Exploring Opportunistic Salpingectomy as a Preventive Strategy for Ovarian Cancer: Uptake in Newfoundland and Labrador, Canada

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Abstract

Ovarian cancer (OC), the fifth deadliest cancer for women, had an estimated 3,100 cases in Canada in 2023, with a 66% mortality rate and approximately 1,950 projected deaths. High-grade serous carcinoma (HGSC), comprising 75% of OC cases, presents challenges in screening and early detection. Advances in understanding the origins of HGSC led to the identification of serous tubal intraepithelial carcinomas (STICs) in the fallopian tubes, introducing opportunistic salpingectomy (OS) as a preventative measure.

The feasibility, safety, cost-effectiveness, and efficacy of OS have been investigated in multiple studies. A narrative review was conducted to address all these elements by assessing the effect of OS on surgical and post-surgical complications and on ovarian reserve. Overall, the addition of OS to hysterectomy or instead of tubal ligation appears to be safe and feasible. Available retrospective studies demonstrated that OS reduces the risk of OC in the general population by 35% to 65%.

Due to the novelty of this approach, our understanding of the uptake of OS is limited in different clinical settings. The second manuscript presented in this thesis is a quantitative retrospective study that assessed the uptake of OS in Newfoundland and Labrador (NL) between 2010 and 2019. All patients who underwent any or any combination of hysterectomy, salpingectomy, oophorectomy, or tubal ligation were included in the analysis. The number of cases with gynecological cancers following the surgery was also reported for each group. Over the study period, the uptake of OS at the time of hysterectomy and as an alternative to tubal ligation increased by 10.3-fold and 28.1-

fold, respectively. However, despite this upward trend, there is still room to enhance its adoption in NL, Canada.

General Summary

The most common type of ovarian cancer (OC) is high-grade serous carcinoma which is the most lethal type of ovarian cancer. Over the past decades, the realization that OC develops in fallopian tubes offers a way forward for opportunistic risk reduction. Opportunistic salpingectomy is the removal of both fallopian tubes, which shows promising results in OC prevention. Many people who are receiving gynecologic surgery for non-cancerous conditions are candidates for this preventive surgery. This thesis reviewed the evidence about the impact and safety of OS, patterns of practice, and cost-effectiveness. There is no trial evidence to show the efficacy of OS in OC prevention, but the harm is low, and retrospective studies have shown a 35-65% risk reduction in OC in the general population.

This thesis also explores OS uptake in Newfoundland and Labrador (NL) and describes the population who received this surgery across the province between 2010 and 2019. Within the hysterectomy group, the proportion of patients who underwent hysterectomy with OS rose from 1.6% in 2010 to 10.1% in 2019 ($p < 0.001$). In the tubal sterilization cohort, the OS rate increased from 0.6% in 2010 to 16.9% of all tubal sterilizations in 2019 ($p < 0.001$).

Findings from this thesis provide baseline knowledge that can be used to define priority research questions, engage clinicians and researchers, and engage clinical practice and policy leaders in discussions about OS as a feasible and beneficial strategy in Canadian jurisdictions.

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We respectfully acknowledge the territory in which we gather as the ancestral homelands of the Beothuk, and the island of Newfoundland as the ancestral homelands of the Mi'kmaq and Beothuk. We would also like to recognize the Inuit of Nunatsiavut and NunatuKavut and the Innu of Nitassinan, and their ancestors, as the original people of Labrador. We strive for respectful relationships with all the peoples of this province as we search for collective healing and true reconciliation and honour this beautiful land together.

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Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations

ACOG	American College of Obstetricians and Gynecologists
AFC	Antral follicle count
AMH	Anti-müllerian hormone
BC	British Columbia
BMI	Body mass index
BSO	Bilateral salpingo-oophorectomy
CA19-9	Cancer antigen 19-9
CIC	Cortical inclusion cysts
EBL	Estimated blood loss
EOC	Epithelial ovarian cancer
FSH	Follicle stimulating hormone
HBOC	Hereditary Breast and Ovarian Cancer Syndrome
HE4	Human epididymis protein 4
HGSC	High grade srous carcinoma
HREB	Health Research Ethics Board
HRR	Homologous recombination repair

ICD-10	International Statistical Classification of Diseases, 10th Revision
ICD-O-3	International Statistical Classification of Diseases for Oncology, third edition
LGSC	Low grade serous carcinoma
LH	Luteinizing hormone
NL	Newfoundland and Labrador
NLCHI	Newfoundland and Labrador Centre for Health Information
NOS	Not otherwise specified
OC	Ovarian cancer
OR	Odds ratio
OS	Opportunistic salpingectomy
OSE	Ovarian surface epithelium
OVCARE	Ovarian cancer research
PARP	Poly (ADP) ribose polymerase
PDAD	Provincial Discharge Abstract Database
PFS	Progression-free survival
PLCO	Prostate, lung, colorectal and ovarian
PPC	Primary peritoneal cancer
RHA	Regional health authorities

ROCA	Risk of ovarian cancer algorithm
RRBSO	Risk-reducing bilateral salpingo-oophorectomy
SCOUT	Secretory cell outgrowth
SD	Standard deviation
SEE-FIM	Sectioning and extensively examining the fimbrial end of the fallopian tube
STICS	Serous tubal intraepithelial carcinomas
STIL	Serous tubal intraepithelial lesions
TIC	Tubal intraepithelial carcinoma
TL	Tubal ligation
TVU	Transvaginal ultrasound
UKCTOS	United Kingdom Collaborative Trial of Ovarian Cancer Screening
WHO	World Health Organization

Declaration of Publication Intent

Chapter 2 of this thesis, "Beyond Sterilization: A Comprehensive Review on the Safety and Efficacy of Opportunistic Salpingectomy as a Preventative Strategy for Ovarian Cancer," has been published in 'Current Oncology,' an open-access, peer-reviewed journal, in November 2023 (1). Chapter 3, "The Uptake of Opportunistic Salpingectomy in Newfoundland and Labrador, Canada, from 2010 to 2019," has not yet been published in a peer-reviewed journal; therefore, no figures or tables are copyrighted. It will be submitted for publication to an open-access, peer-reviewed journal.

Chapter 1: Introduction and Background Literature Review

Purpose

Ovarian cancer (OC) is the most lethal gynecologic cancer, which affects approximately 3000 people in Canada each year. As such, it is crucial to understand the benefits and feasibility of preventative strategies. The purpose of this chapter is to provide a comprehensive understanding of OC as a complex and heterogeneous disease and to evaluate the role of opportunistic salpingectomy (OS) as a preventive measure by reviewing the existing literature. Additionally, this chapter will identify and discuss the existing research gaps that necessitate the studies conducted in this thesis.

1.1 Ovarian Cancer

OC is the most common gynecological malignancy after cervical and uterine cancers and the most lethal cancer among all gynecological cancers. According to Globocan, the Global Cancer Observatory's online dataset, there were 313,959 new cases of OC globally in 2020, resulting in 207,252 deaths (2). It was estimated that the projected number of OC cases in Canada in 2023 would be 3100, which categorizes it as the 10th most common cancer in women. The projected number of deaths from OC in the same year was 1950, which made it the fifth most lethal cancer in women. The 5-year net survival rate in Canada is reported to be 44% (3). The stage and grade at which the cancer is detected are the most important contributing factors to the prognosis. Unfortunately, about 52% of all OC cases are diagnosed at later stages in which cancer has metastasized in the abdominal cavity, leading to a lower 5-year survival rate of 30% (4).

1.1.1 Etiology

Various risk factors have been associated with OC. The incidence rate of OC varies among different ethnicities. Between 2015 and 2019, the highest incidence rates of OC (per 100,000/ year) in the US were observed among non-Hispanic American Indian/Alaska Native (11.4), non-Hispanic White (11.0), and Hispanic (10.3) ethnic groups, respectively. Non-Hispanic White women experienced the highest mortality rate at 6.9/100,000/ year (5). The likelihood of developing OC increases with age and is predominantly diagnosed post-menopause (6). Factors such as null parity, late age at menopause, and endometriosis are also associated with an increased risk (7). Lifestyle factors, including smoking, alcohol consumption, diet, and obesity, have been identified as predisposing factors (8). However, a family history of breast or ovarian cancer is the most significant risk factor (9). Hereditary OC accounts for approximately 23% of all diagnosed OC cases. Familial genetic mutations in BRCA1 and BRCA2 tumor suppressor genes increase the risk of developing ovarian cancer by 40-45% and 15-20%, respectively (10). In addition to hereditary breast and ovarian cancer syndrome (HBOC), Lynch syndrome also predisposes individuals to a lifetime risk of 3% to 17% developing OC (11).

1.1.2 Histology of Ovarian Cancer

In addition to the stage at diagnosis, the tumor type is a significant predictor of survival rates. OC is divided into three main subtypes based on the type of cell from which it originates: epithelial, germ cell, and sex cord-stromal (12). Overall, germ-cell ovarian cancer, which is a rarer tumor type affecting 2-5% of all OC cases, typically presents at early stages in younger women and is associated with a high survival rate (13).

Epithelial tumors represent the majority of malignant cases, constituting up to 95% of OC cases (4). According to the World Health Organization (WHO) classification guideline (2020), high-grade serous carcinoma (HGSC) and low-grade serous carcinoma (LGSC) are two distinct histological types of epithelial ovarian cancer (EOC). Each has its unique molecular pathways and pathogenesis rather than being on a continuum of the same tumor. This category also includes endometrioid, clear cell, and mucinous histological types (14). Endometrioid and clear cell types each represent about 10% of EOC cases, while mucinous and LGSC are the least common types (15). HGSC is the most common histotype, accounting for over 70% of epithelial OC cases. It is highly invasive with a poor prognosis and is characterized by ubiquitous somatic TP53 mutations (16).

1.2 Screening and early detection:

Early detection of OC is notoriously difficult due to its vague, non-specific early symptoms, such as bloating, nausea, fatigue, and back pain, which are easily missed (17). Compounding this issue is the disease's rapid progression, as it often advances from early to late stages within a year (18). High-risk patients typically undergo transvaginal ultrasound (TVU) or abdominal and pelvic ultrasonography to identify the location, size and shape of the pelvic mass (19). However, tumors in the early stages may remain undiagnosed by ultrasound screening due to their undetectable size (20). Alongside imaging, the CA-125 serum biomarker test is common in OC detection, as elevated CA-125 levels are present in roughly 80% of advanced OC cases. Yet, this test's sensitivity in early disease stages is limited (21).

The Prostate, Lung, Colorectal and Ovarian (PLCO) Screening Trial, which included 78,286 women, revealed that CA-125 screening in combination with TVU achieved a positive predictive

value (PPV) of only 26.5% and did not significantly enhance survival after a 15-year follow-up (22). Similarly, results from the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) on more than 200,000 post-menopausal women using the Risk of Ovarian Cancer Algorithm (ROCA), which includes CA-125 levels at different time points, alongside age, menopause status, and genetic risk factors, also failed to demonstrate a significant survival benefit in the intervention arm (23,24).

