83101	Clear cell adenoca, borderline
Others and unspecified		
Mixed carcinomas	83233	Mixed cell adenocarcinoma
	82553	Adenocarcinoma with mixed subtypes
	80453	Combined small cell carcinoma
Malignant brenner tumors and mixed mullerian tumour	90003	Brenner tumor, malignant (C56.9)
	89503	Mullerian mixed tumor (C54)
	89513	Mesodermal mixed tumor
	89803	Carcinosarcoma, NOS
Not otherwise specified (NOS)	81403	Adenocarcinoma, NOS
	80103	Carcinoma, NOS
	80413	Small cell carcinoma, NOS
	80463	Non-small cell carcinoma (C34)
	81402	Adenocarcinoma in situ, NOS
	82463	Neuroendocrine carcinoma, NOS
	85623	Epithelial-myoepithelial carcinoma
	82303	Solid carcinoma, NOS
	80123	Large cell carcinoma, NOS
	85042	Non-infiltrating intracystic carcinoma
	80013	Tumor cells, malignant
	80102	Carcinoma, NOS

2.3   Statistical Analysis

2.3.1   Incidence

I report age standardized incidence rates. I do not report crude incidence rates (number of cancer cases per 100, 000 individuals in the population) because they are influenced by the underlying age distribution of the population in the province. An aging population will result in higher crude rates because incidence for most cancers, including ovarian cancer, increases with age [42]. Age-adjusting the rates ensures that differences in incidence from one year to another are not due to differences in the age distribution of the populations being compared.

To calculate age- standardized rates, the crude incidence rates, stratified by histotype, were standardized to the year 2011 BC standard million population[141]. These rates were categorized into 4- year calendar periods from 1980-1984 to 2011-2015.

2.3.2   Survival

To evaluate trends in survival over time, the overall survival and disease- specific survival probabilities of ovarian cancer patients were calculated using the cohort method. The cohort method is based on evaluating survival experience of specific cohorts, diagnosed with ovarian cancer and followed for a specific length of time (1, 3, and 5 years post diagnosis). Consequently, patients diagnosed between 2011 and 2015 were excluded from the survival analysis since they would not have a minimum 5- year follow up until December 31st, 2015 (the most recent data available).

In addition, I implemented right censoring at five years by marking patients who experienced an event beyond 5 years post diagnosis as censored. The timeline for each patient

began from the date of diagnosis and ended at the censored date (December 31st in the fifth-year post diagnosis), for patients who did not experience an event in that time period and the death date for those who did. A death was considered an event only if occurred on or prior to the censored date.

2.4   Results

2.4.1   Clinical characteristics of women with epithelial ovarian cancer

A total of 12,754 women were identified as having been diagnosed with ovarian cancer between 1980 and 2015 in British Columbia. After excluding women who did not have epithelial ovarian cancer (n= 3209), 9545 were included in our study. The clinical characteristics of BC women diagnosed with EOC between 1980 and 2015 are outlined in Table 1. The entire study cohort included 5245 (55.0 %) serous, 662 (6.9 %) mucinous, 963 (10.1 %) endometrioid, 541 (5.7 %) clear cell and 2134 (22.4 %) 'others and unspecified' EOCs. The majority (48.5 %) of affected women were diagnosed with EOC between 60 and 79 years. All patients were 15 years of age or older, and only 38 (0.4%) patients were under the age of 25.

Table 2: Clinical characteristics of the study cohort.

Year of diagnosis	N	%
1980 – 1983	769	8.1
1984 -1987	876	9.2
1988 – 1991	901	9.4
1992 – 1995	942	9.9
1996 – 1999	1094	11.5
2000 – 2003	1078	11.3
2004 – 2007	1183	12.4
2008 – 2011	1248	13.1
2012 – 2015	1454	15.2

Histology	N	%
Serous	5245	55.0
Mucinous	667	6.9
Endometrioid	963	10.1
Clear cell	541	5.7
Others and unspecified epithelial	2134	22.4
Mixed carcinoma	273	2.9
Malignant Brenner	186	1.9
Not otherwise specified (NOS)	1656	17.5
Age at diagnosis	N	%
<40	440	4.6
40 – 59	3275	34.3
60 – 79	4630	48.5
80+	1200	12.6

2.4.2 Age- standardized incidence rates of epithelial ovarian cancer by year of diagnosis

Figure 1 displays the decreasing pattern of age- adjusted incidence over the period of 1980 to 2015. The age- adjusted incidence rate of EOC decreased gradually from 14.4 cases per 100,000 population in 1980-1983 to 12.5 cases per 100,000 population in 2012-2015. The age-adjusted incidence, stratified by histotype, reported a decreasing trend in serous and mucinous EOCs (Figure 2). A slight increasing trend was observed for clear-cell (from 0.5 per 100,000 in 1980-1983 to 1 in 100,000 in 2012-2015) EOCs, and for 'others and unspecified' EOCs (from 0.3 per 100,000 in 1980 – 1983 to 0.6 per 100,000 in 2012 – 2-15) EOCs across the entire time period. For endometrioid cancers, the age- adjusted incidence rates increased from 1.1 cases per 100,000 in 1980-1983 to 2 cases per 100,000 population in 1992-1995 and then slightly decreased to 1.5 cases per 100,000 by 2015. Between 1980 to 2015, the age- adjusted incidences of serous EOCs decreased from 10.7 per 100,000 in 1980-1984 to 9.3 per 100,000 in 2012-2015; however, the lowest point was reached in 2008-2011 where age-adjusted incidence was 7.1 per

100,000 population. Age-adjusted incidence also decreased for mucinous EOCs, from 2.2 to 0.7 per 100,000 population.

Figure 1: Age standardized incidence rate of EOCs (all histotypes combined), 1980 – 2015.
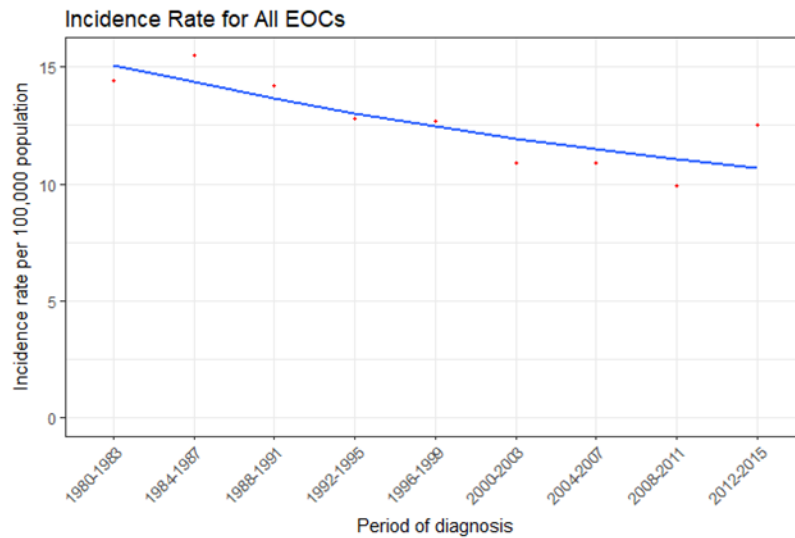
Figure 2: Age standardized incidence rate, stratified by histotype, 1980 – 2015.
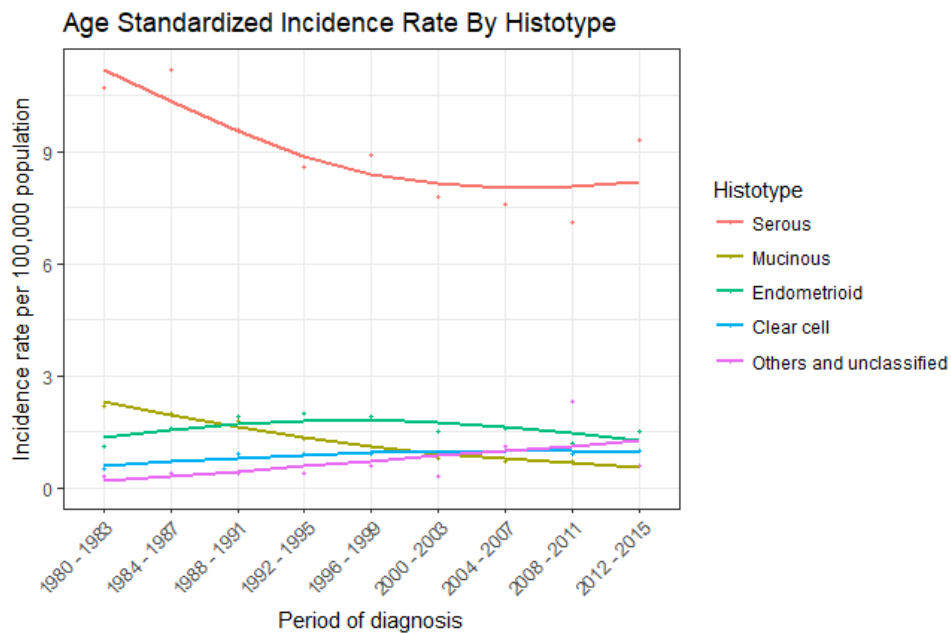
The distribution of each histotype by 4- year time periods relative to the entire EOC population are presented in Table 2. The percentages increased for each histotype except for mucinous and for 'others and unspecified' EOCs throughout the study period. In serous EOCs, the percentage was fairly stable around 50 except in the period 2012- 2015, where the percentage value was 61.9. The percentage of the clear- cell and endometrioid EOCs steadily increased with a value of 2.6 (1980 – 1983) to 6.4 (2012 – 2015) and 6.7 (1980 -1983) to 9.7 (2012 – 2015) respectively. However, the percentage drastically decreased from 11.7 (1980 – 1983) to 3.9 (2012 – 2015) in mucinous EOCs and from 22.1 (1980 – 1983) to 18.1 (2012 – 2015) in 'others and unspecified' EOCs.

Table 3: Percentage distribution of EOC histotypes from 1980 to 2015.

Year of diagnosis N (%)	Serous	Mucinous	Endometrioid	Clear cell	Others and unspecified epithelial
1980 – 1983	441 (57.3)	90 (11.7)	48 (6.2)	20 (2.6)	170 (22.1)
1984 -1987	513 (58.6)	92 (10.5)	74 (8.4)	33 (3.8)	164 (18.7)
1988 – 1991	499 (55.4)	93 (10.3)	101 (11.2)	47 (5.2)	161 (17.9)
1992 – 1995	510 (54.1)	79 (8.4)	123 (13.1)	52 (5.5)	178 (18.9)
1996 – 1999	583 (53.3)	73 (6.7)	127 (11.6)	67 (6.1)	244 (22.3)
2000 – 2003	571 (53.0)	56 (5.2)	112 (10.4)	67 (6.2)	272 (25.2)
2004 – 2007	607 (51.3)	59 (5.0)	133 (11.2)	81 (6.8)	303 (25.6)
2008 – 2011	621 (49.8)	63 (5.0)	104 (8.3)	81 (6.5)	379 (30.4)
2012 – 2015	900 (61.9)	57 (3.9)	141 (9.7)	93 (6.4)	263 (18.1)

I plotted the 1- year (Figure 3), 3- year (Figure 4) and 5- year (Figure 5) age- standardized overall survival rates (OS) separately for all the ovarian cancers (stratified by serous and non serous (clear cell, mucinous and endometrioid) histotype; and excluding 'others and unspecified' EOCs), based on the cohort of diagnosis. In these figures, I added the 95% confidence band to quantify uncertainty in estimates at each point. 1- year, 3- year and 5- year age- standardized

survival rates increased during the study period when examining all ovarian cancers (Figure 3, 4 and 5). I was unable to further stratify into serous, endometrioid, clear cell and mucinous as this resulted in unstable lines due to small numbers of cases within each group. When stratified into serous and nonserous, the survival curves trended downwards over the study period among women with serous EOCs. In general, the 1- year survival rate (80.8%) was nearly twice the 5- year survival rate (43.2%) for all EOC cases by 2010. Whereas, among women with serous EOCs, the 1- year survival rate (77.2%) was approximately four times the 5- year survival rate (25.2%) (Figure 3, Figure 5). Moreover, women with serous EOCs had the lowest 3- year survival rate (43%) and 5- year survival rate (43%), and no major change was observed in their 3- year and 5- year survival rates between 1980 and 2015 (Figure 4, Figure 5). Among women with non- serous EOCs, approximately 69.3% survived 3 years post diagnosis (Figure 4) and 52.3% of women survived 5 years post diagnosis by the end of the study (Figure 5). These non- serous cases showed a slight improvement in their 3- year survival rates, however, the 5- year survival rates decreased throughout the study period. The 1- year and 5- year survival curves for 'others and unspecified' EOCs increased between 1980 and 2015 (Appendix C).