The utility of CA-125 as a standalone screening measure is significantly limited by its low PPV, primarily because it can be elevated due to a variety of non-cancerous conditions such as inflammatory processes, pregnancy, ovarian cysts, and endometriosis, leading to an excessive number of false positives (25). Additionally, factors such as age, race, and obesity impact the CA-125 serum levels, resulting in lower specificity in OC diagnosis (26). The heterogeneity of OC as a disease is another reason for the inefficiency of this biomarker since its expression is significantly lower in some subtypes of OC (27). While other serum biomarkers, such as Human Epididymis Protein 4 (HE4) and Cancer Antigen 19-9 (CA19-9), have been explored to enhance diagnostic sensitivity, a truly effective screening strategy to lower OC mortality rates has yet to be established (28). A newer strategy, circulating tumor DNA testing via blood samples, is under investigation in large clinical trials (29).

1.3 Treatment of Ovarian Cancer:

Current treatment guidelines for OC are tailored based on multiple prognostic indicators, such as the age of the patient at diagnosis, general health status, and the stage of the cancer at the time of detection (30). The possibility of complete surgical removal of the tumor and the need for additional chemotherapy are key considerations in clinical decision-making (31). For stage I

ovarian cancer, surgery is the primary treatment, with subsequent adjuvant therapy being determined by factors such as tumor grade, type of cells involved, and whether the tumor involves nearby tissues (32). Results from clinical trials have demonstrated that patients with early-stage OC who present high-risk characteristics, such as stage IC or II disease, along with clear cell or high-grade histological features, who receive platinum-based chemotherapy regimens following the surgery have better survival outcomes (33). For advanced-stage OC, the timing of debulking surgery and chemotherapy as first-line therapy could vary based on age, the burden of the disease, the location of the mass, and comorbidities (34). The residual disease after cytoreduction is one of the strongest predictive factors for extended median survival in patients with stage III or IV OC. Therefore, regardless of whether surgery occurs before or after neoadjuvant chemotherapy, it is highly recommended to aim for maximal debulking.

When comparing cancers of the same stage and grade, those associated with BRCA1 or BRCA2 mutations are observed to have a better response to chemotherapy, which often translates to an extended survival rate, a benefit that persists across both platinum-based and non-platinum treatment regimens (35).

After the completion of initial standard treatments, maintenance therapy is recommended to slow the progress of residual cancerous cells in order to prevent the cancer's recurrence and prolong the remission (36). Continued chemotherapy, hormonal therapy, immunotherapy and targeted therapy are different available options, which are less intensive treatments compared to the initial chemotherapy (37). Although results from trials show that Poly (ADP)-ribose polymerase (PARP) inhibitors as maintenance therapy prolong progression-free survival (PFS), data on their impact on overall survival in the general population remain limited (38). The only long-term overall survival study focused on patients with newly diagnosed advanced ovarian cancer and a BRCA mutation.

While not statistically significant per prespecified criteria, the findings suggest that olaparib may support long-term remission and potentially enhance treatment rates(39).

1.4 Recurrent Ovarian Cancer

About 25% of cases with early-stage OC and more than 80% of cases with advanced-stage OC experience recurrence of the disease within 18 months of treatment (40). The presence of considerable ascites in patients is often seen as an indicator of increased risk of recurrence and mortality (41). If the interval between the last cycle of platinum-based chemotherapy and the relapse is greater than six months, the patient is considered platinum-sensitive and is therefore eligible for platinum-based chemotherapy. Secondary debulking surgery is also considered a treatment option in this group of patients. However, given the conflicting findings regarding its benefit, secondary cytoreduction is only performed on select patients (42). If the relapse occurs in less than six months, the patient is deemed platinum-resistant and non-platinum drug regimens are suggested (43). Inclusion in clinical trials or palliative care are other options for the management of platinum-resistant relapsed OC (44). Unfortunately, the prognosis for recurrent OC is poor as the median survival for platinum-sensitive OC is only three years, which decreases to about one year in platinum-resistance OC (45)

1.5 Origin of ovarian cancer:

The cell origin of any cancer can provide insights into its carcinogenesis pathways, which is important for understanding prognosis and identifying potential interventions for prevention and

treatment. The origin site of the pathogenesis and tumorigenesis of EOC remained unclear for decades. Historically, clinicians treated EOC as a single disease, believing that all its subtypes arise *de novo* from the ovarian surface epithelium (OSE), a layer of squamous mesothelial cells covering the ovary and the cysts derived from it (46). This theory emerged because the ovary was the dominant site of the tumor mass at the time of diagnosis. Since then, multiple theories regarding the carcinogenesis pathways from the OSE for OC have been postulated, including the gonadotropin, hormonal, and inflammation hypotheses (47).

Numerous theories have been proposed to understand the pathogenesis of ovarian cancer (OC), traditionally focusing on ovarian tissue where tumors are typically found. Among these, the incessant ovulation hypothesis proposed by Fathalla in 1971 suggests that repeated ovulation can cause damage to the ovarian surface epithelium (OSE), leading to inflammation and DNA damage that increases cancer risk (47,48). This process is thought to create cortical inclusion cysts (CICs) where ovarian cancer can originate (49,50). Later, Scully suggested that inclusion cysts are the cell origin of epithelial ovarian carcinogenesis rather than the OSE itself, developing independently from ovulation due to factors like inflammation and hormonal interactions (51).

Despite extensive research, the incessant ovulation theory does not fully explain why ovarian tumors often exhibit a type of tissue morphology more typical of other reproductive organs like the fallopian tubes and endometrium (52). This discrepancy led Dubeau in 1999 to propose the secondary Mullerian system theory, suggesting that ovarian tumors might actually originate from nearby structures called paraovarian and/or paratubal cysts, which are not originally part of the ovary itself (52,53). However, this alternate theory also failed to address one of the key limitations: the absence of precursor lesions in these cysts (54).

Overall, while the focus has predominantly been on ovarian tissue due to the location of tumors, multiple lines of evidence indicate that the origin of these tumors may lie elsewhere, challenging traditional views and underscoring the complexity of ovarian cancer's etiology.

In the early 2000s, more convincing histological and molecular evidence emerged indicating that the fallopian tubes may be the origin site of serous carcinomas. During the same period, for the first time, fallopian tube carcinoma was also linked to BRCA germline mutations in addition to breast and ovarian cancers (55–58). More interestingly, molecular analysis showed a loss of function for *BRCA1* in those tumors located in the fallopian tubes (56). In 2001, seminal findings by Piek et al. laid the foundation for the latest theory of ovarian carcinogenesis by producing compelling evidence in favor of the Mullerian origin of serous OC (59). Histologic examination of the distal end of fallopian tubes, called fimbriae, in *BRCA* mutation carriers who had undergone risk-reducing bilateral salpingo-oophorectomy (RRBSO) demonstrated dysplastic and hyperplastic transformations in their epithelium, which were not captured in specimens from those who underwent RRBSO for benign reasons (59,60). These epithelial abnormalities were later named serous tubal intraepithelial carcinomas (STICs) and serous tubal intraepithelial lesions (STIL), which are usually found in the fallopian tubes and share common features with HGSC, such as somatic TP53 mutation and identical cytology, making them the best candidate to be precursor lesions (61–64). Figure 1.2 demonstrates the invasion of STICs into the ovary, which undergoes neoplastic transformation to HGSC due to the hormonal and inflammatory factors in the ovarian microenvironment (65).

In 2005, researchers at Brigham and Women's Hospital in Boston introduced a significant advancement in ovarian cancer diagnostics with the development of the SEE-FIM protocol—Sectioning and Extensively Examining the Fimbrial end of the Fallopian Tube (66). This protocol,

aimed initially at women with a familial risk of breast and ovarian cancer, has greatly improved the detection of precursor lesions for epithelial ovarian carcinomas across both high- and low-risk groups (67). Such advancements were critical in overcoming previous challenges that pathologists faced in identifying these early signs of cancer.

As the SEE-FIM protocol gained broader application, it revealed a notable prevalence of serous tubal intraepithelial carcinomas (STICs) across various patient groups, reporting rates ranging from 14.5% to 61% in cases with high-grade serous carcinoma (HGSC) (68–71), and as high as 100% in smaller studies (66,72). Notably, its use in individuals without hereditary cancer risk factors showed that STICs were present in a significant majority, suggesting a tubal origin for these cancers more frequently than previously understood. For example, a study without BRCA mutations identified STICs in 66% of cases (73), markedly higher than the 33% detected using traditional 4-mm sectioning (74).

This extensive application and the findings support a paradigm shift in understanding the origins of OC. The application of this protocol in populations diagnosed with nonhereditary HGSC showed a tubal origin in 50–60% of cases (75). Kindelberger et al. reported tubal involvement and tubal intraepithelial carcinomas (TICs) in 71% and 48% of the unselected population, respectively, with primary ovarian serous carcinoma by using SEE-FIM (76). Similar observations were noted by Przybycin et al., who identified TICs in 24 out of 41 sporadic HGSOC cases, with the majority being in the fimbrial end of the fallopian tubes (71). A review of the retrospective case series on non-BRCA carriers with incidental STICs and associated microscopic HGSC detected after undergoing nonprophylactic gynecologic surgery showed that the fallopian tubes were the location of the invasive lesions in 86% of cases (77). It underscores the fallopian tubes, rather than the

ovaries themselves, as the likely initial site for the majority of serous ovarian carcinomas, irrespective of genetic risk factors.

The necessity of sectioning fallopian tubes after risk-reducing surgeries, especially for high-risk women, has been emphasized in various studies to identify hidden neoplasia. (78,79). Semmel et al. highlighted the importance of analyzing the fimbria in the general population, not just those at high risk, to detect potential OC early. (80). The same recommendation was supported by Rabbon et al. after identifying STICs in four out of 522 low-risk individuals undergoing surgery for benign reasons (81). Similarly, Faye et al. observed that 3.4% of such cases had incidental STICs (82). The detection of STICs in cases without a germline *BRCA* mutation provides supporting evidence for the benefit of opportunistic salpingectomy (OS) as a strategy for preventing HGSOC in the general population. This approach gains further importance, considering that approximately 80% of HGSCs are sporadic and have been shown to have a worse prognosis and survival rate than familial HGSCs, especially in the context of current limitations in effective screening methods (83,84).

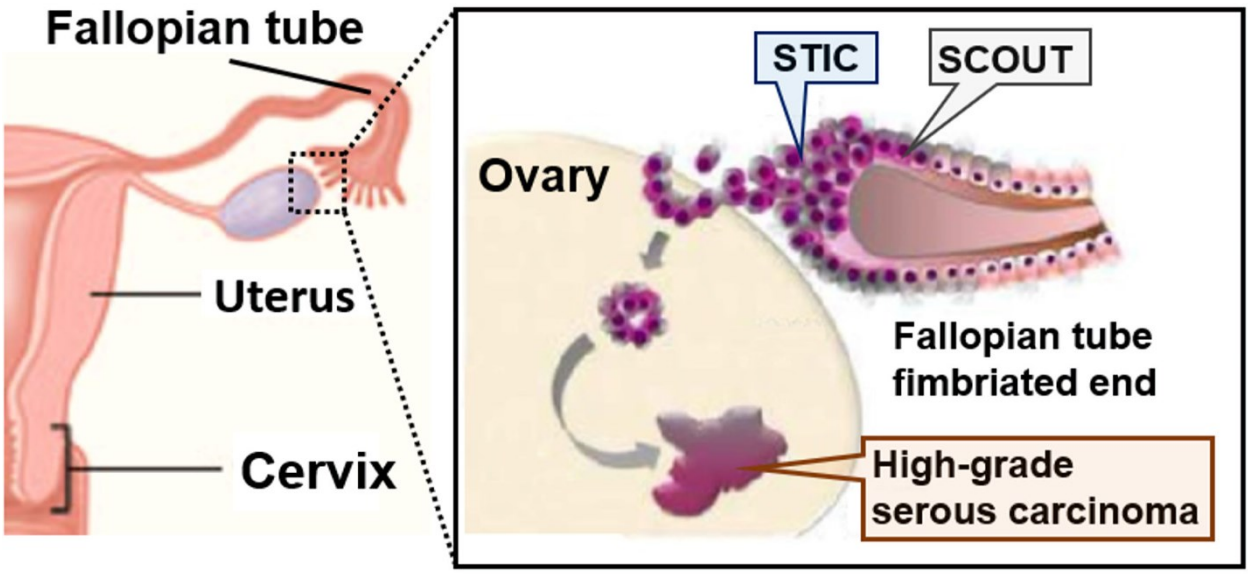

Figure 1.1 Anatomical representation of the female reproductive system highlighting the development of high-grade serous carcinoma. This figure shows the transition from secretory cell outgrowth (SCOUT) to serous tubal intraepithelial carcinoma (STIC) at the fimbriated end of the fallopian tube and subsequent ovarian involvement (65). (This illustration is retrieved from the cited article, which is distributed under the terms of the Creative Commons Attribution Non-Commercial 4.0 International Licence)

1.6 Opportunistic salpingectomy as a potential preventive intervention

The removal of one or both fallopian tubes in a surgical procedure is called salpingectomy, and "opportunistic", "risk-reducing", or "prophylactic" salpingectomy is defined as the removal of both fallopian tubes concurrently with pelvic surgeries conducted for other reasons, with the preservation of ovaries or as an alternative to tubal ligation (85). A number of groups have endorsed OS as a preventive strategy to reduce the burden and mortality of OC.

In September 2010, the Ovarian Cancer Research (OVCARE) group in British Columbia, Canada issued a recommendation encouraging all gynecologists in the province to perform bilateral

salpingectomy during hysterectomy procedures and as an alternative to tubal ligation for women seeking permanent contraception who are at population risk (86). Research by this team revealed a significant increase in the adoption of hysterectomy with bilateral salpingectomy in BC, with rates rising from 5% in 2008 to 35% by 2011, predominantly following their 2010 recommendation. Additionally, the implementation of bilateral salpingectomy instead of tubal ligation for sterilization purposes rose by 22% within a single year (87).

In 2011, the Society of Obstetricians and Gynecologists of Canada endorsed the inclusion of salpingectomy in benign gynecologic surgeries for women who have completed childbearing (87). In the following years, the American College of Obstetricians and Gynecologists (ACOG), Royal College of Obstetricians and Gynecologists and some other European Societies of Obstetrics and Gynecologists advised in favor of risk-reducing salpingectomy (88,89). In 2019, ACOG updated their guidelines to add more information regarding the benefits and feasibility of salpingectomy (90). Also, there are no negative statements regarding opportunistic salpingectomy from the International Federation of Obstetrics and Gynecology members (89).

Many studies showed changes in practice regarding the increased uptake of opportunistic salpingectomy after the publication of these statements. A study on an academic medical center in Virginia, US, between 2012 and 2018 showed that the rate of opportunistic salpingectomy instead of tubal ligation as a surgical sterilization method significantly increased after the release of the Society of Gynecologic Oncology's recommendation on opportunistic salpingectomy in 2013 (91). Moreover, analyses of the US Nationwide Inpatient sample dataset showed that from 2001 to 2010, the rate of hysterectomy with opportunistic salpingectomy increased by 3.3%, while by the year 2015, 60% of women undergoing hysterectomy also had opportunistic salpingectomy, which indicates a 10.2-fold increase in the rate of this operation (92).

In Canada (except the province of Quebec), the rate of hysterectomy with bilateral opportunistic salpingectomy (BOS) increased by 20% from 2011 to 2016 (93). Another study showed a 58% increased rate of hysterectomy with salpingectomy from 2011 to 2014 in the US (94). Also, several studies evaluated the rate of salpingectomy either with hysterectomy or instead of tubal ligation in different American states, and all showed a high rate of adoption over the years (92,95–97).

1.7 Summary

Ovarian cancer (OC) remains one of the most lethal cancers in women, lacking effective screening measures. Although there is a strong genetic component that aids in risk assessment, three-quarters of OC cases are not hereditary. The recent understanding that the fallopian tube is the origin of the most common and lethal histotype of OC has led to the introduction of opportunistic salpingectomy (OS) as a practical and low-risk preventative intervention for people undergoing surgery for benign uterine disease or permanent contraception. The removal of the fimbrial end of the fallopian tubes to prevent OC has gained worldwide attention among gynecologists, although definitive evidence of its effectiveness is not yet available.

1.7.1 Research Gaps: rationale for this thesis

Although OS was adopted as a preventative strategy for OC over a decade ago, a synthesis of its effectiveness, safety, feasibility and cost-effectiveness is lacking. An overview would be useful to inform decision-making by healthcare providers and their patients, as well as in health policy and funding contexts.

Additionally, while many centres in the US have embraced OS as a preventive strategy, the pattern of uptake and practice across Canadian jurisdictions (with the exception of British Columbia) remains unknown. Understanding the prevalence of OS in our province is essential, as this information would enable comparisons of OC health outcomes across the country.

1.7.2 Goal and Objectives

The overall goal of this thesis was to evaluate the uptake of OS in NL and to contribute to the growing evidence base on the use of OS as a preventative measure for OC in the general population. The thesis comprises two manuscripts, each addressing specific objectives:

Objective 1 (manuscript 1): To synthesize the published literature on OS to:

a. quantify its adoption in Canada and the US,
b. summarize the evidence for its effectiveness in preventing OC,
c. summarize the evidence for its safety and feasibility,
d. summarize the evidence for its cost-effectiveness.

Objective 2 (manuscript 2): To investigate the trends and implications of OS performed at the time of hysterectomy or as a contraceptive method:

a. Describe the overall pattern of OS from 2010 to 2019.
b. Determine whether its uptake has significantly increased during the study period.
c. Identify the most prevalent medical conditions associated with each type of surgery.
d. Assess the rate of OC following OS in Newfoundland and Labrador.

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Chapter 2: Manuscript 1

Beyond Sterilization: A Comprehensive Review on the Safety and Efficacy of Opportunistic Salpingectomy as a Preventative Strategy for Ovarian Cancer

This manuscript reports the section of the thesis that addressed Objective 1 by evaluating several key dimensions of OS. Firstly, it quantifies the adoption rate of this surgical practice across Canada and the US, providing a clear picture of its prevalence and trends over recent years. Secondly, it examines the safety and feasibility of OS, summarizing evidence regarding perioperative and postoperative complications, as well as its impact on ovarian reserve. Thirdly, the review explores the cost-effectiveness of OS, reviewing whether its benefits in terms of cancer prevention justify the potential costs. Lastly, it addresses the effectiveness of OS in reducing the incidence of OC, thus contributing crucial insights into its role as a preventive healthcare measure.

Statement of co-authorship:

All authors were involved in the design and identification of the research topic, and all provided important intellectual content. Tahereh Zadabedini Masouleh was responsible for writing the initial draft of the manuscript. All authors reviewed iterations of the paper, and all approved the final version of the manuscript for publication.

Beyond Sterilization: A Comprehensive Review on the Safety and Efficacy of Opportunistic Salpingectomy as a Preventative Strategy for Ovarian Cancer

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(This article belongs to the Section Gynecologic Oncology)

Abstract

Ovarian cancer (OC) is Canada's third most common gynecological cancer, with an estimated 3000 new cases and 1950 deaths projected in 2022. No effective screening has been found to identify OC, especially the most common subtype, high-grade serous carcinoma (HGSC), at an earlier, curable stage. In patients with hereditary predispositions such as BRCA mutations, the rates of HGSC are significantly elevated, leading to the use of risk-reducing salpingo-oophorectomy as the key preventative intervention. Although surgery has been shown to prevent HGSC in high-risk women, the associated premature menopause has adverse long-term sequelae and mortality due to non-cancer causes. The fact that 75% of HGSCs are sporadic means that most women diagnosed with HGSC will not have had the option to avail of either screening or prevention. Recent research suggests that the fimbrial distal fallopian tube is the most likely origin of HGSC. This has led to the development of a prevention plan for the general population: opportunistic salpingectomy, the removal of both fallopian tubes. This article aims to compile and review the studies evaluating the effect of opportunistic salpingectomy on surgical-related complications, ovarian reserve, cost, and OC incidence when performed along with hysterectomy or instead of tubal ligation in the general population.

Keywords: opportunistic salpingectomy; prophylactic salpingectomy; ovarian cancer; prevention; surgical complication; ovarian reserve; risk; safety; efficacy

2.1. Introduction

Ovarian cancer (OC) is the most lethal gynecological cancer with the worst prognosis [1]. According to the American Cancer Society, the lifetime risk of developing OC is 1 in 78, and it is fatal in 1 out of 108 women [2], with a median age of 63 at diagnosis and 70 at death [3]. Age, family history, endometriosis, obesity, hormone replacement therapy, and a greater height are risk factors for OC [1,4]. In contrast, oral contraceptive use and a higher number of pregnancies have been shown to have a protective effect [5]. OC is a significant public health concern, with a high mortality rate. Sung et al. reported 313,959 new cases and 207,252 deaths in 2020 globally, with a mortality rate of 66%. North America has the third highest incidence rate, with 26,630 cases, behind Asia and Europe [6]. The projected incidence rate of OC in Canada for 2022 is 3000 cases, with 1950 projected deaths [7].

OC presents a significant challenge due to late-stage diagnoses and non-specific symptoms, resulting in a low survival rate. The overall 5-year relative survival rate for OC is merely 49.7%, with minimal improvement over the years [3]. In the early stages of the disease (I and II), in which only 15 to 19% of cases are diagnosed, the 5-year survival rate is between 70% and 90%, drastically decreasing to 17% in stage IV [8]. Additionally, tumor cell type plays a role in survival rates, with borderline OC showing the best prognosis and epithelial OC demonstrating the worst survival rate among all OC types [8]. Epithelial OC is the most common subtype, accounting for up to 95% of malignant cases, with high-grade serous carcinoma (HGSC) being the predominant histotype, accounting for over 70% of epithelial OC cases [9]. HGSC is characterized by ubiquitous somatic TP53 mutations, leading to high invasiveness and a poor prognosis [10]. About 15% of all OCs [11] and 25% of all HGSCs [12] are hereditary, often linked to BRCA1/2 gene mutations [13]. However, most OC cases occur sporadically and have worse survival and prognosis than familial

cases [13,14,15]. Despite the need for effective screening methods, two large RCTs in the UK and the US did not find significant improvements in survival rates after intervening early screening, highlighting the necessity of a preventative strategy in the general population [16,17].