Figure 3: 1- year age standardized overall survival rates for all specified epithelial ovarian cancers and stratified by serous and non-serous subtypes, 1980 - 2015.
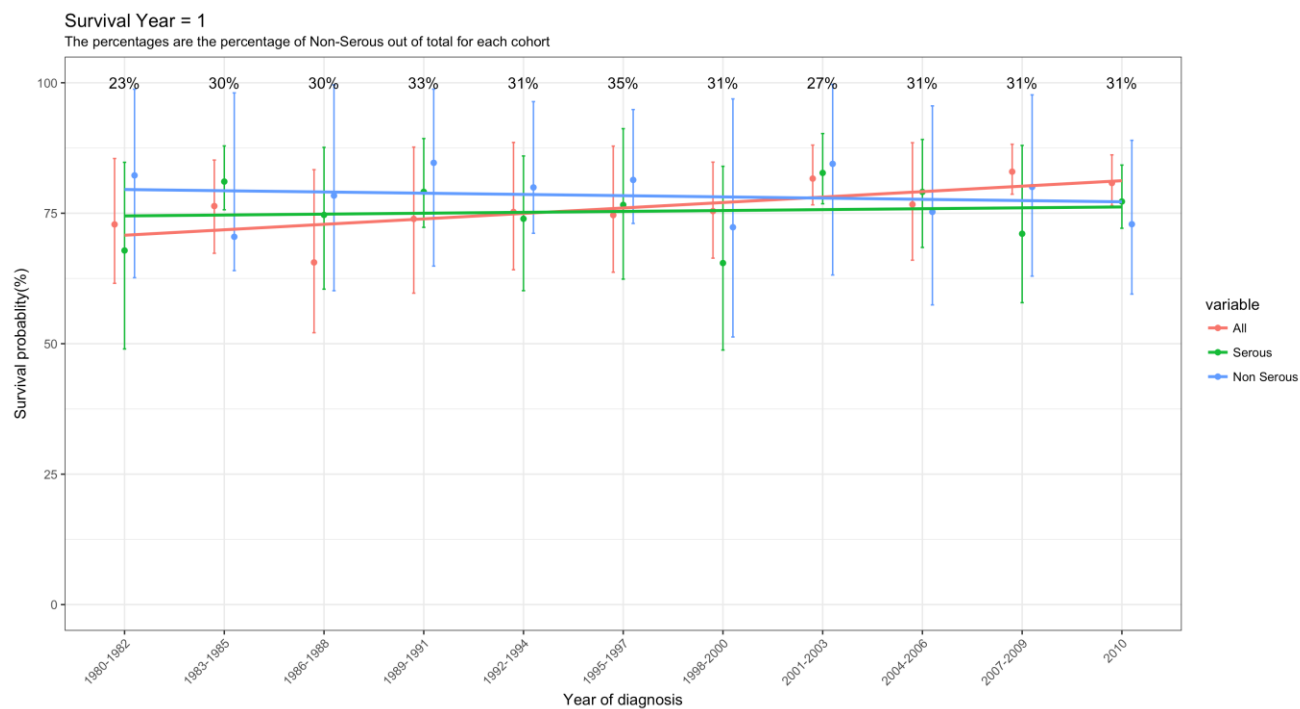
Figure 4: 3- year age standardized overall survival rates for all specified epithelial ovarian cancers and stratified by serous and non-serous subtypes, 1980 - 2015.
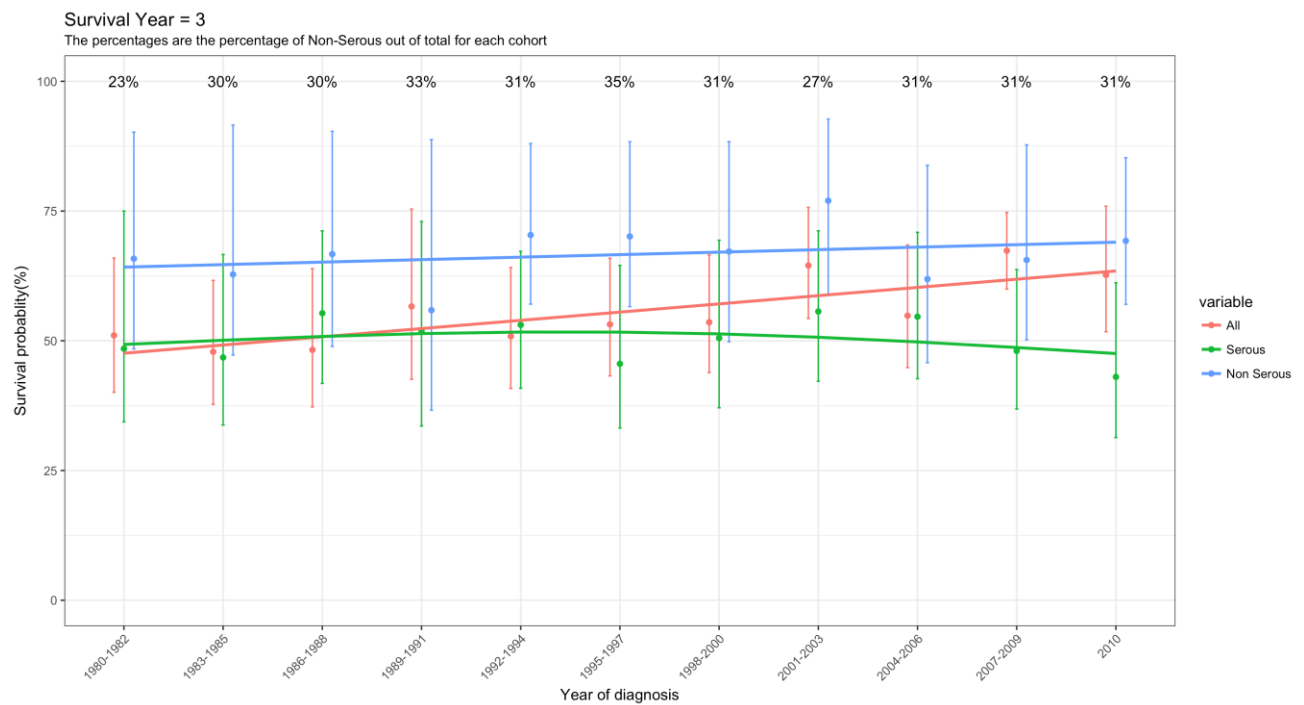
Figure 5: 5- year age standardized overall survival rates for all specified epithelial ovarian cancers and stratified by serous and non-serous subtypes, 1980 - 2015.
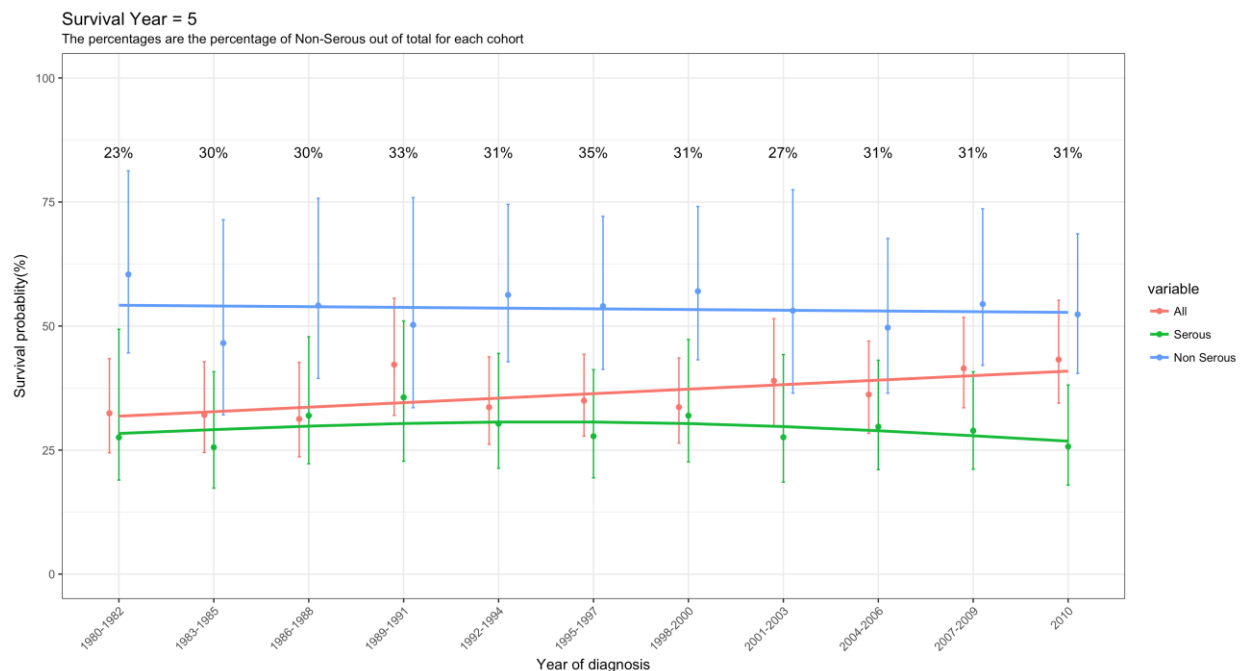
 I plotted the 1- year (Figure 6), 3- year (Figure 7) and 5- year (Figure 8) age- standardized disease specific survival rates (DSS) separately for all ovarian cancers (stratified by serous and non serous histotype; and excluding 'others and unspecified' EOCs), based on the cohort of diagnosis. Consistent with the overall survival rates for all EOCs, 1- year, 3- year and 5- year disease specific survival rates increased during the study period. For all the women with EOC, the 1- year survival rates (82.3%) were nearly twice the 5- year survival rates (45.5%) by 2010. The disease- specific survival rates were either stable or decreasing for serous and non- serous histotypes over the study period. Whereas, there was a dramatic increase in 1- year and 5- year disease specific survival for women with 'others and unspecified' EOCs (Appendix D).

Figure 6: 1- year age standardized disease specific survival rates for all specified epithelial ovarian cancers and stratified by serous and non-serous subtypes, 1980 – 2015.
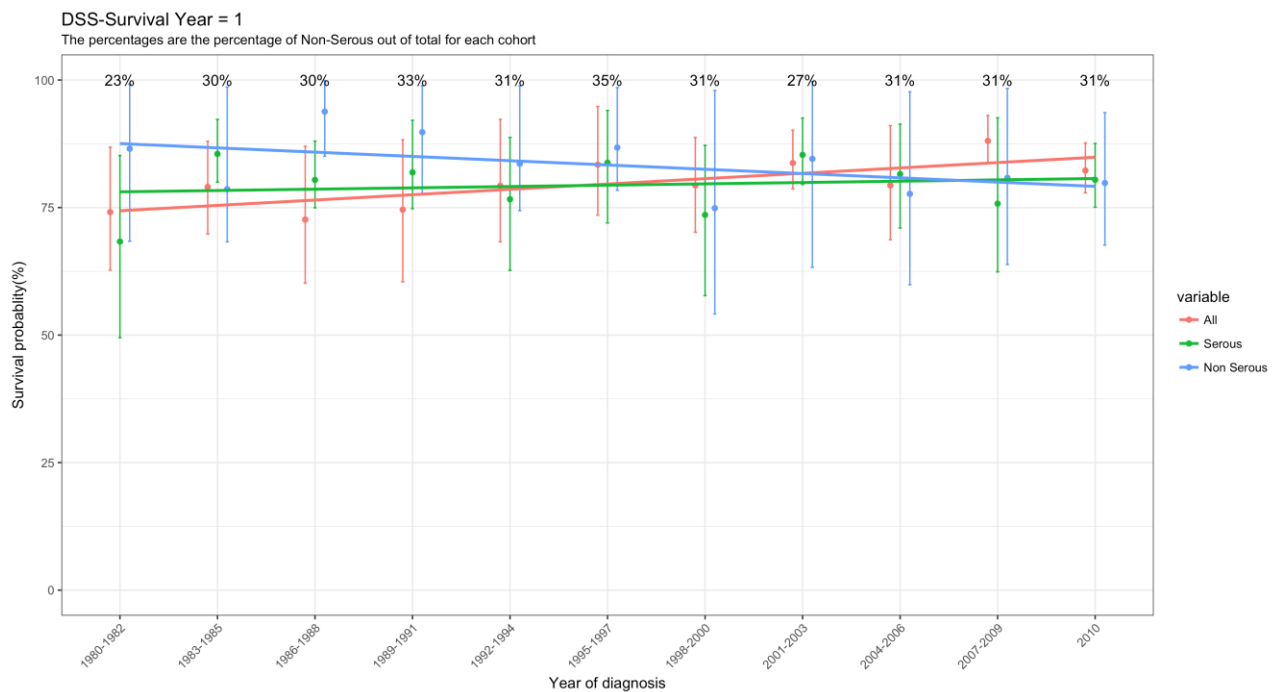
Figure 7: 3- year age standardized disease specific survival rates for all specified epithelial ovarian cancers and stratified by serous and non-serous subtypes, 1980 – 2015.
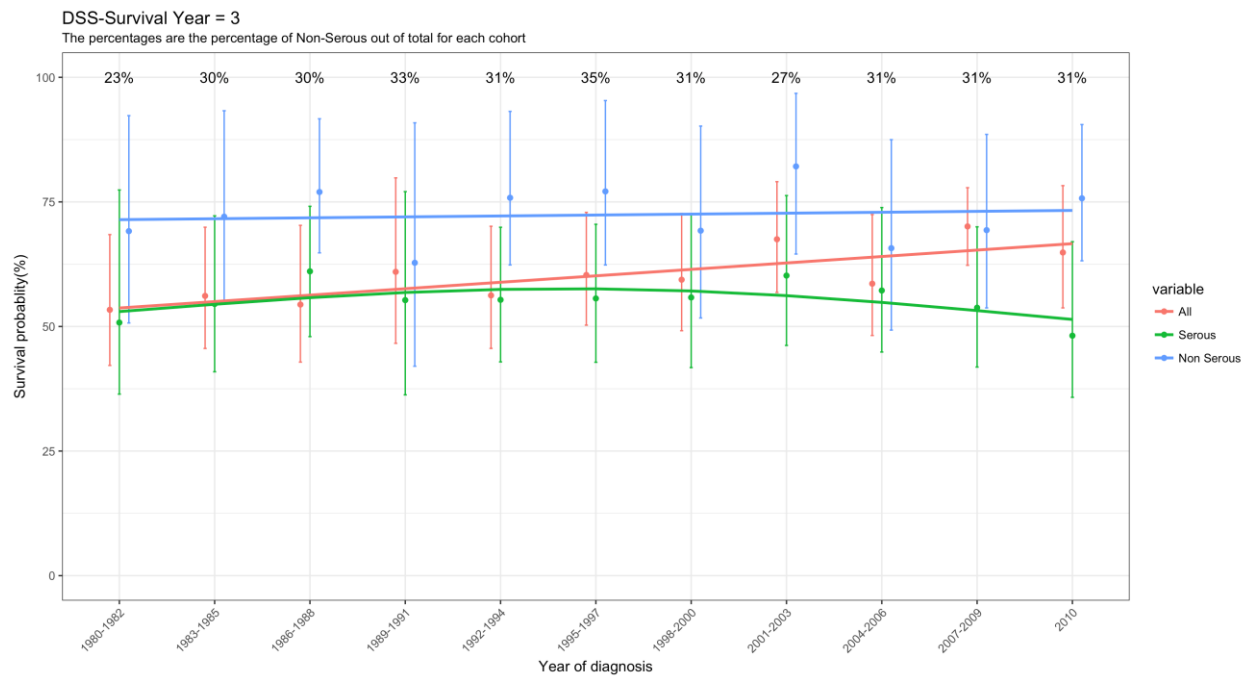
Figure 8: 5- year age standardized disease specific survival rates for all specified epithelial ovarian cancers and stratified by serous and non-serous subtypes, 1980 – 2015.
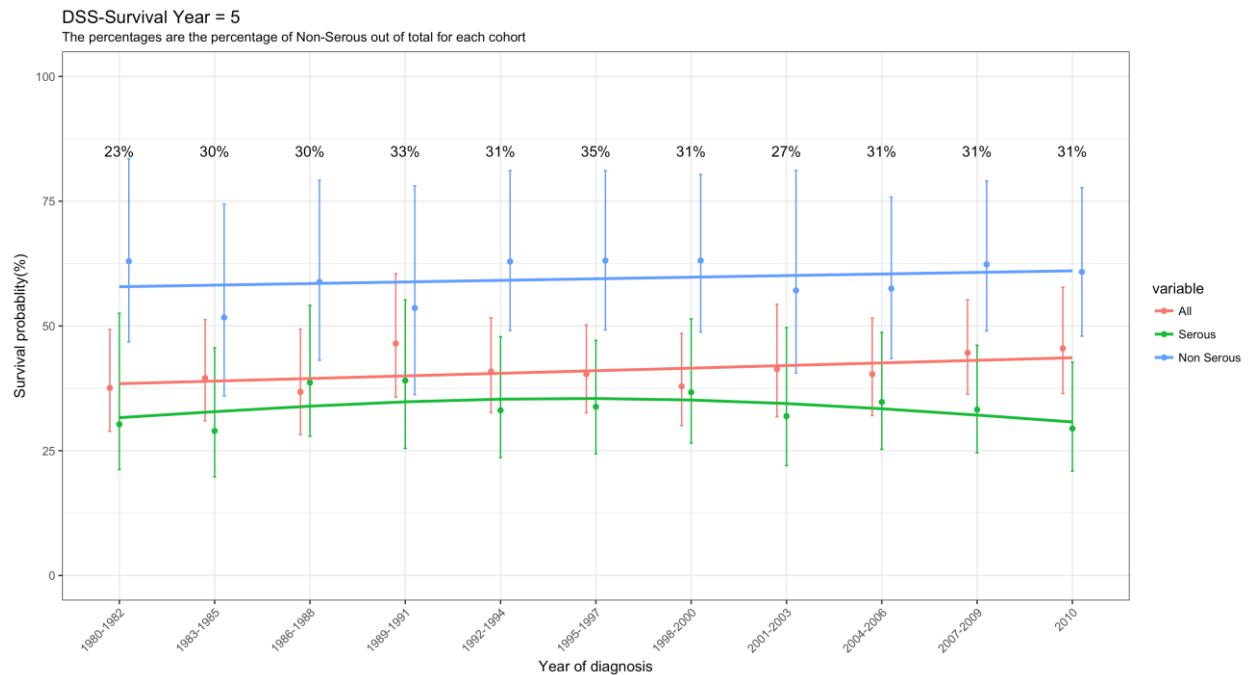
2.5   Discussion

Herein I report that the incidence rate of epithelial ovarian cancer in British Columbia decreased from 1980 to 2015. However, this differed significantly based on histotype. For instance, there was a slight increase in the incidence of endometrioid and clear cell EOCs. Whereas, the incidence of serous and mucinous EOCs decreased in our study period. As a result, endometrioid and clear cells made up a larger proportion/share of epithelial ovarian cancer over time.

Decreasing incidence of epithelial ovarian cancer might be explained by increased use of oral contraceptive pills (OCP) in Canada in the 1960's. Unfortunately, there is a minimal

Canadian literature on the proportion of oral contraceptive users over time. However, a study conducted in France reports that the percentage of women (aged between 20 and 44 years) regularly taking these pills increased from 28.3% in 1978 to 45.4% in 2000. There were approximately 79% of women (aged between 15 and 29 years) who were taking oral contraceptive pills by 2010 [142]. However, the oral contraceptive pill use for many of the women in our study would have occurred many years earlier. A woman diagnosed with ovarian cancer in 1990, at the age of 61, would likely have used oral contraceptive pills during the 1950s and 1960s. A similarly aged women diagnosed in 2010 would likely have used oral contraceptive pills during the 1970s and 1980s. Epidemiologic studies have consistently reported the protective effect of reproductive factors, including oral contraceptives, against ovarian cancer [46,47]. By reducing the number of lifetime ovulatory cycles, oral contraceptives can reduce the risk of developing ovarian cancer [143]. However, the formulation of oral contraceptive pills has changed in important ways since the women in our cohort would have been using them. It is imperative that future research seeks to understand whether the new formulations of oral contraceptive pills, being used by women currently in their 20s and 30s have the same protective effects as the older generation of these medicines.

Previous studies have reported a significant inverse relationship between gynecologic surgeries and risk of ovarian cancer. This likely results from the role of fallopian tube, both as the site of origin for HGSC, and as a conduit for retrograde menstruation from the uterus for endometrioid and clear cell cancers. Thus tubal ligation (a form of permanent sterilization that generally cauterizes fallopian tubes) is associated with a 29% reduction in ovarian cancer with differences in this effect across subtype [73,74]. The rates of these gynaecologic surgeries are changing significantly in British Columbia. Most importantly, there was an educational

campaign in September of 2010 in British Columbia, recommending to all gynecologic surgeons in the province of British Columbia (BC) Canada that, when operating on women at general population risk for ovarian cancer, they consider: 1) performing bilateral salpingectomy at the time of hysterectomy (even when the ovaries are being preserved); and 2) performing bilateral salpingectomy in place of tubal ligation for permanent sterilization. These procedures have come to be referred to as opportunistic salpingectomy (OS). Moreover, hysterectomy (removal of uterus) is also associated with statistically significant reductions in risk for ovarian cancer (HR = 0.79, 95% CI= 0.70, 0.80) [78]. While hysterectomy rates have decreased since the 1980s, [144] rates of hysterectomy with bilateral salpingectomy have dramatically increased in British Columbia. Salpingectomy is performed in lieu of tubal ligation in over half of all tubal sterilization procedures (as of 2014), meaning that many women in British Columbia no longer have fallopian tubes [31]. I expect this will dramatically decrease incidence of ovarian cancer in the future, the effects of which should be noticeable by 2020.

The most common histotype of ovarian cancer in this study was serous EOCs. Though the incidence of this histotype declined between 1980 and 2005, the percentage was fairly stable, whereas the percentages of mucinous EOCs decreased dramatically. This might reflect an improvement in the classification of mucinous tumors, involving differentiation of these tumors from extraovarian metastases (intestinal mucinous carcinomas), benign and borderline tumors [145-147]. This improvement, however, is more applicable to recent cases (cases diagnosed after 2008), hence many tumors might have been misclassified as mucinous in the early years.

Our data also showed an increasing trend of 1- year, 3- year and 5- year overall and disease specific survival rates for epithelial ovarian cancer over the past 35 years. Our findings are consistent with other literature [5,126,127]. A population study comparing the relative survival

ratios over the period of 1992-2005 by age at diagnosis, histotype and geographical location, reported improvement in 2- and 5- year survival based on year of diagnosis across different age groups [126]. Another study has also shown a significant improvement in 1- year, 3- year, and 5- year age- standardized survival estimates for women diagnosed between 2006 and 2008 in comparison to women diagnosed between 1992 and 1994 [5].

When examining increasing overall survival and disease specific survival for all EOCs, I suspect this is partly driven by the increasing proportion of endometrioid and clear cell cancers over time, which both have better survival outcomes than serous cancers and advanced stage mucinous cancers [148]. Hence, the observed increase in overall and disease specific survival rates for all EOCs may not be attributable to recent advances in treatment of ovarian cancer, including platinum-based chemotherapy, (intraperitoneal) IP chemotherapy, and surgeries, which are commonly reported to be improving survival among women with this disease[126].

The population-based nature of the study and its inclusion of all women diagnosed with EOC in British Columbia between 1980 and 2015 is an important strength of our research; however, some limitations are noted. Our reliance on the ICD morphologic codes to classify tumours into histologic subtypes is our most important limitation. This resulted in a large number of ovarian cancers that I was unable to classify by histotype as a significant number of women (22.4%) had ICD morphologic codes that map to "ovarian cancer, not otherwise specified". These included unclassified cases (17.9%), mixed carcinoma (2.9%), malignant Brenner tumors (1.9%). These cases showed a dramatic increase in their 1- year, and 5- year survival rates. It is unclear why women with unclassified ovarian cancers would have improved overall and disease specific survival rates while survival among women with serous and nonserous EOCs slightly decreased. Research is currently underway to properly classify these unspecified cases.

While there have been considerable advances in the categorization of epithelial ovarian cancer subtypes with high interobserver agreement in histotype assignment [12,149] of this disease, our cases include many cancers subtyped prior to these publications, and most cases did not have the benefit of additional immunohistochemical tests to help characterize challenging cases, meaning there is likely histotype misclassification. Recent research illustrated the considerable shift in understanding of histotype classification over our study period. An expert gynecopathologist re-reviewed 286 pathology specimens that he had previously examined in 2002. When re-reviewing these specimens in 2014, he only agreed with his initial 2002 assessment in 54% of cases. In contrast, 98% of these cases were assigned the same histotype independently by two gynecopathologists using 2014 WHO diagnostic criterion[12]. This reflects how better understanding of ovarian cancer pathology has impacted the diagnosis of histotypes over the years and suggests that our histotype classification was likely more accurate in more recent years.

The rarity of ovarian cancer combined with the relatively small BC population has resulted in small numbers of women with histotypes other than serous ovarian cancer, and thus I had to group these histotypes in our analyses. I was also unable to examine survival trends by stage, which is a well-established prognostic factor for survival. Lastly, estimating the effect of treatment therapies, such as cytoreductive surgery and chemotherapy on survival over time were beyond the scope of this study [1].

The results of this study indicate that incidence of ovarian cancer in British Columbia decreased between 1980- 2015, and that both the age- standardized overall and disease- specific survival rate of ovarian cancer increased after 1985. Increasing survival coupled with a

decreasing number of cases over time presents a positive picture of ovarian cancer status among

affected women in British Columbia.

Chapter 3: Long-term mortality among women with epithelial ovarian cancer: A population-based study in British Columbia, Canada

3.1 Introduction

Ovarian cancer is the leading cause of death among gynecologic cancers. Although lifetime risk of ovarian cancer in the general population is relatively low (1.4%) [134], it is the fifth leading cause of cancer deaths among women in Canada, with a 5-year survival rate of 44% [150]compared with nearly 90% [4] for breast cancer, more than 80% [150] for endometrial cancer, and nearly 73% [150] for cervical cancer. While survival is much improved when ovarian cancer is detected in the early stages, there are presently no effective screening methods demonstrated to reduce mortality [98]. Ovarian cancer is also largely asymptomatic in early stages, thus approximately 70% of women are diagnosed when the disease is already at advanced stages (Stage III and IV) [133].

Causes of death among cancer patients has been relatively well studied across many different forms of cancer. It is often reported that within 5 years of a cancer diagnosis, cancer is the most common cause of death. However, the risk of dying from cancer decreases with time from diagnosis and cancer patients become more likely to die from other causes [133]. This has been reported for breast cancer [151], prostate cancer [152], head and neck cancer [153], and lung cancer [154]. With respect to ovarian cancer, a previous American study using Surveillance Epidemiology, and End Results (SEER) data has reported that the probability of dying from ovarian cancer decreases with time, but that ovarian cancer remains the leading cause of death for 15 years among women diagnosed in advanced stages [133].

Here, I have focused on epithelial ovarian cancer (EOC), which represents 90% of all ovarian cancers [155]. Over the past decade, it has become apparent that EOC is a heterogenous disease, comprising of distinct histotypes that differ in presentation, response to therapy, molecular features, hereditary predisposition, site of origin and clinical outcomes. Although EOC histotypes share an anatomical location (the ovary), they are now considered distinct diseases [10-14]. This histotype-specific approach has completely changed the approach to clinical care and research. Histotype and stage remain the strongest prognostic factors in EOC. Some international work examining survival among ovarian cancer patients by histologic-subtypes has reported that survival rates were lowest among women with high-grade serous cancers [13]. However, little is known about causes of death among women with epithelial ovarian cancer, and there is no current evidence on whether causes of death differ among these women by histotype.

Histotype-specific mortality estimates are of clinical importance as information may impact advice given or interventions undertaken for patients and physicians involved in their care. For women with OC histotypes less likely to recur, information is currently lacking on their potential health concerns. I therefore examined survival and causes of death among women with EOC in BC between 1990 and 2014 by histotype and years since EOC diagnosis.

3.2   Methods

3.2.1   Data sources

I built a population-based cohort using data from the BC cancer registry [139], Vital statistics [140], BC hereditary cancer program (HCP) [139], and BC's insurance registry file (the Consolidation file) [156]. The BC Cancer Registry is a population-based registry of all cancers diagnosed in British Columbia residents. It receives notifications of cancer from many sources

including pathology, cytology and other labs, hospital charts, death certificates, and admissions to cancer centers operated by the BC Cancer Agency. The Registry contains personal and demographic information and information about the specific cancer diagnosis. The vital statistics death file is an extract of the deaths registration file provided by British Columbia vital statistics agency. It contains information on all deaths in BC, including underlying cause of death (UCOD) and exact date of death. I accessed data from the HCP, the source of all *BRCA*1 and *BRCA*2 testing in the province of British Columbia. I classified patients as having a *BRCA* mutation if they had either a *BRCA*1 or *BRCA*2 mutation or both. The consolidation file is a comprehensive data set, containing information on individuals receiving health services and/or individuals eligible to receive health services in British Columbia, Canada (˜4.6 million people). It contains demographic and regional information on every individual residing in British Columbia. With the permission of all relevant data stewards, and ethics approval form the University of British Columbia's behavioural research ethics board, all these data were retrieved from PopData BC [157]. All inferences, opinions, and conclusions drawn are those of the authors and do not reflect the opinions or policies of the Data Stewards.

3.2.2   Study cohort

Our study population consists of all patients diagnosed with ovarian cancer in British Columbia between 1990 and 2014. The International Statistical Classification of Diseases codes: tenth revision (ICD-10) was used to identify these women with ovarian cancer with the codes of C56.0 (ovary), and C57. 0 (fallopian tube) in the British Columbia cancer registry. We used the same histotype classification table as reported in section 2.2.2 (Table 1). To ensure I had complete follow-up on women included in our cohort and to prevent misclassifying women as

alive, among women who were not recorded in the death registry, I required that women be registered for health care in BC for at least 5 years after their diagnosis.

3.2.3   Assessment of causes of death

I classified the UCODs using ICD-10 categories. The UCODs were classified into specific categories such as ovarian cancer, breast cancer, colorectal cancer, 'other' cancers (lung cancer, gastrointestinal tract cancer, blood lymph cancer, other malignancy, non malignant and unspecified), cardiovascular diseases (rheumatic, hypertension, ischemic, heart failure, congenital, pulmonary, cardiomyopathy etc), other chronic conditions (diabetes, COPD, AIDS/HIV, pneumonia, other infectious and parasitic disease, asthma, cerebro and other vascular disease, liver disease, pulmonary fibrosis etc), external causes (Motor vehicle accidents, poisoning, falls, suicide, other unintentional injuries etc), and unclassified causes (causes of death that did not meet the criterion of the above categories) (Appendix B). Patients were considered to have died of ovarian cancer if the cause of death was reported as ovarian cancer or cancer-related likely due to ovarian cancer (which included deaths from neoplasm of uterus, cervix, placenta, ovary and adnexa, vagina and external genitalia following an initial diagnosis of ovarian cancer).

3.2.4   Statistical Analysis

In this study, I have described data descriptively. Women were monitored as of the date of their ovarian cancer diagnosis (as recorded in the BC Cancer Registry database) until their death or until December 31st, 2014 (the end of the follow-up period). Causes of death were stratified based on histotype categories (Serous, Mucinous, Endometrioid, Clear cell, Not classified). I further stratified based on age at diagnosis (<60 or >=60 years) and *BRCA* mutation status.

Causes of death were calculated as rates with 95% confidence intervals. All analyses were performed with R version 3.3.2[158].

3.3   Results

A total of 6,975 women were identified as having been diagnosed with ovarian cancer between 1990 and 2014 in British Columbia. After excluding women who did not have epithelial ovarian cancer (n=407), and after excluding women who were not captured in the death registry and were not registered for health care in BC for at least 5 years post diagnosis (n= 141), 6427 were included in our study. The study cohort included 2996 (46.6 %) serous, 366 (5.7 %) mucinous, 719 (11.2 %) endometrioid, 431 (6.7 %) clear cell and 1915 (29.8 %) not classified EOCs.

The clinical characteristics of BC women diagnosed with EOC between 1990 and 2014 are outlined in Table 3. Among all histotypes, serous carcinomas were commonly observed, accounting for approximately 46.6% of total EOCs (66.4% if we remove EOCs that were not classified by histotype). The majority (68.2 %) of affected women were diagnosed with EOC between 50 and 79 years of age and were not *BRCA* mutation carriers (96.9%).

Table 4: Clinical characteristics of the study cohort.

Year of diagnosis	N	%
1990 – 1994	1106	17.2
1995 – 1999	1265	19.7
2000 – 2004	1252	19.5
2005 – 2009	1395	21.7
2010 - 2014	1409	21.9
Histology	**N**	**%**
Serous	2996	46.6
Mucinous	366	5.7
Endometrioid	719	11.2

Clear cell	431	6.7
Not classified	1915	29.8
Age at diagnosis	**N**	**%**
<40	410	6.4
40 – 49	815	12.7
50 – 59	1477	23.0
60 – 69	1457	22.7
70 – 79	1448	22.5
80+	820	12.8
BRCA **status**	**N**	**%**
BRCA wild type	199	3.1
BRCA null	6228	96.9

By the end of this study, 55.9% of the study cohort (all histologies) died from their ovarian cancer, 33.9% were alive, 10.2% of women died from causes other than ovarian cancer; 0.8% from breast cancer, 0.5% from colorectal cancer, 3.5% from 'other' cancers, 1.8% from cardiovascular disease, 1.8% from other chronic conditions, 0.3% from external causes and 1.5% from unclassified causes (Table 4).

Serous: Among women with serous EOCs, 29.3% were alive at the end of follow-up while 62.2% had died from their disease. Of those women who died from other causes, 0.9% died from breast cancer, 0.5% died from colorectal cancer, 2.7% died from other cancers, 1.5% died from cardiovascular disease, 1.2% died from other chronic conditions, 0.4% died from external causes, and 1.3% died from unclassified causes (Table 4).