Understanding the origin of OC is vital for prognosis and prevention. Previous theories implicated the ovarian surface epithelium (OSE) but failed to explain diverse histotypes and genomic profiles [18,19]. Recent evidence suggests that the distal fallopian tube may be the origin of HGSCs [20]. Studies have identified dysplastic and hyperplastic changes in the fallopian tube fimbriae of women with BRCA mutations, known as serous tubal intraepithelial carcinomas (STICs), which share features with HGSC [21]. Utilizing a protocol called sectioning and extensively examining the fimbrial end of the fallopian tube (SEE-FIM) has led to the detection of precursor lesions in HGSC in both high- and low-risk populations [22]. These findings indicate that the fallopian tubes are likely the primary site of origin for most serous ovarian carcinomas, and, therefore, opportunistic salpingectomy (OS) may hold promise for HGSC prevention in the general population in addition to the high-risk population.

2.2. What Is Opportunistic Salpingectomy?

Salpingectomy involves the removal of one or both fallopian tubes surgically, typically for contraception or the treatment of fallopian tube abnormalities, such as ectopic pregnancy or hydrosalpinx, whereas opportunistic, risk-reducing, or prophylactic salpingectomy refers to the removal of both normal fallopian tubes during pelvic surgeries while preserving the ovaries [23].

In September 2010, the gynecologic cancer research team OVCARE in BC urged gynecologists to consider performing bilateral salpingectomy at the time of hysterectomy and as an alternative to tubal ligation when women at population risk seek permanent contraception [24]. Their study

demonstrated a significant increase in the rate of hysterectomy with bilateral opportunistic salpingectomy (BOS) from 5% (2008) to 35% (2011) of all hysterectomy procedures in BC, Canada, with most of this change occurring after September 2010. Additionally, the number of bilateral salpingectomies for sterilization in place of tubal ligation increased by 22% in one year [25]. In 2011, the Society of Obstetricians and Gynecologists of Canada recommended that physicians consider the practice of salpingectomy during benign gynecologic surgeries in the general population when childbearing is complete [26]. As a result, in Canada (excluding the province of Quebec), the rate of hysterectomy with BOS increased by 20% from 2011 to 2016 [27], indicating an increasing trend in the adoption of salpingectomy in gynecologic surgeries in the country.

2.3. Opportunistic Bilateral Salpingectomy during Hysterectomy

Hysterectomy ranks as the second most frequent surgical procedure in women after cesarean section [28], and its prevalence is influenced by factors like age, ethnicity [29], race [30], and socioeconomic status [31]. In total, 90% of the hysterectomies performed are due to benign diseases, mainly uterine fibroids, abnormal uterine bleeding, and endometriosis, totaling around 400,000 inpatient procedures annually in the US [32]. Canada has a similarly high rate of hysterectomy, with about one-third of women undergoing the procedure by age 60 [33]. The age-standardized rate for this surgery was 234 per 100,000 cases in 2021 in Canada (excluding the province of Quebec), with Saskatchewan recording the highest rate at 326 per 100,000 [34].

In recent years, surgical techniques have evolved, favoring minimally invasive approaches like laparoscopic and robotic-assisted hysterectomy for benign reasons [35]. This shift has led to increased outpatient procedures and same-day discharges due to reduced complications, lowered

medical costs [36], and improved feasibility [37,38]. Notably, Moawad et al. showed that 44% of hysterectomies for benign indications shifted to same-day discharge between 2008 and 2014 [39]. It is estimated that approximately 100,000 to 200,000 outpatient hysterectomies are carried out annually in the US [40]. Given the large number of hysterectomies performed each year, the incorporation of bilateral salpingectomy creates an opportunity to remarkably increase the adoption of this procedure among premenopausal women and potentially reduce OC incidence on a substantial scale. However, this approach also raises important considerations regarding safety, effects on ovarian function, and cost-effectiveness, which is thoroughly explored in the following section.

2.3.1. Surgical and Post-Surgical Complications of Hysterectomy with Salpingectomy Regardless of the Approach

Hysterectomy can be performed in different settings and with differing surgical approaches, laparotomy, and vaginal or inimally invasive techniques. Several studies have evaluated the surgical complications associated with concomitant salpingectomy while considering all approaches combined. The main objective measures of the surgical complications assessed in these studies include the length of hospitalization and operation, blood transfusion and readmission rates, and estimated blood loss (EBL). In the following section, a summary of these studies is presented.

Three retrospective studies examined peri- and postoperative complications and found no significant increase in adverse events when salpingectomy was added to hysterectomy [41,42,43]. A nationwide Canadian registry-based study comparing 10,697 cases with bilateral salpingectomy to 195,238 cases with hysterectomy alone showed no differences in blood transfusion, hospital

stay, post-surgical fever, or infection [41]. Similarly, no significant changes in EBL, the length of stay, or the occurrence of any events causing complications during or after the surgery were reported by a retrospective cross-sectional study, including 4890 cases with OBS [42]. A multicenter clinical trial also supported these findings, showing no increase in operative time, blood loss, complications, or hospitalization with the addition of bilateral salpingectomy to hysterectomy [43].

Regarding surgery duration, two studies indicated a modest increase when bilateral salpingectomy was added to hysterectomy. Till et al. reported an average 12 min increase in operation time regardless of surgical approach [42]. This is supported by another population-based cohort study in the province of BC, Canada (2008–2011), which indicated an average 16 min extension of operation time [25]. Of interest, the hospitalization duration was shorter by an average of 3.6 h in those who had bilateral salpingectomy. Other than that, no statistically significant differences were observed regarding the readmission and blood transfusion rates in both groups [25]. These findings align with the result of another cohort study in which only laparoscopic and abdominal approaches were included. No significant differences in surgical or post-surgical-related complications between both groups were shown, except for a 10.2 h reduction in hospitalization for the OBS group, the mean length of hospitalization [44]. In contrast, a separate retrospective cohort study comparing laparoscopic or abdominal hysterectomy with or without salpingectomy reported longer hospitalization by 2 h and 24 min in the salpingectomy group [95% CI 0.02–0.18] but with 20 mL less blood loss [95% CI 0.02–0.18] [45].

A retrospective cohort study evaluating minor postoperative complications reported that performing salpingectomy with hysterectomy, regardless of approach, did not increase the rate of physician visits for any surgery-related complications or infections two weeks after being

discharged. The only increased risk for the OBS group was a 20% higher likelihood of being prescribed analgesics during those two weeks, which disappeared after one month [46].

Overall, the evidence evaluating all types of hysterectomy, regardless of approach, suggests that the addition of salpingectomy to any route of hysterectomy appears safe and does not increase complications, apart from a modest increase in the duration of surgery. Although the findings on hospitalization duration are mixed, most studies did not show the negative effects of salpingectomy on this parameter. Further research is encouraged to better understand the benefits and potential risks associated with incorporating bilateral salpingectomy during hysterectomy.

2.3.2. Ovarian Reserve

The fallopian tubes run alongside the ovary, raising concerns about the potential compromise of blood supply to the ovaries and subsequent impact on ovarian reserve or early menopause due to salpingectomy. Premature surgical menopause is associated with multiple negative long-term sequelae, such as early osteoporosis, cardiac disease, and dementia, making the long-term safety of salpingectomy a crucial consideration.

To understand the effect of salpingectomy on ovarian reserve, a meta-analysis included eight studies with a follow-up time of 3 to 18 months in which cases the fallopian tubes were removed either through laparoscopic hysterectomy, through sterilization, or due to ectopic pregnancy. The pooled results showed no significant changes in anti-Müllerian hormone (AMH) serum levels after salpingectomy, suggesting no short-term negative impact on ovarian reserve [47].

However, a prospective study on 84 women who underwent hysterectomy with bilateral salpingectomy reported a significant decline in AMH levels (delta AMH = −0.49 ng/mL $p < 0.001$)

and a significantly higher level of follicle-stimulating hormone (FSH) (delta FSH = −7.21 mIU/mL $p < 0.001$) six weeks postoperatively, suggesting diminished ovarian reserve after hysterectomy with bilateral salpingectomy [48]. It is worth noting that this study had a relatively short follow-up period, which could have influenced the hormonal levels since they tend to be unstable after adnexal surgery [49]. Moreover, 37% (31/84) of patients had cervical cancer, which has been shown to lower the ovarian reserve and can be a confounder in the analysis [50]. The reported extent of FSH change was relatively small, and some authors would argue that this level of difference is not clinically significant or a meaningful predictor of true increased rates of menopause.

A clinical trial examining the levels of FSH and luteinizing hormone (LH) before and six months after hysterectomy with/without salpingectomy revealed elevated levels of both hormones at six months postoperatively in both groups, with no significant differences between the groups, indicating no increased risk of impaired ovarian function due to salpingectomy [51]. A prospective cohort study of 859 patients who completed a follow-up at 48 months in which FSH, LH, and estradiol (E2) levels and perimenopausal symptoms were checked showed no significant hormonal level difference at the 48th month other than a lower level of FSH in the salpingectomy group (34.9 U/L) than in the hysterectomy-only group (38 U/L; $p = 0.043$). However, at 24 months, the number of patients experiencing perimenopausal symptoms was 7.3% higher in the no-salpingectomy group, and the salpingectomy group had a significantly lower rate of pelvic pseudocysts [52].

Measurements of the AMH concentration before and six months after surgery in a clinical trial, including abdominal or laparoscopic hysterectomies, demonstrated that the addition of bilateral salpingectomy does not significantly alter ovarian reserve [43]. Likewise, a prospective study comparing AMH and FSH levels three months after surgery in women who underwent

hysterectomy with or without OBS found no significant differences either within or between groups [53].

In conclusion, the available evidence suggests that salpingectomy during hysterectomy does not adversely affect ovarian reserve. However, further research with longer follow-up periods is essential to confidently assess the impact of salpingectomy on ovarian function and its overall safety during hysterectomy procedures.

2.4. Total Salpingectomy instead of Tubal Ligation

In 2019, approximately 12% of women worldwide had undergone a form of permanent sterilization, making it the most common form of contraception [54]. Supporting evidence on the preventative role of OBS has shifted the purpose of this surgery from treatment for certain medical conditions, such as ectopic pregnancies or the presence of hydrosalpinx, to a contraception method [55].

The uptake of postpartum and interval opportunistic salpingectomy as a mode of sterilization is increasing. A multicenter cohort study demonstrated an approximately 72% increase in the interval salpingectomy rate between 2013 and 2016, with an opposite trend in the rate of bilateral tubal ligation over the study period [56]. Wagar et al. showed that 80% of all postpartum sterilizations after vaginal delivery occurred through salpingectomies in 2019, compared to 5.9% in 2014 [57].

2.4.1. Surgical and Post-Surgical Complications of Salpingectomy instead of Tubal Ligation

When comparing bilateral salpingectomy with tubal ligation (TL), McAlpine et al. reported an increased length of operation by an average of 10 min in those who underwent salpingectomy for

sterilization (61 min in the TL group vs. 71.2 min in the OS group; $p < 0.001$), but no significant differences were observed for the length of hospital stay, rate of readmission, or blood loss [25].

A meta-analysis performed on five RCTs compared surgical-related complications, including the duration of operation and hospitalization, blood loss, changes in hemoglobin, the risk of wound infections, rehospitalization, reoperation, and other postoperative complications in bilateral salpingectomy vs. tubal ligation. The results showed no significant difference in the aforementioned parameters between the two groups [58].

Many patients request sterilization in the immediate postpartum period or at the time of cesarean section. Salpingectomy can therefore be performed in three circumstances: during cesarean delivery, within 24 to 48 h after vaginal delivery, or as a non-postpartum interval procedure. In the following, the surgical-related complications of each scenario vs. tubal ligation are reviewed.

The majority of studies focused on salpingectomy during cesarean delivery. A meta-analysis, including nine observational and experimental studies, reported six minutes of extra operative time in the salpingectomy group during cesarean delivery compared to tubal ligation, while no significant difference with regard to intra- or postoperative complications was observed between the two groups [59]. The same results were obtained by an additional meta-analysis on 11 studies in which the only significant difference was a 6.3 min longer operative time in eight cohort studies [60]. A more recent retrospective cohort study also reported comparable results when comparing tubal occlusion with total salpingectomy at the time of cesarean delivery, with a 6.5 min difference in operative time in favor of tubal occlusion [61].

With bilateral salpingectomy as a non-postpartum interval procedure, a retrospective cohort study assessed its feasibility and safety compared with laparoscopic tubal ligation. Both groups showed

comparable intra- and postoperative complications, except for the average operative time, which was 11 min longer in the laparoscopic salpingectomy group ($p < 0.0001$) [56]. The findings from another cohort study also showed no significant changes in EBL or complications when interval salpingectomy was performed instead of tubal ligation. The operation time was reported to be 6 min longer in laparoscopic salpingectomy, but it was not statistically significant [62].

The available evidence suggests that bilateral salpingectomy after vaginal delivery does not substantially increase the rate of complications. A single-centered retrospective case series studied postpartum sterilization after vaginal delivery and found that the average surgical time was 11.31 min longer in the bilateral salpingectomy cohort via mini-laparotomy ($p = 0.003$) vs. tubal ligation using Pomeroy or Parkland techniques, but there were no significant differences in EBL or complication rates [63]. However, the results of a cohort study showed that bilateral salpingectomy operation on women who have delivered vaginally takes 4 min less and has slightly more EBL (5 mL) than bilateral tubal ligation ($p = 0.03$ and 0.15, respectively). Other examined parameters, including the length of hospitalization, the risk of readmission, and emergency visits, were similar between the two groups [64]. The shorter operative time and lower amount of blood loss in the salpingectomy group in the mentioned study may be due to the fact that 94% (106/113) of all bilateral salpingectomies were performed using a bipolar electrocautery device [64].

A retrospective cohort study consisted of two sets of comparisons, namely, one for salpingectomy after vaginal delivery and one for salpingectomy with cesarean delivery, and it showed that, in both groups, salpingectomy had a statically significant but modestly longer operation time than tubal ligation (the addition of 10 and 9.9 min, $p = 0.05$, respectively), whereas similar rates of blood loss were stated for salpingectomy in both types of deliveries vs. tubal ligation [65].

Overall, when comparing bilateral salpingectomy with tubal ligation for sterilization, there are data reporting that bilateral salpingectomy may result in longer operation times. However, this difference is not statistically significant in all studies. There is also no significant difference in the length of hospital stay, rate of readmission, or blood loss between the two groups. However, when considering the specific circumstances of the surgery, such as whether it is performed during cesarean delivery or as an interval procedure, there may be slight differences in operation time and blood loss. These inconsistent findings are likely attributed to the heterogeneity of surgical techniques and study designs. In conclusion, the evidence suggests that bilateral salpingectomy is a feasible and safe alternative to tubal ligation, with similar rates of complications.

2.4.2. Ovarian Reserve

Multiple studies have examined the effect of bilateral salpingectomy as an alternative to tubal ligation on ovarian reserve, focusing on evaluating hormonal and ultrasonographic markers. A triad-center clinical trial compared the effect of bilateral salpingectomy with a bipolar device and bilateral partial salpingectomy on ovarian reserve in women undergoing cesarean delivery after one year. The results showed no significant differences between the two procedures in terms of hormonal (AMH and FSH) and ultrasonographic (PSV, AFC, VI, FI, ovarian volume, and calculated ovarian age) parameters [66]. In another randomized trial, the measurement of AMH levels before and six–eight weeks postdelivery in women who underwent salpingectomy via monopolar electrosurgery or tubal ligation using the Parkland method during C-section showed no significant difference either within or between groups [67]. Similarly, a prospective cohort study showed no statistically significant differences in AMH, FSH, or E2 levels between laparoscopic tubal ligation, bipolar bilateral salpingectomy, and healthy controls at one month or three months after surgery [68]. Pooled data from five studies in a recent meta-analysis showed no significant

difference in FSH hormone levels between salpingectomy and proximal tubal ligation cohorts [69]. With regard to antral follicle count (AFC) and AMH, those with bilateral salpingectomy had higher levels in the short term (AFC: mean difference −0.80 IU/L, 95% CI [−1.46, −0.14]; AMH: mean difference −1.01 IU/L, 95% CI [−1.28, −0.74]) [69]. However, a subsequent prospective study compared AMH levels and AFC three and six months following cesarean delivery with bilateral salpingectomy with those who only had a C-section, with no significant changes in either marker reported at any time point between the study groups [70]. In summary, the results of these studies suggest that bilateral salpingectomy is not associated with a significant difference in ovarian reserve compared to tubal ligation as measured by hormonal and ultrasonographic parameters in the short term.

2.5. Cost-Effectiveness

OC imposes a significant economic burden on individuals, the healthcare system, and society as a whole [71,72,73]. Moreover, studies show that the families of OC patients also shoulder the economic impact, as they allocate time and/or resources to caregiving [74,75]. OC is one of the highest-cost cancers similar to brain, esophageal, and gastric cancers [76], and it has the highest healthcare cost per patient amongst gynecologic cancers in the US [77]. Diagnosis at an advanced stage of this cancer is associated with early progression (within 12 months) of the disease and, therefore, a higher level of financial costs [78]. A US study of 2991 cancer patients with private insurance who were <65 years old showed that their all-cause total cost was annually USD 104,964 more than the respective control cohort [79]. This aligns with the USD 93,632 expenditure reported on the care of commercially insured women with OC during the first year after surgery [80]. To assess the average cost of treatment for older patients, Urban et al. focused on Medicare users with late-stage OC, for whom it was estimated to be USD 65,908 for the first year following diagnosis

[81]. Frailty is also shown to be associated with a greater cost of care in OC patients [82]. The evidence reviewed here highlights the need for cost-saving approaches to lighten the financial burden on society.

A number of studies have investigated the socioeconomic aspect of opportunistic salpingectomy. Kwon et al. studied the cost-effectiveness of opportunistic salpingectomy in the Canadian healthcare system for the first time based on life expectancy gain in a decision model analysis in which they found that opportunistic salpingectomy is a cost-effective approach compared to hysterectomy with or without bilateral salpingo-oophorectomy and instead of tubal ligation and that it can also be cost-saving in the long term [83]. These findings are supported by Dilley et al.'s study in which opportunistic salpingectomy was shown to be cost-effective based on gained quality-adjusted life years assuming a minimum prevention rate of 54% for OC using data from the US [84]. Their model also predicted that bilateral salpingectomy is a cost-saving option when performed with laparoscopic hysterectomy [84]. A decision analysis, with a focus on vaginal hysterectomy as a more complex surgical approach, showed that the addition of bilateral salpingectomy to the operation increases major complications by 0.61 for every cancer case prevented and is cost-effective with or without the inclusion of the cancer treatment costs [85]. In a conservative model, the mortality rate caused by OC was reduced by 8.13% and 6.34% when opportunistic salpingectomy was compared with tubal ligation and when hysterectomy with opportunistic salpingectomy was compared with hysterectomy alone, respectively, which leads to savings of USD 445 million per year in the US [86]. Including a wider number of laparoscopic non-gynecologic procedures along with hysterectomy and tubal ligation, such as appendectomy, colon resection, hernia, and cholecystectomy, in an analysis model demonstrated favorable results

to the addition of opportunistic salpingectomy, along with the opportunity to save approximately USD 877M in the US annually [87,88].

For postpartum sterilization, two studies investigated the socioeconomic benefits of opportunistic salpingectomy solely at the time of cesarean delivery [89,90]. Both models identified opportunistic salpingectomy as a cost-effective alternative to tubal ligation when particular conditions are met. Venkatesh et al. defined a minimum 52% risk reduction and no more than 2% perioperative morbidity compared with tubal ligation for salpingectomy [89]. In contrast, the minimum risk reduction in Subramaniam's model was 41% with a cost difference of USD 3163.74 between opportunistic salpingectomy and tubal ligation [91]. These results seem promising with the advent of novel low-cost approaches to salpingectomy at the time of C-section [90]. In a recent decision analysis study, Wager et al. evaluated the cost-effectiveness of opportunistic salpingectomy following vaginal delivery and estimated that there would be USD 6.48 million in cost savings when chosen over tubal ligation [92]. In regard to different forms of sterilization, the economic impacts of laparoscopic tubal ligation, tubal clips, and laparoscopic bilateral salpingectomy were compared by Tai et al., and bilateral salpingectomy was introduced as the most cost-effective strategy for sterilization [93]. The simulation model, including 10,000 women, showed that bilateral salpingectomy might reduce healthcare expenditure by USD 7823 and USD 6325 per life year gained compared to tubal clips and tubal ligation, respectively [93]. The cost-effectiveness of OBS is still being studied and is currently a topic of ongoing research, especially due to the lack of population-based data; however, based on the theoretical decision model, it appears to be cost-effective and cost-saving under some circumstances.

2.6. Efficacy of Opportunistic Bilateral Salpingectomy

In recent years, the implementation of OBS as a strategy for reducing the risk of OC has gained attention in the medical community. Several studies have been conducted to evaluate the effectiveness of this intervention on the incidence of OC in the general population. In this section, we aim to review the findings from six studies that focus on the topic of opportunistic salpingectomy and its impact on reducing the risk of OC. A comprehensive summary of the articles reviewed can be found in Table 2.1.

A nationwide case-control study conducted in Denmark between 1982 and 2011 found that bilateral salpingectomy is associated with a 42% decrease in the incidence of epithelial ovarian cancer (EOC) [94]. A retrospective Swedish population-based cohort study conducted between 1973 and 2009 observed a 35% lower risk of OC in the salpingectomy group vs. the control group after an average of 18 years of follow-up [95]. Additionally, a sub-analysis comparing the effects of unilateral with bilateral salpingectomy showed that bilateral salpingectomy was associated with an additional 50% decrease in the risk of OC compared to unilateral salpingectomy (unilateral salpingectomy: HR = 0.71 95% CI = 0.56–0.91; bilateral salpingectomy: HR = 0.35 95% CI = 0.17–0.73) [95]. A US-based case–control study also reported that excisional tubal sterilization, including complete and partial salpingectomy and distal fimbriectomy, was associated with a 64% reduced risk of EOC and primary peritoneal cancer (PPC) compared to controls without sterilization or with non-excisional tubal sterilization [96]. A meta-analysis of the aforementioned three studies found a 49% decrease in the incidence rate of OC after bilateral salpingectomy (OR = 0.51, 95% CI = 0.35–0.75, I2 = 0%) [97].