Mucinous: 54.4% women with mucinous EOCs were alive while 32% died from ovarian cancer. The majority of women with mucinous EOCs died from other cancers (5.2%), followed by deaths from cardiovascular diseases (3.0%) and deaths from other chronic conditions (3.0%). Although minimal in percentage, I also observed deaths from external causes (0.3%), deaths

from colorectal cancer (0.3%), deaths from breast cancer (0.5%), and 1.4% died from unclassified causes (Table 4).

Endometrioid: In all histotypes, the greatest number of women alive at the end of follow-up was observed among women with endometrioid EOC (62.0%). Among the women who had died, 26.7% died from ovarian cancer, 0.7% died from breast cancer, 0.8% died from colorectal cancer, 2.6% died from other cancers, 2.5% died from cardiovascular disease, 2.4% died from other chronic conditions, 0.3% died from external causes, and 2% died from unclassified causes (Table 4).

Clear cell: There was a considerable number of women with clear cell EOCs who were alive at the end of follow-up (55.9%). Among women who died, 35.3% died from ovarian cancer, 0.7% died from breast cancer, 0.5% died from colorectal cancer, 2.1% died from other cancers, 0.9% died from cardiovascular disease, 1.9% died from other chronic conditions, 0.9% died from external causes, and 1.9% died from unclassified causes (Table 4).

Not classified: Among women with EOCs that could not be classified into histotypes, 21.8% of cases were alive at the end of follow-up while 66.2% died from ovarian cancer. Of those women who died from other causes, 0.7% died from breast cancer, 0.6% died from colorectal cancer, 5.1% died from 'other' cancers, 1.9% died from cardiovascular disease, 2.1% died from other chronic conditions, 0.1% died from external causes, and 1.5% died from unclassified causes (Table 4).

Differences between age groups in the causes of death, stratified by histotype, are reported in Table 5. In each histotype group, a greater number of women who were diagnosed under 60 years of age survived than older women. Women diagnosed with serous cancer at 60 or older were most likely to die from ovarian cancer (66.8%), whereas women diagnosed with

endometrioid cancer under the age of 60 were least likely to die from ovarian cancer (19.5%)

followed closely by women diagnosed with mucinous cancer under the age of 60 (21.3%). For

each age cohort, and for each histotype ovarian cancer was the leading cause of death. In all,

death from ovarian cancer was most common, followed by 'other' cancers.

The outcomes of women with ovarian cancer and a *BRCA* mutation, stratified by serous or

non- serous histotype is reported in Table 6. I was unable to stratify by other histotypes due to

small sample sizes. Among women diagnosed with serous cancer, those with a *BRCA* mutation

(*BRCA* null) face greater risk of death from breast cancer (4%) in comparison to women without

a mutation (0.7%). In all, regardless of a woman's *BRCA* mutation status, and for all histotypes

ovarian cancer was the leading cause of death.

Table 5: Cause of death stratified by histotype

Cause of death, N (%; 95% CI)	All EOC patients (n= 6427)	Serous (n=2996)	Endometrioid (n = 719)	Clear cell (n= 431)	Mucinous (n= 366)	Not classified (n= 1915)
Alive	2181 (33.9; 32.8, 35.1)	877 (29.3; 27.7, 30.9)	446 (62.0; 58.4, 65.5)	241 (55.9; 51.2, 60.5)	199 (54.4; 49.3, 59.4)	418 (21.8; 20.0, 23.7)
Ovarian cancer	3592 (55.9; 54.7, 57.1)	1864 (62.2; 60.5, 63.9)	192 (26.7; 23.6, 30.1)	152 (35.3; 30.9, 39.9)	117 (32; 27.4, 36.9)	1267 (66.2; 64.0, 68.2)
Breast cancer	49 (0.8; 0.6, 1)	26 (0.9; 0.6, 1.3)	5 (0.7; 0.3, 1.6)	--	--	13 (0.7; 0.4, 1.2)
Colorectal cancer	34 (0.5; 0.6, 0.7)	14 (0.5; 0.3, 0.8)	6 (0.8; 0.4, 1.8)	--	--	11 (0.6; 0.3, 1)
Other cancer	227 (3.5; 3.1, 4.0)	82 (2.7; 2.2, 3.4)	19 (2.6; 1.7, 4.1)	9 (2.1; 1.1, 3.9)	19 (5.2; 3.4, 8)	98 (5.1; 4.2, 6.2)
Cardiovascular disease	116 (1.8; 1.5, 2.2)	46 (1.5; 1.2, 2.1)	18 (2.5; 1.6, 3.9)	--	11 (3.0; 1.7, 5.3)	37 (1.9; 1.4, 2.7)
Other chronic	114 (1.8; 1.5, 2.1)	37 (1.2; 0.9, 1.7)	17 (2.4; 1.5, 3.8)	8 (1.9; 1, 3.6)	11 (3.0; 1.7, 5.3)	41 (2.1; 1.6, 2.9)
External causes	20 (0.3; 0.2, 0.5)	12 (0.4; 0.2, 0.7)	--	--	--	--
Unclassified causes	94 (1.5; 1.2, 1.8)	38 (1.3; 0.9, 1.7)	14 (2; 1.2, 3.3)	8 (1.9; 1, 3.6)	5 (1.4; 0.6, 3.2)	29 (1.5; 1.1, 2.2)

-- suppressed due to small cell sizes

Table 6: Cause of death stratified by histotype and age at diagnosis

Cause of death, N (%; 95% CI)	Serous (n=2996)		Endometrioid (n = 719)		Clear cell (n= 431)		Mucinous (n= 366)		Not classified (n= 1915)	
	<60 (n= 1153)	>=60 (n= 1843)	<60 (n= 446)	>=60 (n= 273)	<60 (n= 293)	>=60 (n=138)	<60 (n= 216)	>=60 (n=150)	<60 (n= 594)	>=60 (n= 1321)
Alive	462 (40.0; 32.3, 42.9)	415 (22.5; 20.7, 24.5)	340 (76.2; 72.1, 79.9)	106 (38.3; 33.2, 44.7)	191 (65.2; 59.6, 70.4)	50 (36.2; 28.7, 44.5)	158 (73.1; 66.9, 78.6)	41 (27.3; 20.8,34.9)	299 (50.3; 46.3, 54.4)	119 (9; 7.6, 10.7)
Ovarian cancer	633 (54.9; 52, 57.8)	1231 (66.8; 64.6, 68.9)	87 (19.5; 16.1, 23.4)	105 (38.5; 32.9, 44.4)	92 (31.4; 26.4, 36.9)	60 (43.5; 35.5, 51.8)	46 (21.3; 16.4, 27.2)	71 (47.3; 39.5, 55.3)	253 (42.6; 38.7, 46.6)	1014 (76.8; 74.4, 79)
Breast cancer	13 (1.1; 0.7, 1.9)	13 (0.7; 0.4, 1.2)	--	--	--	--	--	--	--	9 (0.7; 0.4, 1.3)
Colorectal cancer	--	12 (0.7; 0.4, 1.1)	--	--	--	--	--	--	--	8 (0.6; 0.3, 1.2)
Other cancer	15 (1.3; 0.8, 2.1)	67 (3.6; 2.9, 4.6)	6 (1.4; 0.6, 2.9)	13 (4.8; 2.8, 8)	--	8 (5.8; 3, 11)	7 (3.2; 1.6, 6.5)	12 (8; 4.6, 13.5)	22 (3.7; 2.5, 5.5)	76 (5.8; 4.6, 7.1)
Cardiovascular disease	8 (0.7; 0.4, 1.4)	38 (2.1; 1.5, 2.8)	--	17 (6.2; 3.9, 9.8)	--	--	--	8 (5.3; 2.7, 10.2)	--	35 (2.7; 1.9, 3.7)
Other chronic	11 (1.0; 0.5, 1.7)	26 (1.4; 1, 2.1)	--	13 (4.8; 2.8, 8)	--	5 (0.3; 0.1, 0.8)	--	11 (7.3; 4.1, 12.7)	5 (0.8; 0.4, 2)	36 (2.7; 2, 3.8)
External causes	--	9 (0.5; 0.3, 0.9)	--	--	--	--	--	--	--	--
Unclassified causes	6 (0.5; 0.2, 1.1)	32 (1.7; 1.2, 2.5)	--	12 (4.4; 2.5, 7.5)	--	8 (5.8; 3, 11.0)	--	5 (3.3; 1.4, 7.6)	6 (1.0; 0.5, 2.2)	23 (1.7; 1.2, 2.6)

- suppressed due to small cell sizes

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Table 7: Cause of death stratified by histotype and *BRCA* status

Cause of death, N (%; 95% CI)	Serous (n=2996)		Non- serous (n = 1516)	
	BRCA wild type (n= 2846)	*BRCA* null (n= 150)	*BRCA* wild type (n= 1502)	*BRCA* null (n= 14)
Alive	798 (28.0; 26.4, 29.7)	79 (52.7; 44.7, 60.5)	879 (58.5; 56.0, 60.1)	7 (50; 26.8, 73.2)
Ovarian cancer	1802 (63.3; 61.5, 65.1)	62 (41.3; 33.8, 49.3)	455 (30.3; 28.0, 32.7)	--
Breast cancer	20 (0.7; 0.5, 1.1)	6 (4; 1.8, 8.4)	10 (0.7; 0.4, 1.2)	--
Other causes	214 (7.5; 6.6, 8.6)	--	151 (10.1; 8.6, 11.7)	6 (42.9; 21.4, 67.4)

-- suppressed due to small cell sizes

Figure 7 displays the frequency distribution of deaths for all histotypes. It reveals that ovarian cancer is the leading cause of death among women diagnosed with ovarian cancer for 10 years post diagnosis. It is first surpassed by other causes of deaths 11 years post diagnosis. Figure 8 displays the frequency distribution of deaths for serous EOCs. Ovarian cancer remains the leading cause of death among women diagnosed with serous EOCs for 12 years following diagnosis. Figure 9 depicts the frequency distribution of deaths for non- serous (endometrioid, clear cell, mucinous) EOCs. Other causes of death surpass ovarian cancer as the leading cause among women diagnosed with non-serous EOCs at 8 years post diagnosis. Figure 10 and figure 11 display the frequency distribution of deaths for serous EOCs by age group. Figure 12 and Figure 13 displays the frequency distribution of deaths for non-serous EOCs by age group. Ovarian cancer remains the leading cause of death for longer among younger women (<60 years) than among older women (60 years or more). Other causes of death first surpass ovarian cancer as the leading cause of death among older women with serous EOCs at 8 years post diagnosis. Whereas ovarian cancer is the leading cause of cause among younger women with serous EOCs for 12 years post diagnosis. Among women with non- serous EOCs, ovarian cancer is the leading cause of death among older women for 5 years after diagnosis in comparison to younger women where it is 8 years after diagnosis. There were too few deaths from causes other than ovarian cancer in the women with a *BRCA* mutation to reliably examine causes of death over time in this group.