In their single-center case–control study, Chen et al. found that salpingectomy for benign reasons can decrease the overall EOC rate by approximately 52% compared to women whose fallopian tubes had been reserved [98]. Moreover, a retrospective case–control study with the aim of assessing the effects of hysterectomy, salpingectomy, and tubal ligation on the risk of EOC Types I and II was carried out while including cases diagnosed with EOC or PPC from 2008 to 2014 in Sweden. The findings specific to salpingectomy suggest that this surgical procedure was linked with a significant reduction in the risk of EOC Type II (Type II consists of HGSC, undifferentiated carcinoma, and malignant mixed mesodermal carcinomas), with a risk reduction of 38% [99].

These findings are supported by the most recent retrospective cohort study conducted by Hanley et al. in the province of British Columbia, Canada. The study findings show that the observed rates of EOC and serous OC in the OS group, including 25,889 individuals, and in the control group, including 32,080 individuals who had hysterectomy alone or tubal ligation, were <=5 vs. 21 and 0 vs. 15, respectively [100]. Importantly, the calculated expected case numbers, based on the age-adjusted incident rate in the control group and follow-up duration, were 8.68 (for EOS) and 5.27 (for serous OC), which were greater than the observed rates of less than or equal to 5 (for EOS) and 0 (for serous OC) in the OS group [100]. Due to the relatively recent implementation of this preventative strategy and the long latency period of OC, we have only retrospective studies to inform evidence, which together suggest a 35–65% risk reduction in OC in the general population after salpingectomy.

Table 2.1 Characteristics of six observational articles included in this review

Article	Madsen et al. [95]	Falconer et al. [96]	Lessard et al. [97]	Chen et al. [99]	Darelius et al. [100]	Hanley et al. [101]
Design	Nationwide case–control	Retrospective cohort	Population-based nested case–control	Case–control	Nationwide case–control	Retrospective cohort
Country	Denmark	Sweden	USA	China	Sweden	Canada (BC)
Study period	1982–2011	1973–2009	1966–2009	2007–2017	2008–2014	2008–2017
Cases	Patients with EOC n = 13,241	Previous gynecologic surgery on benign indications n = 251,465	All patients with EOC or PPC n = 194	Patients with EOC or PPC and history of gynecological surgery for benign reason n = 198	Patients with EOC, fallopian tube cancer, or PPC n = 4040	Previous hysterectomy with OS n = 14,066, or OS for sterilization n = 11,823
Controls	15 age-matched controls per case n = 194,689	Unexposed women (no surgery) n = 5,449,119	2 age-matched controls per case n = 388	2 age-matched controls with no previous OC n = 389	10 age-matched controls n = 39,100	Previous hysterectomy (alone) n = 10,446, or tubal ligation n = 21,634
Exclusion	Previous cancer, previous bilateral oophorectomy (controls only)	Primary OC and/or any gynecologic surgery before entering the cohort, inconsistencies in the data, emigration out of Sweden	Not residing in Olmsted County, previous fallopian tube carcinoma, non-serous cancers	Previous OC	Unable to subtype, previous EOC, previous bilateral oophorectomy	Any previous gynecological cancer
Outcome	EOC and borderline ovarian tumors	Ovarian and tubal cancer	Serous EOC or PPC	EOC or PPC	Types I and II EOC	Serous and epithelial OC
Confounder *	Age, parity, tubal ligation	Age, parity, calendar year, education status	Hysterectomy, salpingo-oophorectomy, use of oral contraceptive,	Age, child number, menopause status	Pelvic inflammatory disease, endometriosis, other surgical procedures	NA

			endometriosis, parity, gravidity			
Result **	Unilateral salpingectomy: OR: 0.90 95% CI: 0.72–1.12 Bilateral salpingectomy: OR: 0.58 95% CI: 0.36–0.95	HR: 0.65 95%CI: 0.52–0.81 $p = 0.0001$	OR: 0.36 95%CI: 0.13–1.02 $p = 0.054$	OR: 2.080 95%CI: 1.340–3.227 $p = 0.001$	Type I: OR: 1.16 95%CI: 0.75–1.78 $p = 0.51$ Type II: OR: 0.62 95%CI: 0.45–0.85 $p = 0.0032$	Number of observed vs. expected serous cancer and EOC were 0 vs. 5.27 and 5 or less vs. 8.68 cases, respectively

* The confounders included in the fully adjusted model are named. ** Only the results specific to salpingectomy and from a fully adjusted model are displayed.

2.7. Conclusions

In conclusion, the available data suggest that opportunistic bilateral salpingectomy during pelvic surgeries or as tubal sterilization is a safe procedure with minimal complications. The addition of bilateral salpingectomy to hysterectomy appears to be a viable option with minimal added risk of surgical and post-surgical complications, regardless of the surgical approach. The comparison between bilateral salpingectomy and tubal ligation for sterilization reveals several important findings. Bilateral salpingectomy has emerged as a viable alternative to tubal ligation, with a shift in its purpose from treatment for specific medical conditions to a method of contraception. The procedure shows comparable rates of complications to tubal ligation, with minor differences in operation time and blood loss depending on specific circumstances and surgical techniques.

Overall, opportunistic salpingectomy has emerged as a promising strategy for reducing the risk of OC. Although a longer follow-up time and prospective studies will be required to strengthen the evidence, the existing retrospective studies have demonstrated a significant decrease in OC incidence following bilateral salpingectomy, with risk reductions ranging from 35% to 65% in the general population.

Opportunistic salpingectomy holds promise in reducing the risk of OC and can be safely implemented in most OB-GYN practices. Ongoing research and long-term follow-up studies are essential to fully understand its impact on OC incidence and optimize its implementation in clinical practice.

Author Contributions

Conceptualization, L.D. and T.Z.M.; investigation, L.D. and T.Z.M.; resources, L.D.; writing—original draft preparation, T.Z.M.; writing—review and editing, T.Z.M., L.D., H.E., K.H. and B.J.W.; supervision, L.D. and H.E.; project administration, T.Z.M. and L.D.; funding acquisition, L.D. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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Chapter 3: Manuscript 2

The Uptake of Opportunistic Salpingectomy in Newfoundland and Labrador, Canada, from 2010 to 2019

This manuscript reports the section of the thesis that addressed Objective 2 by investigating the prevalence of opportunistic salpingectomy either during hysterectomy or as a method of sterilization in Newfoundland and Labrador, Canada, from 2010 to 2019. Additionally, it examined the incidence of gynecologic cancers following the procedure in these populations.

Statement of co-authorship:

All authors contributed to study design and identification of the research topic. Tahereh Zadabedini Masouleh cleaned the database and led the data analysis. Lesa Dawson, Holly Etchegary, and Zhiwei Gao assisted with the data analysis and overall interpretation of the data. Tahereh Zadabedini Masouleh was responsible for writing the initial draft of the manuscript. All authors reviewed the manuscript for important intellectual content, and all approved the final version, which is to be submitted for publication.

The Uptake of Opportunistic Salpingectomy in Newfoundland and Labrador, Canada, from 2010 to 2019

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The authors declare no conflict of interest.

Abstract

Background:

Ovarian cancer remains a leading cause of gynecologic cancer deaths worldwide, with limited effectiveness of current screening methods. The discovery that many high-grade serous carcinomas, the most lethal ovarian cancer subtype, likely originate in the fallopian tubes has shifted the focus towards prophylactic measures such as opportunistic salpingectomy (OS).

Objectives:

We assessed the prevalence of OS during hysterectomy or as a method of sterilization, observing the evolution of these rates throughout the study. We also described subsequent gynecologic cancer incidence following the surgeries.

Methods:

We performed a retrospective analysis on women who had bilateral salpingectomy during hysterectomy for benign indication or tubal sterilization in Newfoundland and Labrador (NL), Canada, from 2010-2019. Data were obtained from the Provincial Discharge Abstract Database, Client Registry, and Cancer Registry, facilitated by Newfoundland and Labrador Centre for Health Information (NLCHI). We included patients undergoing any or any combination of hysterectomy, salpingectomy, oophorectomy, or tubal ligation, excluding those who were under 15 at the time of surgery, over 64 at the time of tubal sterilization, and those with prior cancer diagnoses in female genital organs. Procedures were stratified into groups for detailed assessment of surgery rates, age distribution, and diagnostic indications using ICD-10 and ICD-O classifications. Cancer incidence post-surgery was also examined and compared between groups.

Results:

A total of 21,287 hysterectomy cases and 4,356 tubal sterilization cases were analyzed. Among the hysterectomy cases, 17,676 (83%) underwent the procedure alone with a mean age of 47.8 years, 2,302 (11%) in conjunction with bilateral salpingo-oophorectomy (BSO) with a mean age of 52.5 years ($p < 0.001$), and 1,309 (6%) with opportunistic salpingectomy (OS) with a mean age of 42.8 years ($p < 0.001$). The proportion of OS alongside hysterectomies rose from 1.6% in 2010 to 10.1% in 2019 ($p < 0.001$). The total number of ovarian and fallopian tube cancers observed was 20 in the hysterectomy alone group and 10 in the hysterectomy with BSO group. In the tubal sterilization cohort, 4,134 (95%) underwent tubal ligation with a mean age of 33.8 years, and 222 (5%) underwent OS with a mean age of 37 years ($p < 0.001$). The OS rate increased to 16.9% of all tubal sterilizations in 2019, up from 0.6% in 2010 ($p < 0.001$). Regarding cancer outcomes, only one case of ovarian cancer was observed in the tubal ligation group.

Conclusion:

Despite a notable shift in gynecological surgical practices in NL, with an increased uptake of OS during hysterectomy and as a contraception method, its adoption as a preventative measure against ovarian cancer remains relatively low. Identifying the barriers to the broader adoption of OS is essential for future studies. Moreover, to comprehensively understand the long-term benefits and cancer prevention implications of OS, there is a need for studies with extended follow-up periods and pooled data analysis.

3.1. Introduction

Ovarian cancer ranks fifth for women worldwide. In Canada, it ranks tenth in incidence, with 3100 new cases in 2023 (1). The non-specific symptoms and lack of effective screening methods lead to low survival rates (2), currently 44% at five years (1). Without a specific etiological target, primary prevention is also challenging.

Within the spectrum of malignant ovarian tumors, epithelial tumors predominate, with high-grade serous carcinoma (HGSC) as the most common histotype (3). Growing evidence suggests that the origin of HGSC is the fimbrial end of fallopian tube rather than the ovary (4–6). The observation of serous tubal intraepithelial carcinoma lesions (STICs) within fallopian tubes offers a potential preventive strategy for the general population in the form of opportunistic salpingectomy (7–9). In 2010, the OVCARE team in British Columbia (BC), Canada, recommended the consideration of opportunistic salpingectomy (OS) in the form of bilateral salpingectomy (BS) as an alternative to tubal ligation for people seeking permanent contraception and as an addition to elective hysterectomy procedures (10). Subsequent guidelines from the American College of Obstetricians and Gynecologists (ACOG), the UK Royal College of Obstetricians and Gynecologists (RCOG) and other professional groups contained similar recommendations (11–14).

Retrospective analyses of OS suggest a risk reduction of 35-65% in ovarian cancer incidence in people undergoing the procedure (15–19). Furthermore, a recent retrospective study conducted in BC, Canada, revealed significantly lower incidences of epithelial and serous ovarian cancer among women who underwent bilateral salpingectomy compared to those who underwent traditional hysterectomy or tubal ligation (20). The addition of OS, as described above, has been shown to be

both safe and feasible, with minimal increase in blood loss and little impact on operative time (21–23).

Comprehensive data on the uptake of OS across various healthcare settings in Canada is limited. In Canada, health care policy and delivery are largely under provincial jurisdictions, and unified national datasets are yet to be fully developed to allow comprehensive analyses and comparisons. This exploratory study focuses on a single province, Newfoundland and Labrador (NL), to examine recent trends in OS. The goals of the current study are to compare trends with BC, where advocacy for the strategy is better established, determine the extent to which further potential benefits (including reduction of population level ovarian cancer burden) might be achievable with systematic implementation efforts, and inform policy and practice discussions.

3.2. Methods

3.2.1. Study Design

We report a secondary analysis of healthcare administrative and cancer registry data pertaining to the province of NL, Canada. The total NL population is 510,550 (24), with healthcare delivery provided during the study period by four regional health authorities (RHAs): Eastern, Central, Western, and Labrador-Grenfell. Eastern Health is the largest RHA, with a population of 322,759 (25).

3.2.2. Data Sources and Definitions

The data custodian for NL is the Newfoundland and Labrador Centre for Health Information (NLCHI) (26). NLCHI holds comprehensive data on individuals covered by the provincial health insurance system (Medical Care Plan, MCP). Three datasets provided the source data for the study: the Client Registry (which provides unique identifiers), the Provincial Discharge Abstract Database (PDAD) (which comprises inpatient and day case surgeries), and the NL Cancer Registry, which comprises data on new cancer diagnoses in NL residents.

The procedure data included demographic information, as well as procedures performed, dates and diagnostic indications. We used the International Statistical Classification of Diseases, 10th Revision (ICD-10) to classify the most likely indication for surgery into one of 11 categories (see Table 3.2). For cancer diagnoses, a list of codes was developed from the International Statistical Classification of Diseases for Oncology, third edition (ICD-O-3) (129). The de-identified PDAD dataset was merged with the dataset from the Client Registry to allow the calculation of age at surgery.

3.2.3. Participants

We included all patients who had undergone any or any combination of hysterectomy, oophorectomy, salpingectomy, or tubal ligation for benign indication in the province of NL, Canada, between the calendar years of 2010 and 2019 (refer to the flow chart in Appendix 1). We excluded those who were less than 15 years old at the time of any surgery and more than 64 at the time of tubal sterilization. We also excluded anyone who had been diagnosed with cancer(s) in female genital organs (ICD-O codes of C51.X to C58.X) before or at the time of surgery. Regarding

opportunistic salpingectomy, we only included those with bilateral salpingectomy either at the time of hysterectomy or tubal sterilization. Also, those with unilateral or unknown laterality tubal ligation were excluded from the analysis in the tubal sterilization group. Patients with two unilateral salpingectomies on opposing sides were included, but only the latter date of surgery was considered the date of surgery.

3.2.4. Data Analysis

We used Excel and Python software for data management and analyses, which were conducted in the NLCHI Provincial Data Lab, a secure, virtual environment.

For the data analysis, we categorized patients into two groups based on their procedures: hysterectomy and tubal sterilization. For hysterectomies, further stratification into hysterectomies with no concomitant salpingectomy or oophorectomy (referred to as hysterectomy alone), hysterectomy with bilateral salpingectomy (hysterectomy with OS), and hysterectomy with bilateral salpingo-oophorectomy (hysterectomy with BSO) was done. For tubal sterilization, patients were divided into tubal ligation (TL) and bilateral salpingectomy alone (OS). Those patients who underwent TL and hysterectomy were counted as hysterectomy alone.

We produced descriptive analyses of demographic attributes and summaries of procedure types. We examined trends in the use of OS procedures by year (using the date of the most recent procedure for those with multiple surgeries), age, and clinical indication for the primary procedure, using the International Statistical Classification of Diseases, 10th Revision (ICD-10). Diagnosis codes pertaining to diagnostic laparoscopy were omitted from the count for all groups. Also,

diagnosis codes for tubal ligation were omitted, except when the count pertained explicitly to the tubal ligation group.

Differences in the age of patients at the time of surgery were analyzed by independent sample t-test, and p-values < 0.05 were considered significant. The 'hysterectomy alone' group was used as the reference group for comparisons. The trend in the proportion of each surgery type within each group was assessed using logistic regression.

To evaluate rates of OC, de-identified PDAD data was merged with the cancer registry and patient registry. Cancer diagnoses were classified into 15 categories and presented in Table 1 supplemental. To calculate the duration of follow-up for each case, the date of the surgery was subtracted from June 30, 2022. Subsequently, the mean follow-up duration was calculated for each group and converted to months. We also calculated the mean length of follow-up from the date of surgery for the study population in months.

3.2.5. Ethics approval and considerations

Ethics approval was received from the provincial Health Research Ethics Board (HREB) (file #:20211119). Additional approval was received from the Secondary Uses Committee of NLCHI.

3.3. Results

Of 31,187 individuals undergoing gynecologic surgery for benign indications in the time period of interest, 25,643 (21,287 hysterectomy, 4,356 tubal sterilization) met the inclusion criteria for the study.

Of 21,287 hysterectomies, 1,309 (6.1%) fulfilled the definition of OS as outlined in section 3.2.3 of the Methods. The remainder (not fulfilling OS definition) were hysterectomy alone (17,676 (83.0%)) and hysterectomy with BSO (2,302, (10.8%)). Among those who had a form of tubal sterilization in the studied population, 4,134 (94.9%) had tubal ligation, and 222 (5.1%) had OS (see Table 3.1).

3.3.1. Trends over time

Hysterectomy:

Table 3.1 shows that all three forms of hysterectomy experienced an increase over the study period. However, the percentage of increase from 2010 to 2019 in the rate of hysterectomy with OS was more substantial than hysterectomy alone or with BSO (933% vs. 52% vs. 30%, respectively).

Figure 3.1A also shows a significant upward trend in the uptake of hysterectomy with OS ($p < 0.001$). In 2010, OS was performed in 1.6% of all hysterectomy cases, equating to 27 out of 1,696 cases. By 2019, this figure had risen markedly to 10.1%, or 279 out of 2,769 cases. Concurrently, there was a significant decrease in the proportion of hysterectomies performed without concomitant procedures ($p < 0.001$). In 2010, 86.5% of hysterectomy cases (1,467 out of 1,696 cases) were performed without additional surgeries. By the end of the study period in 2019, this proportion had diminished to 80.4% (2,227 out of 2,769 cases). Similarly, the data revealed a significant downward trend in hysterectomies with BSO ($p=0.002$). In 2010, hysterectomies with BSO constituted 11.9% of cases (202 out of 1,696). In 2019, this proportion had decreased to 9.5% (263 out of 2,769 cases).

Tubal sterilization:

The study also assessed trends in tubal sterilization methods, observing a significant shift in preference over the 10-year period. In 2010, 539 out of the total 4,134 tubal ligations recorded during the 10-year period were performed, representing 13% of all tubal ligations. By 2019, the annual number had decreased significantly, with only 340 procedures accounting for approximately 8.2% of the total tubal ligations over the study period ($p < 0.001$). Conversely, the practice of OS showed a significant increase in frequency towards the latter years of the study period ($p < 0.001$). Starting from a baseline where OS was virtually nonexistent in 2010, with only 3 recorded instances, there was a substantial rise to 69 such procedures by 2019 (Table 3.1). Figure 3.1B compares the proportion of OS procedures relative to tubal sterilizations over 10 years. When comparing the first and last year of the study period, OS consisted of 0.6% of all tubal sterilizations (3 out of 542), which gradually increased to 16.9% (69 out of 409) in 2019.

3.3.2. Demographic distribution

3.3.2.1. Age distribution

Hysterectomy

Demographic characteristics varied among the surgical groups. Among women who underwent a form of hysterectomy, those who had hysterectomy with BSO had the highest mean age, at 52.5 ± 9.8 years. In contrast, the lowest mean age was observed in the hysterectomy with OS group at

42.8 ± 6.9 years. The differences in mean age at the time of surgery between these groups and the group undergoing hysterectomy alone were statistically significant ($p < 0.001$).

When the distribution of the surgeries was analyzed by age categories, the age group 35-44 had the highest rate of hysterectomy with OS, followed by the age groups 45-54 years and 23-34 years. The majority of women undergoing hysterectomy with or without BSO were in the 45-54 age range (45.3% and 32.8%, respectively). The number of hysterectomies with OS drastically decreased in people over the age of 54 (3.2% of all hysterectomies with OS), whereas 36.4% of all hysterectomies with BSO and 25.5% of all hysterectomies alone were operated on people over the age of 54.

Tubal sterilization

The mean age of those who had a form of sterilization was significantly higher in the OS group compared to the tubal ligation group, 37 ± 7.1 vs 33.8 ± 5.7, respectively ($p < 0.001$). Correspondingly, the majority of TL and OS surgeries were performed on women in the age range of 25-34 and 35-44 years, respectively. The uptake of tubal ligation decreased in women over the age of 44, who constituted 3.6 of all tubal ligations. Whereas approximately 15% of women who underwent OS were older than 44.

3.3.2.2. Geographic distribution

The data indicate a notable variation in the distribution of surgical procedures among the different RHAs in the study. The Eastern RHA emerged as the leading region, with over 50% of the individuals undergoing each surgical procedure located there. The Western RHA was the second region where the highest percentage of all hysterectomies with OS and OS as a tubal sterilization method took place, 22.9% and 23.4%, respectively. Labrador-Grenfell had the lowest number of all types of hysterectomies and tubal sterilization, as detailed in Table 3.1. Specifically, within the Western RHA, 9.6% of all hysterectomies in this region were combined with OS, which is higher compared to 6.4% in Eastern, 4.7% in Labrador-Grenfell, and 4.2 in Central. Regarding tubal sterilization, the percentage of OS out of all tubal sterilizations within the region was slightly higher in Western RHA (6.0%) compared to Eastern (5.6%), followed by Labrador-Grenfell (4.3%) and Central (3.1%).