Figure 9: Frequency distribution of deaths among patients diagnosed with all the histotypes.
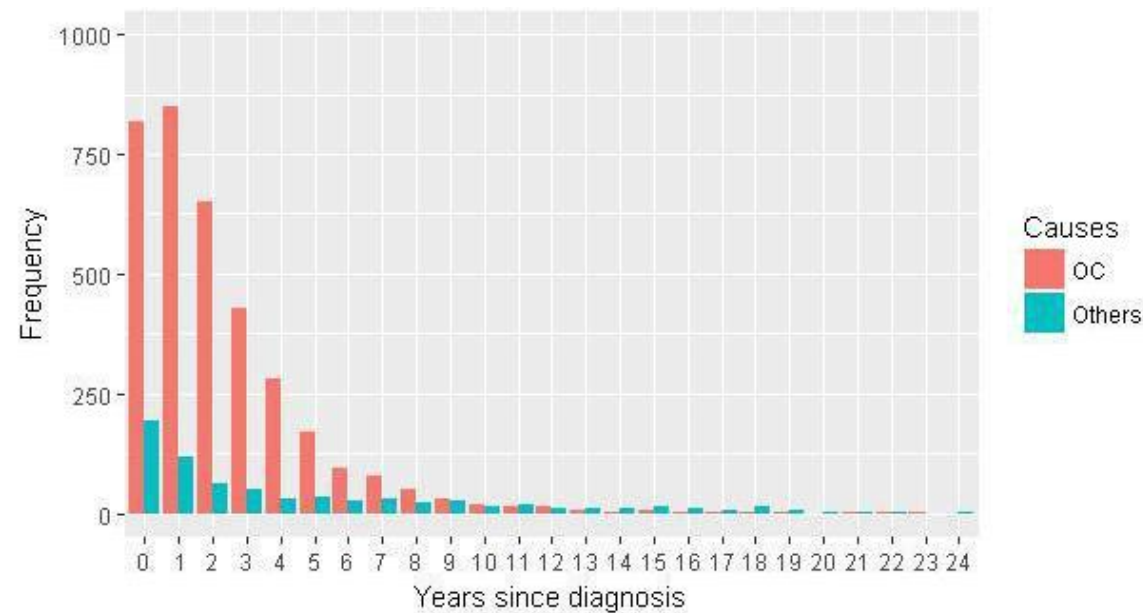
Figure 10: Frequency distribution of deaths among patients diagnosed with serous epithelial ovarian cancers.
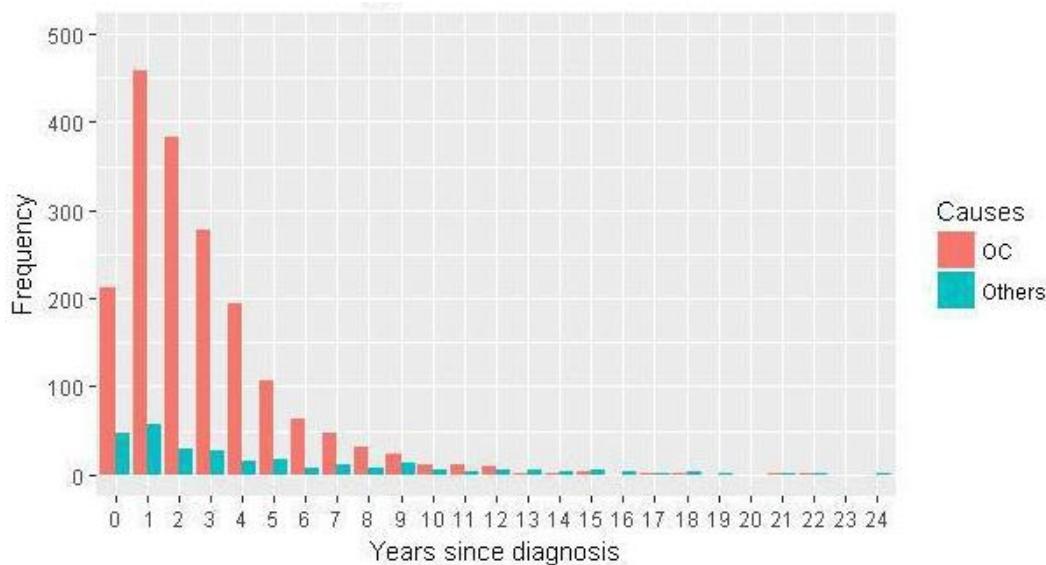
Figure 11: Frequency distribution of deaths among patients diagnosed with non- serous epithelial ovarian cancers.
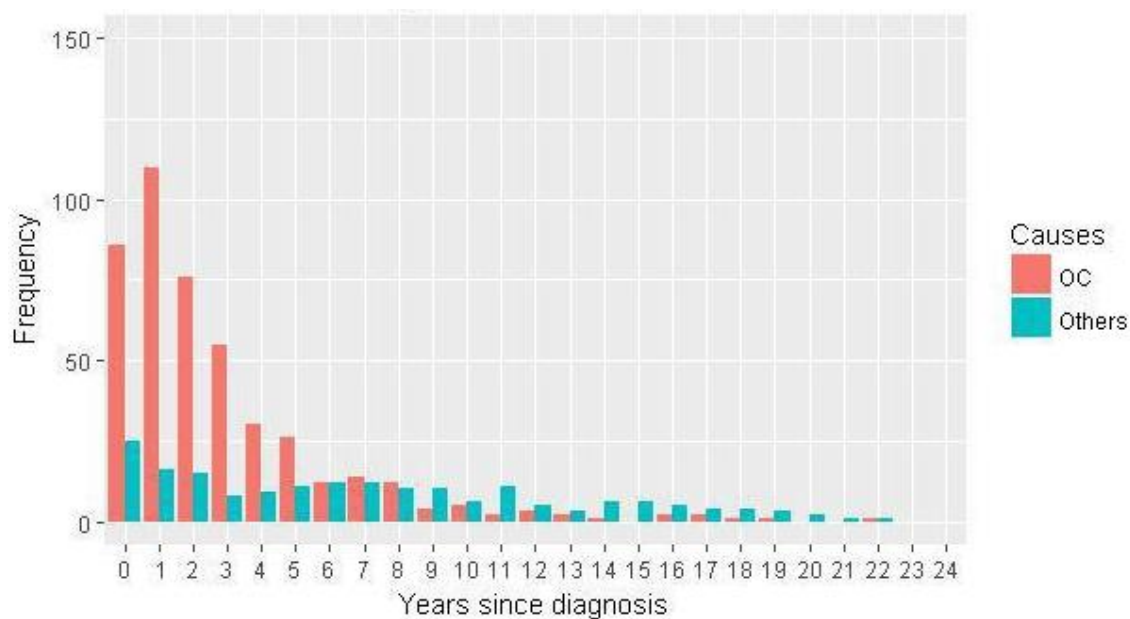
Figure 12: Frequency distribution of deaths among older patients (>= 60 years) diagnosed with serous epithelial ovarian cancers.
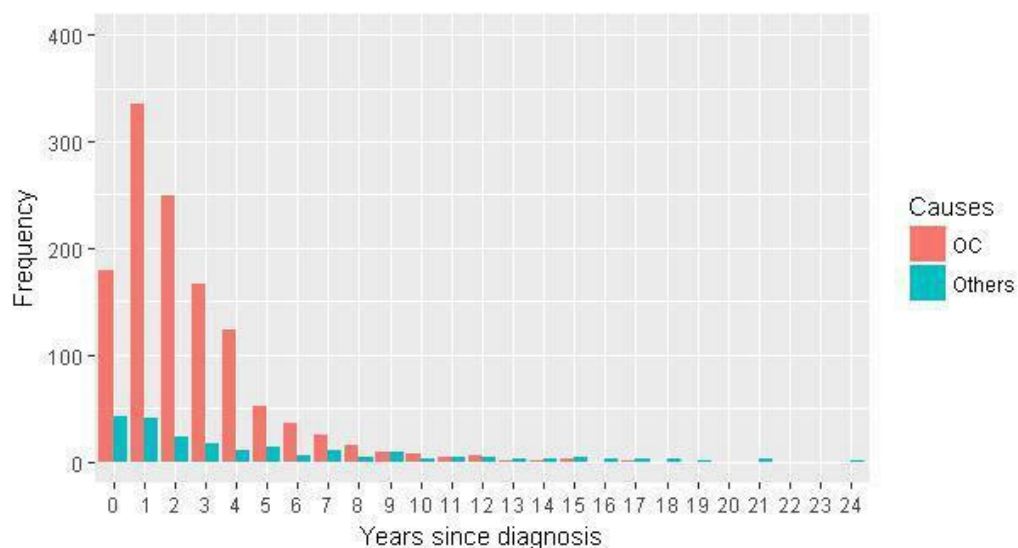
Figure 13: Frequency distribution of deaths among younger patients (aged under 60 years) diagnosed with serous epithelial ovarian cancers.
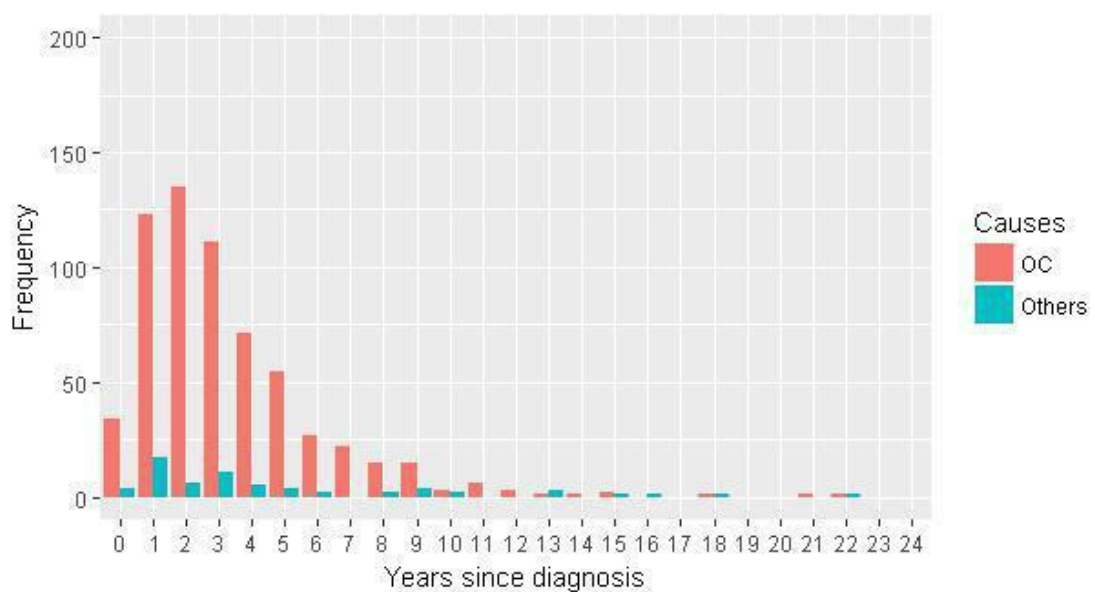
Figure 14: **Frequency distribution of deaths among older patients (aged 60 years or more) diagnosed with non- serous epithelial ovarian cancers.**
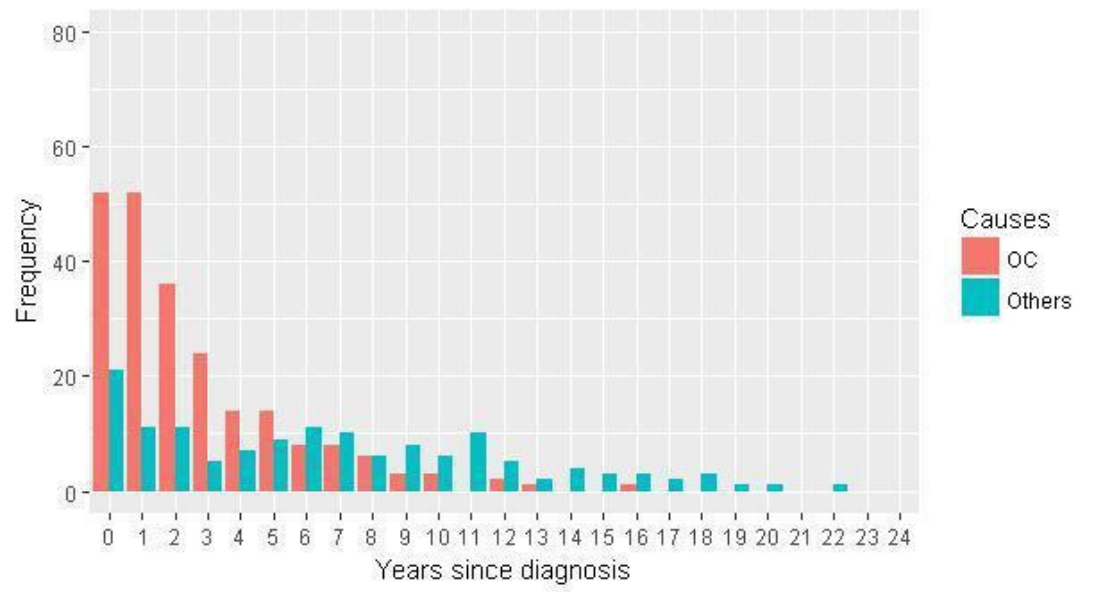
Figure 15: Frequency distribution of deaths among younger patients (aged under 60 years more) diagnosed with non- serous epithelial ovarian cancers.
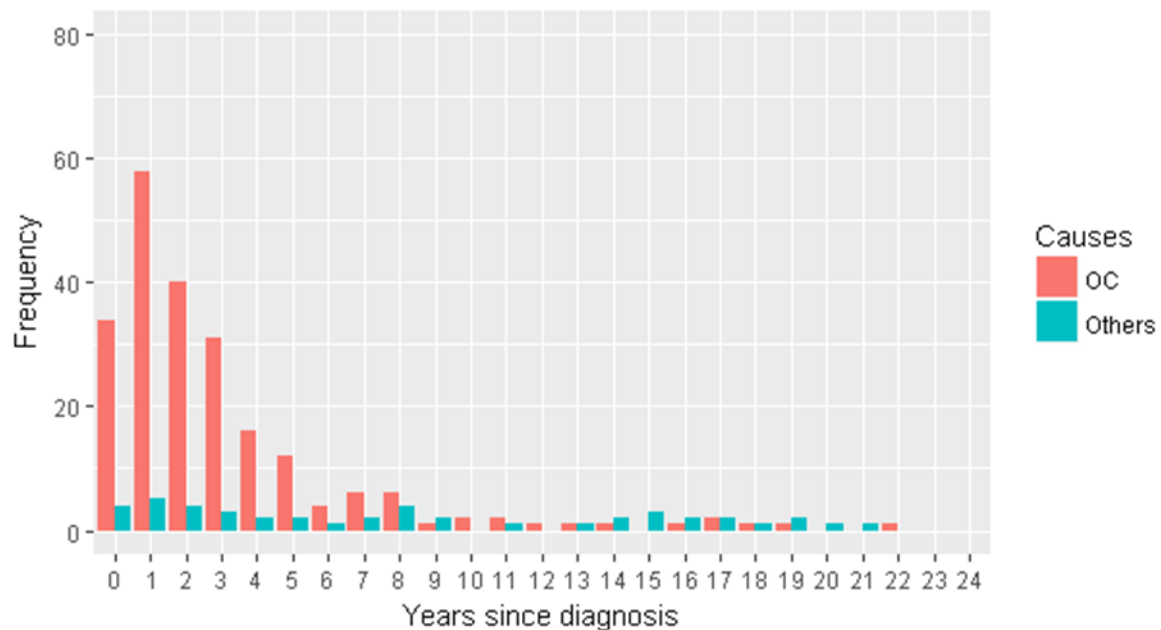
3.4   Discussion

Herein I report that among EOC patients, ovarian cancer is the leading cause of death for 10 years post diagnosis before it is surpassed by other causes of death. However, this differed significantly based on histotype and age at diagnosis. For example, among women with serous EOC, ovarian cancer was the leading cause of death for 12 years compared to 8 years among women with non- serous EOCs. When stratified by age, ovarian cancer was the leading cause of death for 8 years post diagnosis among women with serous EOCs diagnosed after age 60 compared to 12 years among younger women (<60 years of age) with serous EOCs. Our results suggest that women with non- serous EOCs were more likely to die from causes other than ovarian cancer in comparison to serous patients, as the majority of women with serous EOCs died from ovarian cancer. For instance, women with endometrioid and mucinous EOCs were

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more vulnerable to die from cardiovascular diseases, chronic conditions and unclassified causes than women with serous EOC.

Although the rates of death from breast cancer were not significantly different across the histotypes, I found that these rates varied when stratified by *BRCA* status. Women with a *BRCA* mutation and with serous carcinomas were less likely to die from other causes, and more likely to die from ovarian cancer, than women without a *BRCA* mutation. Whereas women with a *BRCA* mutation and a non- serous cancer were at relatively comparable risk of death from other causes as women without a *BRCA* mutation and a non- serous cancer.

Our results reporting a significant risk of death from ovarian cancer for many years post diagnosis is consistent with those previously reported using SEER data [133]. The SEER study reported that the probability of death from ovarian cancer decreases with increased survival years post diagnosis and the probability of death from all other causes increases. I observed that ovarian cancer is the leading cause of death among BC women diagnosed with EOC for 10 years post diagnosis. The SEER study reported that ovarian cancer was surpassed by other causes of death 7 years after diagnosis.

Our results are also consistent with a small body of literature reporting minimal risk of breast cancer among women with EOC and a *BRCA* mutation [159]. Our findings indicate a low incidence of death from breast cancer among women with ovarian cancer and a *BRCA* mutation. When stratified by histotype, *BRCA* mutation carriers diagnosed with serous EOCs were at the greater risk of death from breast cancer, breast cancer was only responsible for 4% of deaths among these women. This supports the assertion that there is no need to rush to perform mastectomy to prevent breast cancer among women with a *BRCA* mutation and EOC.

The population-based nature of the study and its inclusion of all women diagnosed with EOC in British Columbia between 1990 and 2014 is an important strength of our research; however, some limitations are noted. Our reliance on the ICD morphologic codes to classify tumours into histologic subtypes likely introduced some misclassification. As outlined in section 2.5, there have been considerable advances in categorization of epithelial ovarian cancer subtypes with high interobserver agreement in histotype assignment for this disease over our study period [12,149], and we have reason to expect that our histotype classification improved considerably toward the end of our study period, resulting in higher rates of misclassification in the earlier years of our study. In addition, the rarity of ovarian cancer combined with the relatively small BC population has resulted in small numbers of women with histotypes other than serous ovarian cancer, and thus I had to group these histotypes in some analyses. Also, I cannot comment on the lynch syndrome status of our study population as I lack these data. Based on the past literature, women with endometroid and clear cell EOCs were observed to be at risk of Lynch syndrome [66]. Associated with a high risk of colorectal cancer, lynch syndrome status may have factored into the risk of death from colorectal cancer.

Importantly, I was unable to examine long-term mortality by stage because these data were missing in our cancer registry. Previous research has shown that women diagnosed with early stage EOC are less likely to die from ovarian cancer [133], but this has never been examined by histotype. Future research should examine whether stage influences long-term mortality differently by histotype. The high number of deaths from unclassified causes is unexpected and may reflect inaccuracies or missing information in the death certificates for some of those women. To limit this possible bias, our main analysis compared ovarian cancer specific mortality to all other causes of death.

The results of this study have implications for clinicians and ovarian cancer patients. The findings can help clinicians better understand the differences in outcomes among women with ovarian cancer based on histotype, age at diagnosis and *BRCA* status.

Chapter 4: Causes of death among women with epithelial ovarian cancer by length of survival post-diagnosis: A population-based study in British Columbia, Canada

4.1 Introduction

Ovarian Cancer is the most lethal gynecologic cancer with a 5- year survival rate ranging between 40 and 45% [150]. It is the fifth most common cause of cancer-related deaths among Canadian women [5]. While 5-year survival rates are better when ovarian cancer is detected in Stages I and II, the majority of women are diagnosed in advanced stages (Stage III and IV), due to its asymptotic presentation in early stages [133]. There is also no effective screening method for ovarian cancer. Despite considerable international effort to develop one [94-97], no screening trial to date has reported a significant reduction in mortality [160].

Among cancer patients, the most common cause of death within 5 years of diagnosis is cancer itself. However, as the length of time from diagnosis increases, the risk of death from cancer significantly decreases, and patients begin to die from other causes [133]. Largely because 5-year ovarian cancer survival rates have remained relatively low, little attention has been paid to long-term ovarian cancer survivors. Most studies examining ovarian cancer survivors have focused on improving their quality of life and reported primarily on psychosocial and emotional needs [130-132,161]. The most commonly reported health issues among long-term ovarian cancer survivors are bowel obstruction, bladder dysfunction, gastro-intestinal side effects, and peripheral neuropathy [130]. However, the research on the health of ovarian cancer survivors remains sparse.

Understanding whether ovarian cancer survivors are at increased risk of dying from causes other than ovarian cancer compared to the general population can improve our understanding of the health consequences they face, which can in turn improve follow-up and care provided to ovarian cancer patients. Therefore, I examined the causes of death among women diagnosed with ovarian cancer between 1990 and 2014 in BC. In particular, I focused on long-term ovarian cancer survivors (women surviving for 5 to 9 and 10 or more years after their ovarian cancer diagnosis) and compared their causes of death with those of women in the general population following age-standardization.

4.2 Methods

4.2.1 Study context

British Columbia has a provincially administered, universal medical and hospital health insurance program that is implemented and governed by the province and performs according to the specified conditions and criteria established in the Canada Health Act. It covers everyone residing in the province (4.6 million Canadians) and the provincial ministry of health collects detailed health data, which is regularly made available for research purposes.

4.2.2 Data sources

I built a population-based cohort of all women diagnosed with ovarian cancer between 1990 and 2014 using data from the BC cancer registry [139], vital statistics data [140], and the BC Ministry of Health (the consolidation file)[156]. The BC Cancer Registry is a population-based registry of all cancers diagnosed in British Columbia resident that contains personal and demographic information, and information about the specific cancer diagnosis. The vital statistics death file is an extract of the deaths registration file provided by British Columbia vital

statistics agency. It contains information on all deaths in BC, including underlying cause of death (the primary condition that lead to death) and the exact date of death. The consolidation file contains information on individuals receiving health services and/or individuals eligible to receive health services in British Columbia, Canada. It contains demographic and regional information on every individual residing in British Columbia. With the permission of all relevant data stewards, and ethics approval from the University of British Columbia's behavioural research ethics board, all these data were retrieved from PopData BC [157]. All inferences, opinions, and conclusions drawn are those of the authors and do not reflect the opinions or policies of the Data Stewards.

4.2.3 Study cohort

I examined a population based- cohort of women diagnosed with epithelial ovarian cancer (EOC) between 1990 and 2014 in British Columbia (BC). The International Statistical Classification of Diseases and Related Health problems: tenth revision (ICD-10) was used to identify women with ovarian cancer with the code of C56.0 (ovary), and C57. 0 (fallopian tube) in the British Columbia cancer registry. To ensure I had complete follow-up on women included in our cohort and to prevent misclassifying women as alive if they were not recorded in the death registry but had actually moved out of the province and then perished, I required that women be registered for health care in BC for at least 5 years after their diagnosis. I stratified women into three groups. The first group contained all the patients diagnosed with EOC between 1990 and 2014. The second group, (drawn from the first) includes only women who survived 5-9 years following their ovarian cancer diagnosis, while the third group contains women who have survived ovarian cancer for 10 years or more post diagnosis.

Deaths in the general population were obtained from publicly available tables, publishing sex-specific death rates for the BC population by detailed causes of deaths (https://www2.gov.bc.ca/gov/content/life-events/statistics-reports/annual-reports). I averaged across three time periods (2005, 2010 and 2015) in order not to rely too heavily on one specific year of data.

4.2.4   Assessment of causes of death

Among ovarian cancer patients, I classified the underlying cause of death (UCOD) using ICD-10 categories. The UCODs were classified into specific categories such as ovarian cancer, 'other' cancers (lung cancer, breast cancer, colorectal cancer, etc.), cardiovascular diseases (rheumatic, hypertension, heart failure etc), other chronic conditions (diabetes, COPD, other infectious and parasitic disease, cerebro and other vascular disease etc), external causes (motor vehicle accidents, poisoning, falls, suicide, other unintentional injuries etc), and unclassified causes (causes of death that did not fall into any of the above categories) (Appendix B). Patients were classified as having died from ovarian cancer if the cause of death was reported as ovarian cancer or a cancer likely related to ovarian cancer (which included deaths from neoplasm of uterus, cervix, placenta, ovary and adnexa, vagina, external genitalia and cancer without specified site following an initial diagnosis of ovarian cancer). The publicly available death tables had enough detail to use these same groupings for causes of death among the general population.

4.2.5   Statistical Analysis

Women diagnosed with EOC were monitored as of the date of their diagnosis until their death or until December 31st, 2014 (the end of follow up period). I calculated the length of survival from the date of ovarian cancer diagnosis to the date of death or the end of follow-up.

Causes of death (COD) analyses were stratified based on age categories (<45, 45-64, 65-79, 80+). Age-standardized mortality ratios (SMRs) with two- sided 95% confidence interval (95% CI), were calculated to assess significant differences in causes of death between the women with ovarian cancer and the general population. All analyses were performed with R version 3.3.2 [158].

4.3   Results

A total of 6,975 women were identified as having been diagnosed with ovarian cancer between 1990 and 2014 in British Columbia. After excluding women who did not have EOC (n=407), and after excluding women who were not captured in the death registry and were not registered for health care in BC for at least 5 years post diagnosis (n= 141), 6427 were included in our study.

The clinical characteristics of BC women diagnosed with EOC between 1990 and 2014, including long-term survivors of EOC are outlined in Table 1. Of the 6427 women with ovarian cancer, 810 patients survived for 5-9 years and 962 women survived for 10 years or more (10+ years). The median age of diagnosis was around 60 among all EOC patients (63; SD, 15) and EOC patients surviving 5 to 9 years (59.5; SD, 14.1). However, the median age of diagnosis for EOC patients surviving 10+ years was 52.5 years (SD, 14.6). The rate of women diagnosed under 45 years (24.7%) was more than double in the group surviving 10+ years compared to all EOC patients (11.1%). While the number of deaths among all EOC patients (66.1 %) was high, only 18.3 % of EOC patients surviving 10+ years died by the end of follow-up (Table 1).

Table 8: Clinical characteristics of the study cohort.

	All EOC patients (N= 6427)	EOC patients surviving 5-9 years (N= 810)	EOC patients surviving 10+ years (N= 962)
Age by end of follow-up (2014), **n** (%)			
<45	364 (5.7)	45 (5.6)	56 (5.8)
45 – 64	2204 (34.3)	321 (39.6)	278 (28.9)
65 – 79	2566 (39.9)	296 (36.5)	406 (42.2)
80+	1295 (20.1)	146 (18.0)	222 (23.1)
Age at diagnosis, **n** (%)			
<45	714 (11.1)	110 (13.6)	238 (24.7)
45 – 64	2665 (41.5)	394 (48.6)	529 (55.0)
65 – 79	2228 (34.7)	260 (32.1)	169 (17.6)
80+	820 (12.8)	46 (5.7)	26 (2.7)
Age at diagnosis median (SD)	63 (15)	59.5 (14.1)	52.5 (14.6)
Year of diagnosis mean (SD)	2002.5 (7.1)	2003.3 (5.8)	1997.3 (4.3)
Deaths, n (%)	4246 (66.1)	417 (51.5)	176 (18.3)
Year at Death mean(SD)	2003.6 (6.7)	2005.9 (5.4)	2008.9 (3.7)

Table 8 displays calculated age-standardized SMRs. All- cause mortality among all the

EOC patients, under the age of 45, was 886 times higher than the mortality in the age-

standardized general population (SMR= 886; 95% CI, 748.1 - 1042). And mortality from all-

causes among the EOC patients, under the age of 45, surviving 5 to 9 years was 421 times higher

than the mortality in the age- standardized general population (SMR= 421; 95% CI, 195.5 –

799.6). The SMRs observed among EOC patients surviving 10+ years were considerably

smaller. For instance, among women aged 45 years or less surviving 10+ years, the SMR was 83

(95% CI, 14 – 275.3), and dropped to 5 (95% CI, 3.8 – 5.7) among those aged 80 years or older

surviving 10+years.

Table 9: Standardized Mortality Ratios (SMRs) in women with ovarian cancer according to years of survival post-diagnosis by age.

Age group (years), SMR (95% CI)	SMR all EOC patients	SMR EOC patients surviving 5-9 years	SMR EOC patients surviving 10+ years
<45	886 (748.1 – 1042)	421 (195.5 – 799.6)	83 (14 – 275.3)
45 – 64	187 (176.8 – 197.4)	133.7 (112.3 – 158.1)	27 (17.5 – 39.7)
65 – 79	47 (44.7 – 49.0)	38 (32.7 – 44.3)	11 (8.3 – 13.6)
80+	9.8 (9.2 – 10.4)	9 (7.4 – 10.8)	5 (3.8 – 5.7)

Abbreviations: CI, confidence interval.

The number of deaths in all the study cohorts and in the general population, stratified by causes is reported in Table 9. By the end of this study, 55.9% of all the EOC patients had died from ovarian cancer, and 33.9% were still alive. Of those women who had died of causes other than ovarian cancer (10.2%), 4.8% died from other cancers, 1.8% died from cardiovascular diseases, 1.8% died from other chronic conditions, 0.3% died from external causes and 1.5% died from unclassified causes. Among EOC patients surviving 5 to 9 years post diagnosis, 37.9% died from ovarian cancer by the end of follow-up and 48.5% were alive. The second most common cause of death was other cancers, representing 5.6% of women who died. In all the groups of women with EOC, the greatest number women alive at the end of follow-up were among EOC patients surviving 10+ years post diagnosis (81.7%). Among these women, 6.4% died from ovarian cancer by the end of follow-up. The next most common causes of death were other cancers (3.3%) and cardiovascular diseases (2.8%). Ovarian cancer was the leading cause of death among all women with EOC, regardless of years of survival since diagnosis.

Table 10: Causes of death among women with ovarian cancer and in the general population

Cause of death, N (%)	All EOC patients (N=6427)	EOC patients surviving 5-9 years (N = 810)	EOC patients surviving 10+ years (N = 962)	General population (N = 2242627)
Alive	2181 (33.9)	393 (48.5)	786 (81.7)	2228849 (99.4)
Ovarian cancer	3592 (55.9)	307 (37.9)	62 (6.4)	0 (0)
Other cancers	310 (4.8)	45 (5.6)	32 (3.3)	4344 (0.2)
CVD	116 (1.8)	18 (2.2)	27 (2.8)	4776 (0.2)
Other chronic	114 (1.8)	24 (3.0)	18 (1.9)	909 (0)
External cause	20 (0.3)	4 (0.5)	8 (0.8)	562 (0)
Unclassified	94 (1.5)	19 (2.3)	29 (3.0)	3187 (0.1)

Abbreviations: N, sample size of the cohort; CVD, cardiovascular diseases.

Cause specific SMRs in women with ovarian cancer are outlined in Table 10. When compared with the general population, women with ovarian cancer were more likely to experience death from ovarian cancer, and other causes (other cancers, cardiovascular diseases, other chronic conditions, external causes and unclassified causes) regardless of length of survival since diagnosis. Women with EOC were 28 times more likely to die from all causes than women of the same age in the general population (SMR= 28; 95% CI, 26.9 – 28.5). Among EOC patients surviving 5 to 9 years post diagnosis, all cause mortality rate was 24 times higher than in the age-standardized general population (SMR= 24; 95% CI, 21.5 – 26). Women surviving 10+ years since their ovarian cancer diagnosis were still at higher risk of death than would be expected based on the age-standardized general population (SMR= 7; 95% CI, 5.9 – 8).

Table 11: Standardized Mortality Ratios (SMRs) in women with ovarian cancer by years of survival post diagnosis according to cause of death.

Cause of death, SMR (95% CI)	All EOC patients	EOC patients surviving 5-9 years	EOC patients surviving 10+ years
All causes	28 (26.9 – 28.5)	24 (21.5 – 26)	7 (5.9 – 8)
Other cancers	8 (7.4 – 9.2)	10 (7.6 – 13.6)	5 (3.7 – 7.3)
CVD	2 (1.8 – 2.7)	3 (1.9 – 4.7)	3 (2.1 – 4.4)
Other chronic	4 (3.5 – 5.1)	8 (5.1 – 11.4)	4 (2.4 – 6.2)
External cause	5 (3.2 – 7.8)	9 (2.8 – 21.2)	12 (5.8 – 23.7)
Unclassified	3 (2.4 – 3.6)	1 (0.7 – 1.7)	1 (0.8 – 1.6)

Abbreviations: CI, confidence interval; CVD, cardiovascular diseases.

The SMRs for specific causes of death indicate that women diagnosed with EOC are significantly more likely to die from other cancers and external causes than those in the age-standardized general population, with SMRs of 5 or higher across all ovarian cancer groups. The SMRs for other cancers indicates that risk of death from other cancers was significantly higher compared to what would be expected in the general population among those surviving 5-9 years after their diagnosis (SMR=10; 95% CI, 7.6 – 13.6), and the same was true for external causes (SMR=9; 95% CI, 2.8 – 21.2). Women surviving 10+ years since their EOC diagnosis had the highest SMR for deaths from external causes (SMR=12; 95% CI, 5.8 – 23.7), followed by SMR for other cancers (SMR= 5; 95% CI, 3.7 – 7.3).

4.4   Discussion

Unsurprisingly, our study found significantly higher all-cause mortality among women with ovarian cancer compared with what would be expected in an age-standardized general

population. However, this differed significantly based on age and the number of years a woman had survived since her ovarian cancer diagnosis. The SMRs for all EOC patients stratified by age paint a clear picture of how devastating a diagnosis of ovarian cancer is—EOC patients under age 45 years had 886- fold increase in mortality from all causes compared with the general population, followed by 187- fold increase among those between 45 and 64 years, 47- fold increase among those between 65 and 79 years and 9.8- fold increase among those aged 80 years or older.

I also found that ovarian cancer remains the leading cause of death for all women diagnosed with EOC regardless of time since diagnosis. When compared with the general population, the next highest number of deaths were from other cancers, followed by deaths from external causes and deaths from other chronic conditions. Deaths from other cancers can largely be explained by deaths from breast cancer (15.8%), lung cancer (12.3%), and colorectal cancer (11%). Of note, the mortality associated with external causes were predominately deaths from falls (44.4% of deaths associated with external causes were deaths from falls). Deaths from other chronic conditions are primarily due to cerebro and vascular diseases, chronic obstructive pulmonary disease (COPD), and diabetes. Among long term survivors of EOCs, deaths from other cancers and external causes were particularly problematic with SMRs of 5 or higher in all groups; however, the mean age of the women dying from falls was 91.9 (SD: 7.9) years for EOC patients surviving 10+ years and this is based on 8 EOC women, so the result should be interpreted with caution.

Our results are consistent with those previously reported using Surveillance Epidemiology and End Results (SEER) data. As per the Dinkelspiel et al study using SEER data [133], the risk of ovarian cancer- related death decreases as the time since diagnosis of ovarian cancer

increases. I observed that the proportion of deaths from ovarian cancer decreased dramatically with increased years since diagnosis. The SEER study also reported that other causes of death (e.g. cardiovascular diseases, other cancers, and other chronic conditions) surpassed ovarian cancer as the leading cause of death 15 years after diagnosis among women with advanced EOCs. To this existing literature, I have shown that women diagnosed with EOC remain at increased risk for virtually all causes of death (except unclassified causes) compared with the general population. While the SMRs become smaller as years since diagnosis increase, even long-term survivors are at increased risk of death from other cancers, other chronic conditions, cardiovascular disease and external causes.

Prior to this investigation, little was known about the all- cause specific mortality and cause specific mortality among patients with EOC compared with the general population. However, previous studies have described major health conditions experienced by women after an ovarian cancer diagnosis. Women with ovarian cancer, particularly women of 50 years or under, were observed to have an increased risk of ischemic stroke post diagnosis [162]. Another study reported higher incidence of venous thromboembolism among women with ovarian cancer [163]. Moreover, previous research has illustrated that women with ovarian borderline tumors are at increased risk of colorectal cancer and breast cancer (although this result was not statistically significant) [164,165]. Our study also revealed a considerable number of women with ovarian cancer who died from colorectal cancer (11%). I also observed a large number of deaths from breast cancer (15.8%) and lung cancer (12.3%). In fact, other cancers were a leading cause of death among long-term ovarian cancer survivors after ovarian cancer. Moreover, the mortality risk from other chronic conditions was primarily attributable to deaths from

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cerebrovascular disease, disease of arteries and veins, hypotension and other circulatory system disease (37.7%).

Our study is strengthened by using several large population-based datasets dating back to 1990 in British Columbia. However, the study is not without limitations. First, the death certificates in British Columbia include codes for contributing causes of death. Herein I have considered only underlying cause of death, and there is likely some amount of misclassification as it can be arbitrary to assign a single cause to some deaths. Second, while I chose to report major groups of causes of deaths, I ended up with nearly 100 deaths that were from unclassified causes. Larger studies in the future may want to further categorize to detect any meaningful trends in 'unclassified' causes of death that our study has missed. Third, the new era of ovarian cancer research has illustrated the importance of histotype-specific research. Ovarian cancer is not one single disease, but five distinct diseases, with important clinical differences (i.e. high-grade serous, mucinous, endometrioid, clear cell, and low-grade serous ovarian carcinoma) [10,12,13]. While I was unable to classify our study cohort based on histotype due to small sample size, future research should examine age and cause specific SMRs stratified by histotype.

Our study has implications for women with ovarian cancer and their clinicians. The findings can help clinicians better understand the differences in mortality risk among women with ovarian cancer based on age and years since diagnosis. For example, I show that risk of death from other cancers was high in all groups when compared with the general population, and looking in further detail, our data suggest that breast, lung and colorectal cancer are especially common among women with a previous EOC diagnosis. If corroborated by future research, more careful screening for these cancers could be considered among women surviving 5 or more years since their ovarian cancer diagnosis. Women surviving their ovarian cancer were also at

increased risk of death from external causes, primarily explained by deaths from falls. While numbers were small and thus should be interpreted with caution, if corroborated in future research, factors leading to deaths from falls among long term survivors would be worth exploring in future studies.

Our results also illustrate the continued devastation of, ovarian cancer, as it remains the leading cause of death among women with EOC, regardless of how many years they have survived since their diagnosis. However, women surviving 10 or more years since their EOC diagnosis were nearly twice as likely to die from another cause than to die from their ovarian cancer.

Chapter 5: Conclusion

Ovarian cancer is the deadliest cancer of the female reproductive system. However, some sparse evidence has hinted at a possible improvement in survival rates over the past few decades [5,126]. It is important to understand whether survival rates are increasing among ovarian cancer patients, as historically very little attention has been paid to understanding the long-term health consequences and challenges faced by ovarian cancer survivors, likely a result of the poor 5-year survival rates for women with this disease. If women are, in fact, surviving their ovarian cancer at higher rates and for longer times, that suggests that research on survivorship should be given a higher priority. It is also important to update survival rates in order to provide accurate counsel to patients. At present, epidemiological evidence investigating possible outcomes among women with ovarian cancer and among women surviving ovarian cancer is limited.

Previously it was believed that ovarian cancer originated from the ovarian surface epithelium. However, this is not true for all histotypes of EOCs and different histotypes can have different cellular origins [166]. For instance, most high- grade serous cancers appear to originate in the fallopian tube, and clear cell and endometrioid ovarian cancers appear to originate from endometrial cells [167]. Owing to such drastic differences in molecular features, ovarian cancer is not considered a single disease. There are five main distinct histotypes of EOC- high- grade serous, low- grade serous, endometrioid, clear cell and mucinous cancers with varying clinical behavior (genetics, treatment response and survival) [13,37]. At present, limited data is available that could reflect this new understanding of the diversity of ovarian cancer. This histotype-specific information is needed to better understand the differences in epidemiological features across histotypes, which may be effective in improving clinical outcomes from EOC.

The primary goal of this thesis was to address these current gaps in ovarian cancer epidemiology, with a focus on understanding how survival varied by histotype. This concluding chapter is structured to answer four questions. First, what were the key findings and implications of this thesis? I briefly summarize the results and implications of the three studies presented in this thesis (chapter 2 to 4). Second, how have these findings have contributed to the existing literature? Third, what were the main strengths and limitations of the work presented in this thesis? Fourth, what are the recommendations for future research that stem from this thesis?

5.1 Summary of key findings and implications

The objectives of this thesis were to: 1) evaluate the incidence rates and survival rates (1-year, 3- year and 5- year overall and disease specific survival rates) of women with epithelial ovarian cancer (EOC) in British Columbia (BC) between 1980 and 2015 and to conduct histotype-specific analysis of survival rates; 2) determine the causes of death among women with epithelial ovarian cancer by histotype, age at diagnosis and *BRCA* status and examine when other causes of death surpass ovarian cancer as the leading cause of death following diagnosis; 3) compare causes of death among women with epithelial ovarian cancer according to length of survival post-diagnosis with the causes of death among ovarian cancer- free women in the general population of the same age group.

5.1.1 Trends in incidence and survival rates among women with epithelial ovarian cancer in British Columbia, 1980- 2015.

In chapter 2, 'Trends in incidence and survival rates among women with epithelial ovarian cancer in British Columbia, 1980- 2015', I presented the most recent statistics on incidence and survival (overall survival and disease specific survival) of ovarian cancer in British Columbia.

These estimates were also studied to evaluate the incidence and survival of different histotypes over time.

I observed declining incidence rates of ovarian cancer between 1980 and 2015 for all women with EOCs. This declining trend might be explained by the increased use of oral contraceptive pills (OCP) in Canada since the 1960's, which is a well-established protective factor for ovarian cancer. Another factor that may have contributed to this decline are changing rates of gynecological surgeries, for e.g. hysterectomy and tubal ligation. These surgeries reduce the risk of ovarian cancer and increased during key parts of our study period that would affect incidence rates. I expect that more recent decreasing rates of hysterectomy and tubal ligation will be more than offset by the risk reduction of opportunistic salpingectomy, a surgical practice change that occurred far too late to be reflected in our incidence statistics but will likely reduce future incidence of EOC in British Columbia. With respect to histotype- specific incidence, I found a slight increase in the incidence of endometrioid and clear cell EOCs, whereas a declining trend was reported for serous and mucinous EOCs.

This study also showed an increasing trend of 1- year, 3- year and 5- year overall and disease specific age- standardized rates for epithelial ovarian cancer over the past 35 years. When examining the increasing survival rates for all EOCs, I suspect that it was driven by the increasing proportion of endometrioid and clear cell cancers over time, which both have better survival outcomes than serous cancers and advanced stage mucinous cancers[148].

In all, I reported a positive picture of ovarian cancer in British Columbia. Previously, not many population-based studies have provided incidence and survival statistics by histology in Canada. This study is able to give insights into the progress against ovarian cancer from a histotype- specific perspective.

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5.1.2   Long-term mortality among women with epithelial ovarian cancer in British Columbia, 1990- 2014

In chapter 3, 'Long-term mortality among women with epithelial ovarian cancer in British Columbia, 1990- 2014', I studied the most common causes of death among women with epithelial ovarian cancer by histotype, age at diagnosis and *BRCA* status. Specifically, I focused on evaluating the duration of time in which ovarian cancer is the leading cause of mortality following diagnosis. Among BC women with EOC, ovarian cancer is the leading cause of death for 10 years post diagnosis before deaths from other causes surpass it. I also report that: 1) women with serous EOCs are more likely to die from ovarian cancer than any other cause for 12 years in comparison to 8 years among women with non- serous EOCs; 2) women with non-serous EOCs are more likely to die from causes other than ovarian cancer compared to women with serous EOCs; 3) Among older women (60 years or older) with serous EOCs, death from other causes surpasses ovarian cancer as the leading cause of death at 8 years post diagnosis. Whereas, younger women (under 60 years) with serous EOCs had ovarian cancer as the leading cause of death for 12 years post diagnosis. These histotype-specific findings have not been reported elsewhere.

The results of my study display a timeline when risk of mortality from ovarian cancer decreases enough to be surpassed by other causes during the clinical course of the disease. This timeline can be used, when combined with further research such as that done in Chapter 4, to inform follow-up and management of women who have survived their ovarian cancer for more than 5 years.

5.1.3 Causes of death among women with epithelial ovarian cancer by length of survival post-diagnosis, 1990 – 2014.

Chapter 4, 'Causes of death among women with epithelial ovarian cancer by length of survival post-diagnosis, 1990 – 2014', investigate the causes of death among women with EOC, stratified by years since diagnosis and compares these with causes of death in an age-standardized population of women who were never diagnosed with ovarian cancer, using standardized mortality ratios (SMR). When compared with an age-standardized general population, all- cause and cause- specific SMRs among women with EOC, including women surviving 5 to 9 years post diagnosis and women surviving 10 years or more post diagnosis, were significantly higher compared to what would be expected in the general population. This was not surprising given the high mortality rate of EOC.

More interesting were the results among women who had survived their ovarian cancer for 5-9 and 10+ years. I report that among women who have survived their ovarian cancer at least 5 years, women with a previous diagnosis of ovarian cancer were significantly more likely to die from other cancers, deaths from external causes and from other chronic conditions compared to age-standardized women who had never been diagnosed with ovarian cancer. Women who had survived their EOC for 5-9 or 10+ years were particularly at risk for from breast cancer (15.8%), lung cancer (12.3%), and colorectal cancer (11%). These women were also at increased risk for death from external causes, the majority of which were from falls (44.4%). Deaths from chronic conditions can largely be explained by deaths from cerebral and vascular diseases (45.9%), chronic obstructive pulmonary disease (COPD) (16.2%), and diabetes (8.1%).

I focused mainly on the causes of death with an SMR value of 5 or more (deaths from other cancers and external causes). These causes of death represent areas of important future

inquiry to inform surveillance among women surviving their ovarian cancer for 5 or more years. The findings can assist affected women and their health care providers in facilitating timely intervention to augment survivors long- term health. In particular, our research suggests that long- term survivors may benefit from closer surveillance for breast, lung and colorectal cancer. Also, careful attention to bone health may be helpful in this population.

5.2   Research contribution to literature

In the context of epidemiological research in Canada, the survival statistics of ovarian cancer are limited, particularly data for trends over time by histotype. Also, there is little information on how survival from ovarian cancer would impact the long- term health among women with EOC and/or among women at risk of developing EOC. Health care practitioners, specifically gynaecologic oncologists have affirmed that there is a need for updated statistics that could reflect differences in survival outcomes across ovarian cancer histotypes. Furthermore, a better understanding of long- term health conditions among ovarian cancer survivors could be used to assist evidence- based clinical practice and to improve quality of life in long- term survivors of ovarian cancer.

Chapter 2 reported the most- current trends in incidence and survival in ovarian cancer in a Canadian setting. Additionally, it is the only BC- specific study that reports these trends by histotype. This study contributed to the existing literature by evaluating incidence and survival rates over the span of 35 years. As a result, my study sample covered a long time period than previous work, including women diagnosed between 1980 and 2015[5,126].

The results presented in chapter 3 represent a Canadian study on long- term morality among women with EOC. This work was possible because I had access to high quality

administrative datasets, containing information on histotype, age at diagnosis, *BRCA* status, and causes of death for all BC women diagnosed with EOC. A similar study was done by H.E. Dinkelspiel et al in the US, evaluating the causes of death among long- term ovarian cancer survivors by stage and years since diagnosis. This research included women with EOC diagnosed between 1980 and 2012. In my research, I focused primarily on recently diagnosed cohorts of women in BC (1990 – 2014), providing more recent assessment on causes of death among long-term ovarian cancer survivors, with an additional benefit of evaluating mortality in the context of ovarian cancer histotypes.

Among women with EOC and a *BRCA* mutation, few deaths from causes other than ovarian cancer were reported. In particular, I observed a low incidence of death from breast cancer among these *BRCA* mutation carriers. Deaths attributed to breast cancer among women with serous EOCs and a *BRCA* mutation were only 4% among these women. This informs clinicians that rushing to mastectomy among *BRCA* null women with EOC is unlikely to offer a significant survival advantage. While my study is not the first one to report low breast cancer incidence among women with EOC and a *BRCA* mutation, it is the first one to implement histotype- specific approach to estimating breast cancer risk among women with EOC and a *BRCA* mutation.

Chapter 4 offers a greater understanding on causes of death among women with EOC, particularly among women surviving their ovarian cancer by comparing them to the causes of death in an age-standardized population of women without ovarian cancer. This type of investigation is a first step to painting a more complete picture on the possible adverse outcomes following ovarian cancer diagnosis, and to informing a more appropriate and specific way of following up with women who survive their ovarian cancer for at least 5 years.

As a whole my thesis indicates that 1- 3- and 5-year survival rates have improved in BC over the past 35 years (although this is a largely a result of an increasing distribution of non-serous cancers). Regardless, this increases the importance of understanding the challenges faced by ovarian cancer patients who survive their cancers. Chapter 3 examining when other causes of death overtake ovarian cancer as the leading cause of death suggests that after surviving 12 years for women with serous cancer and 8 years for women with non- serous cancers, women are more likely to die from causes other than ovarian cancer. This can have important implications for follow-up in this group of women. While vigilance for recurrences of their ovarian cancer is still required, they also need to pay attention to other leading causes of death. Chapter 4, presenting SMRs for women who survived 5-9 and 10+ years following their diagnosis points to a few specific areas that warrant increased vigilance in women surviving their ovarian cancer for extended periods of time. Most notably, I report significantly higher risk of death from breast cancer, lung cancer, and colorectal cancer, all of which are cancers that have effective screening methods. Thus, if these findings are replicated in other populations, future work could examine whether women surviving their ovarian cancer for more than 5 years would benefit from enhanced screening for these cancers. Other noteworthy findings include data on minimal risk of breast cancer after ovarian cancer diagnosis among *BRCA* mutation carriers. This information is aimed at clinicians, suggesting that preventive mastectomy (surgical removal of breasts to prevent breast cancer) need not be rushed among women with ovarian cancer and a *BRCA* mutation.

5.3 Strengths and limitations

I have included a discussion on the strengths and limitations associated with the methods and the data used in each of the research chapters (Chapter 2 to 4). This section underlines the strengths and limitations of the thesis as a whole.

5.3.1 Limitations

First, there were considerable number of women with EOC who were not classified in any histotype category in my study. For instance, 22.4% cases were unclassified among women diagnosed between 1980 and 2015 (chapter 2) and 29.8% cases were unclassified among women diagnosed between 1990 and 2014 (chapter 3 and chapter 4). This reduces power to understand the differences between histotypes, and creates this large unclassified category of EOCs for which we can draw few conclusions. Second, there have been considerable changes in the classification of EOC histotypes over the past decade. For instance, a study evaluating the diagnostic shift in histotype classification re-reviewed 286 pathology specimens in 2014, which were previously examined in 2002. Only 54% of cases were rendered the same ovarian cancer histotype when re-reviewed in 2014. In contrast, 98% of these cases were assigned the same histotype independently by two gynecopathologists using 2014 WHO diagnostic criterion [12]. Further changes include the fact that the most recent 2014 WHO diagnostic classification guidelines relabeled high- grade endometrioid, transitional and undifferentiated tumors as high grade serous EOCs [167]. Recently, this EOC histotype classification was further refined using immunohistochemical tests [37]. Cases that were defined prior to the new WHO guidelines and/or immunochemical tests may have been misclassified or not classified at all, and there is good reason to believe that misclassification of histotypes would be considerably higher in the earlier years of our study period.

Third, despite my best efforts to present histology-specific estimates in this thesis, I was frequently forced to combine endometrioid, clear cell and mucinous cancers into a non-serous category. Given that these are three distinct diseases, I was missing important nuance and distinction by combining these groups. Future work should combine data from BC with data from other provinces in order to properly study each of these histologic subtypes separately. Fourth, this work was conducted using BC- specific datasets, hence there are some questions about the generalizability to other provinces of Canada. However, I expect that most results would apply beyond British Columbia.

5.3.2   Strengths

Despite these limitations, there are some notable strengths of the studies presented. One of such important strengths is the inclusion of data on the entire population of British Columbia diagnosed with EOC, thus eliminating any source of selection bias. By using the population-based administrative data, I was able to eliminate biases related to self- reported data such as recall bias and non- response biasMuch of this work was possible by merging the datasets: the BC Cancer Registry, Vital statistics data, BC Cancer hereditary cancer program, and BC Ministry of Health file (the consolidation file). All the studies reported in this thesis are built on de-identified data; ensuring confidentiality of all the women involved in my research.

5.4   Recommendations for future research

Recommendations specific to each of the study findings have been highlighted in each of the research chapter (chapter 2 to 4). However, there are several recommendations that should be taken into consideration in future research. First and foremost, studies should be conducted to update statistics of ovarian cancer at the national level. This is important given the changing trends of ovarian cancer and introduction of advanced treatment strategies. Future research

should validate the findings in this thesis after properly classifying the histotypes of the cancers that I considered 'unclassified or other' in this thesis. By properly classifying these cases, I could identify differences in survival by histotype with increased power [167].

In Chapter 1, my results report the latest trends in ovarian cancer incidence and survival among women with EOC in BC. However, further research on how changes in the patterns of OCP use, which have been shown to be protective against ovarian cancer [168], have impacted ovarian cancer incidence over time would be insightful. There has been considerable changes in OCP formulations (decreased doses of estrogen and inclusion of progastrin), usage among different age- groups, and intake patterns (monthly v/s continuously cycles), and there is limited evidence regarding whether the protective effects of OCP against ovarian cancer reported in earlier studies will remain after accounting for all of these important changes in modern day OCP use [167].

The findings in Chapter 3 suggest variations in outcomes of ovarian cancer based on histotype, and age at diagnosis. For instance, among older women (60 years or older) with serous EOCs, death from other causes surpasses ovarian cancer as the leading cause of death at 8 years post diagnosis. Further research on whether this timeline differs based on stage, and grade information would be helpful. Better understanding regarding the combined effects of stage, grade and histotype data on outcomes following ovarian cancer diagnosis would be useful for counselling patients at the time of diagnosis.

As observed in Chapter 4, all- cause and ovarian cancer- specific mortality risks among women with EOC and among women surviving EOC are significantly higher than what would be expected in the general population. While this study has offered insights into possible outcomes, histotype- specific data is needed to reflect new understanding of the heterogenous nature of

ovarian cancer. For instance, a study focused on evaluating SMRs among women with EOC and women surviving EOC based on histotypes would be helpful.

5.5   Conclusions

My thesis suggests that ovarian cancer survival rates are improving over time and that histotype plays an important role in long-term survival. My thesis also reports that other causes of death surpass ovarian cancer as the leading cause of death 10 years after diagnosis among women with EOC. When stratified by histotype, the timeline of mortality from ovarian cancer and other causes differs. For instance, among women with serous EOCs, ovarian cancer was the leading cause of death for 12 years post diagnosis, whereas ovarian cancer was the leading cause of death for 8 years among women with non- serous EOCs.

While continued vigilance for recurrence in women surviving ovarian cancer is important, my research does suggest potential timeframes when women and their providers can feel less concerned about ovarian cancer recurrence. My research also suggests that after survival for 5-9 and 10 plus years there may be reason to increase vigilance for other causes of death, including breast, lung and colorectal cancer. If supported with future research, some enhanced screening for these cancers could potentially result in an even longer survival time for women who survived their ovarian cancer. This may be worth consideration as the quality of life of all women at risk and/or diagnosed with ovarian cancer could be improved by introducing necessary interventions to prevent and/or manage these possible long- term health outcomes of EOC.

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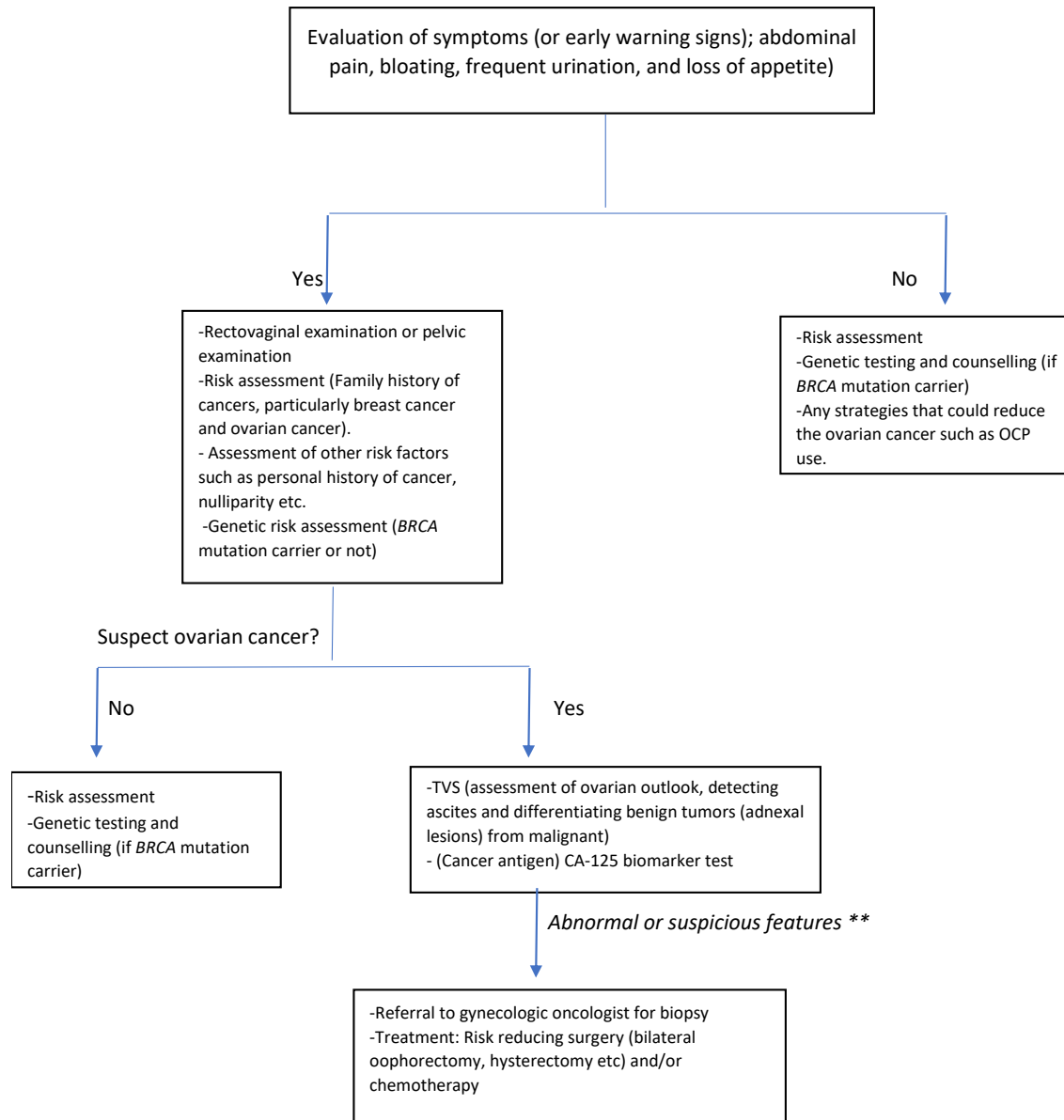
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Appendices

Appendix A   Stepwise diagnostic evaluation of ovarian cancer

```
┌─────────────────────────────────────────────────┐
│ Evaluation of symptoms (or early warning signs); │
│ abdominal pain, bloating, frequent urination,    │
│ and loss of appetite)                            │
└─────────────────────────────────────────────────┘
```

Yes

```
┌─────────────────────────────────────────┐
│ -Rectovaginal examination or pelvic      │
│ examination                              │
│ -Risk assessment (Family history of      │
│ cancers, particularly breast cancer      │
│ and ovarian cancer).                     │
│ - Assessment of other risk factors       │
│ such as personal history of cancer,      │
│ nulliparity etc.                         │
│  -Genetic risk assessment (BRCA          │
│ mutation carrier or not)                 │
└─────────────────────────────────────────┘
```

No

```
┌─────────────────────────────────────────┐
│ -Risk assessment                         │
│ -Genetic testing and counselling (if     │
│ BRCA mutation carrier)                   │
│ -Any strategies that could reduce        │
│ the ovarian cancer such as OCP           │
│ use.                                     │
└─────────────────────────────────────────┘
```

Suspect ovarian cancer?

No

```
┌─────────────────────────────────────┐
│ -Risk assessment                     │
│ -Genetic testing and                 │
│ counselling (if BRCA mutation        │
│ carrier)                             │
└─────────────────────────────────────┘
```

Yes

```
┌───────────────────────────────────────────────┐
│ -TVS (assessment of ovarian outlook, detecting │
│ ascites and differentiating benign tumors      │
│ (adnexal lesions) from malignant)              │
│ - (Cancer antigen) CA-125 biomarker test       │
└───────────────────────────────────────────────┘
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*Abnormal or suspicious features ***

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┌───────────────────────────────────────────────┐
│ -Referral to gynecologic oncologist for biopsy │
│ -Treatment: Risk reducing surgery (bilateral   │
│ oophorectomy, hysterectomy etc) and/or         │
│ chemotherapy                                   │
└───────────────────────────────────────────────┘
```

**CA-125 >200U per mL in premenopausal women or elevated levels in after menopause; volume of ovaries >20mL in non- pregnant

premenopausal women or >10mL at postmenopausal stage;

abnormal or persistent pelvic mass, evidence of abdominal metastasis.

Appendix B Underlying causes of death and their ICD-10 codes

Causes of Death	ICD-10 codes
Ovarian cancer or ovarian cancer related	C510-C58
Breast cancer	C500-C509
Colorectal cancer	C180-C218
Other cancer	Lung: C33, C340-C349, C384, C450; GI: C150-C179, C220-C269; Blood lymph: C810-C969, C463; Other malignancy: C000-C148, C300-C449, C451-C462, C467-C499, C609, C620-C768, C5091, C80; Non malignant and unspecified: D000-D489
Cardiovascular	Rheumatic/Valvular: I050-I099, I340-I38; Hypertension: I10-I159; Ischemic: I200-I259; Conductive & Dysrhythmic: I440-I499; Heart failure: I500-I509; Congenital: Q200-Q249; Pulmonary: I260-I289; Cardiomyopathy: I420-I429; Unspecified: I312-I318, I510-I513, I515-I519
Other chronic	Diabetes: E100-E149; COPD: J440-J449; AIDS/HIV: B200-B24; Pneumonia: J120-J181, J188-J189;

	Other infectious and parasitic disease: A000-B199, B250-B999, U049;
	Asthma: J450-J459, J46;
	Cerebro and other vascular disease: I600-I698, I700-I879, I950-I959, I880-I899;
	Liver disease: K700-K7699;
	Pulmonary fibrosis: J841;
	ALS/MS: G122, G1221, G35;
	Lung disease due to external agents: J60-J709
External causes of death	Motor vehicle accidents (MVA): V020-V049, V090-V099, V120-V149, V190-V196, V200-V799, V803-V805, V820-V821, V823-V839, V840-V878, V880-V888, V8900-V8909,V8920-V8929, V8990-V8999, Y850; Poisoning: X40-X49; Falls: W00-W19; Suicide: X60-X84, Y870; Other external: Y10-Y369, Y890-Y899; Other unintentional injuries: V010, V019, V050-V069, V091, V099, V100-V119, V150-V189, V198-V199, V250-V259, V350-V359, V450-V459, V550-V559, V650-V659, V750-V759, V800-V802, V806-V819, V822, V879, V889, V910-V919, V930-V949, V950-V978, V98-V99, W20-W64, W75-W99, X20-X39, X50-X59, Y40-Y849, Y859, Y86, Y880-Y883
Unclassified cause of death	Codes that did not meet criterion above

Appendix C 1- year, 3- year and 5- year age standardised overall survival rates among women with 'others and unspecified' EOCs, 1980 – 2015
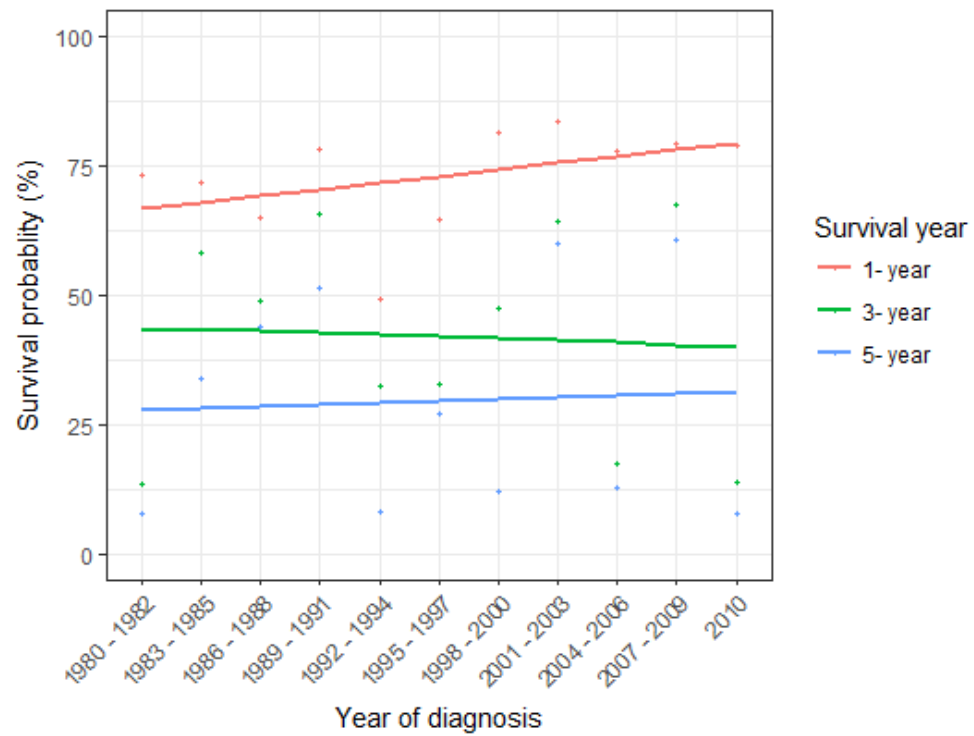
Appendix D 1- year, 3- year and 5- year age standardised disease specific survival rates among women with 'others and unspecified' EOCs, 1980 – 2015