Table 3.1 Comparison of Different Gynecologic Procedures by Demographic Factors Between 2010 and 2019 in NL

Parameters	Hysterectomy n = 21 287			Tubal sterilization n = 4 356	
	Alone n = 17 676	With OS n = 1 309	With BSO n= 2 302	Tubal ligation n = 4 134	OS n = 222
Year, n (%)[a]					
2010	1467 (8.3)	27 (2.1)	202 (8.8)	539 (13.0)	3 (1.4)
2011	1522 (8.6)	45 (3.4)	223 (9.7)	448 (10.8)	4 (1.8)
2012	1502 (8.5)	80 (6.1)	227 (9.9)	444 (10.7)	9 (4.1)
2013	1538 (8.7)	98 (7.5)	214 (9.3)	465 (11.2)	13 (5.9)
2014	1788 (10.1)	120 (9.2)	222 (9.6)	409 (9.9)	5 (2.3)
2015	1860 (10.5)	144 (11.0)	233 (10.1)	410 (9.9)	14 (6.3)
2016	1946 (11.0)	163 (12.5)	229 (9.9)	401 (9.7)	15 (6.8)
2017	1965 (11.1)	158 (12.1)	241 (10.5)	376 (9.1)	40 (18.0)
2018	1861 (10.5)	195 (14.9)	248 (10.8)	302 (7.3)	50 (22.5)
2019	2227 (12.6)	279 (21.3)	263 (11.4)	340 (8.2)	69 (31.1)
Age, yr, mean ± SD (*P* value[b])	47.8 ± 12.3	42.8 ± 6.9 (<0.001)	52.5 ± 9.8 (<0.001)	33.8 ± 5.7	37 ± 7.1 (<0.001)
Age range, yr, n (%)					
15–24	326 (1.8)	0 (0)	4 (0.2)	211 (5.1)	3 (1.4)
25–34	1942 (11.0)	143 (10.9)	52 (2.3)	2039 (49.3)	86 (38.7)
35–44	5100 (28.9)	629 (48.1)	367 (15.9)	1736 (42.0)	99 (44.6)
45–54	5790 (32.8)	496 (37.9)	1042 (45.3)	147 (3.6)	31 (14.0)
55–64	2580 (14.6)	27 (2.1)	547 (23.8)	1 (0)	3 (1.4)
65–74	1452 (8.2)	9 (0.7)	252 (10.9)	0 (0)	0 (0)
≥ 75	486 (2.7)	5 (0.4)	38 (1.7)	0 (0)	0 (0)

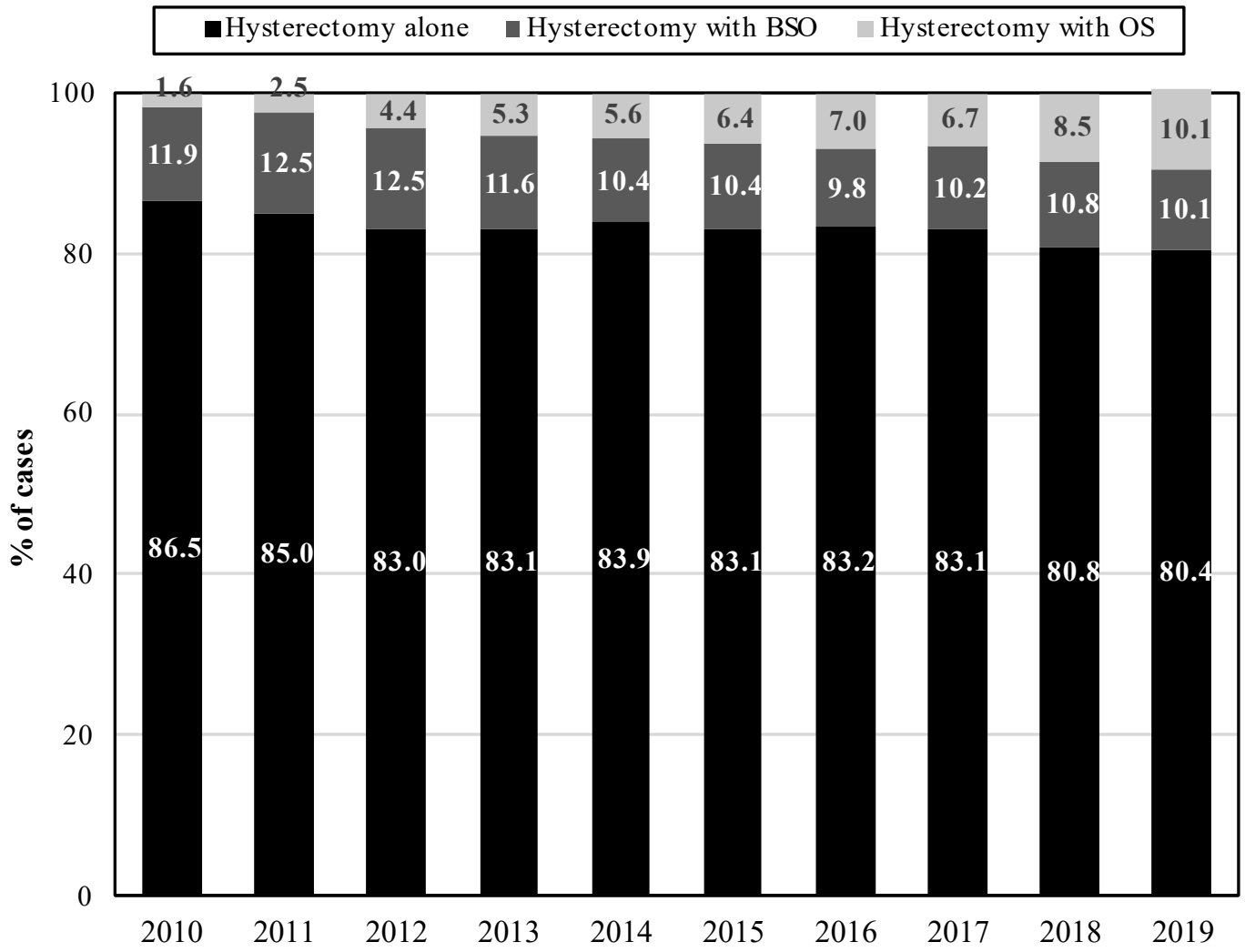
RHA, n (%)					
Eastern	8905 (50.4)	690 (52.7)	1263 (54.9)	2070 (50.1)	122 (55.0)
Central	5201 (29.4)	251 (19.2)	461 (20.0)	750 (18.1)	24 (10.8)
Western	2441 (13.8)	300 (22.9)	396 (17.2)	815 (19.7)	52 (23.4)
Labrador-Grenfell	983 (5.6)	57 (4.4)	170 (7.4)	447 (10.8)	20 (9.0)
Missing	146 (0.8)	11 (0.8)	12 (0.5)	52 (1.3)	4 (1.8)

Abbreviations: BSO = bilateral salpingo-oophorectomy, OS = opportunistic salpingectomy, SD = standard deviation, RHA = regional health authorities

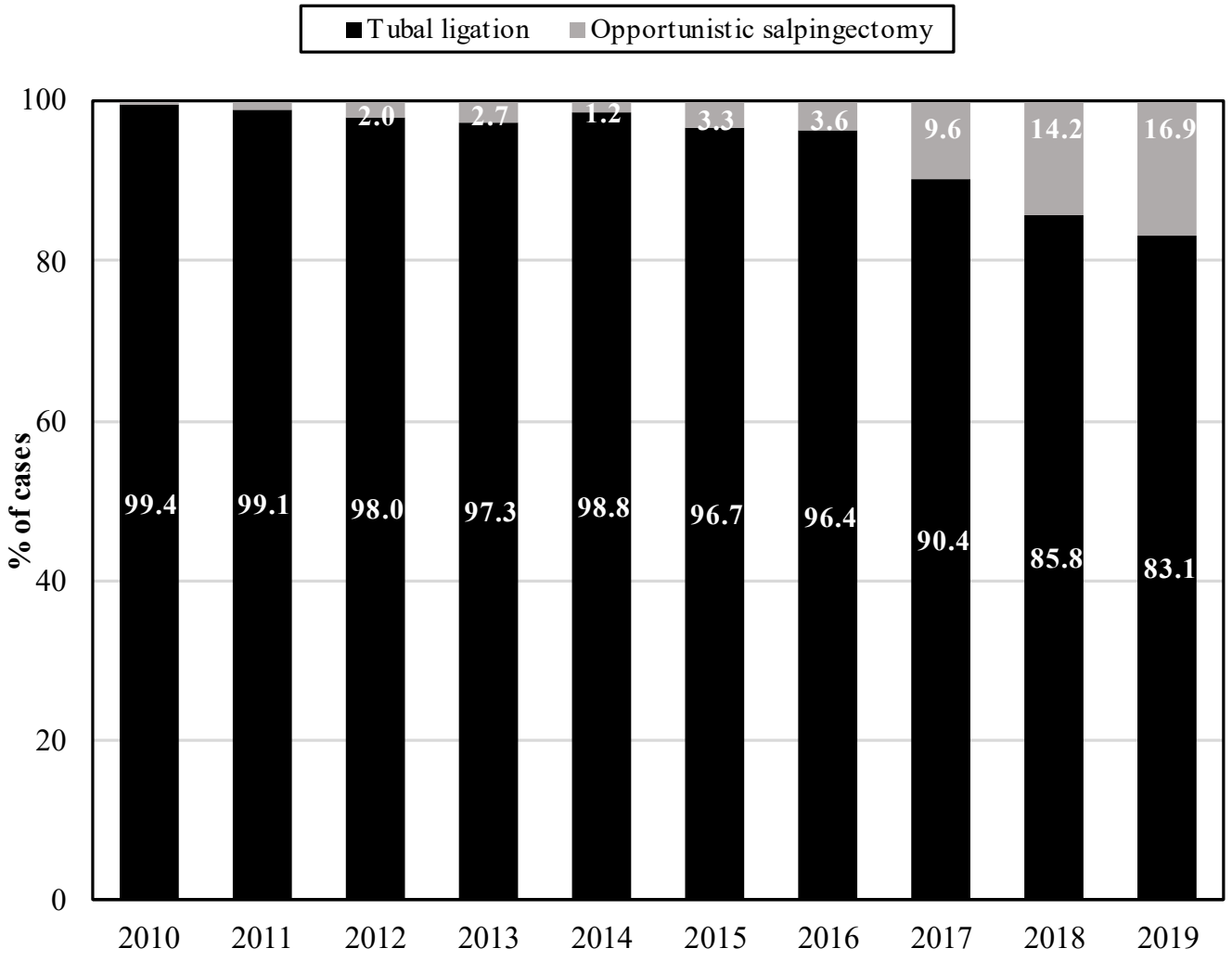
[a]In patients with multiple surgeries, the most recent surgery date is included.

[b]The reference in hysterectomy group was hysterectomy alone procedure and the reference in tubal sterilization group was tubal ligation procedure.

Figure 3.1 (A) Trends in the share of different types of hysterectomies in NL from 2010 to 2019. (B) Trends in the share of different types of tubal sterilization in NL from 2010 to 2019.



Total number of hysterectomies per year	1,696	1,790	1,890	1,850	2,130	2,237	2,338	2,364	2,304	2,769



Total number of tubal sterilizations per year	542	452	453	478	414	424	416	416	352	409

3.3.3. Clinical Indications Associated with the Surgery

Hysterectomy:

Table 3.2 shows the distribution of various diagnostic codes in patients who underwent one of the relevant surgeries. Excessive and abnormal bleeding (N92.X-N93.X) was the most repeated diagnostic code associated with hysterectomy with or without OS. In contrast, the majority of patients who had hysterectomy with BSO (89.5%) were diagnosed with noninflammatory disorders of ovary, fallopian tube and broad ligament (N83.X). Polyp of female genital tract (N84.X) and menopause (N95.X) were the second and third most frequent diagnostic codes in women who had hysterectomy alone. Leiomyoma of the uterus (D25.X) was the second most common diagnosis in hysterectomy with OS or BSO, 78.3% and 83.0% of all cases, respectively. Endometriosis (N80.X) was the third most repeated diagnostic code for those with hysterectomy with OS/BSO (49.6% and 73.5%, respectively).

Tubal sterilization:

The frequency of ICD-10 diagnostic codes varied between TL and OS groups. Sterilization (Z30.X) was coded for 95.2% of patients who had TL and 70.7% of patients with OS.

Noninflammatory disorders of ovary, fallopian tube and broad ligament (N83.X) and inflammatory diseases of female pelvic organs (N70.X-N77.X), and endometriosis (N80.X) were coded in 20.3%, 13.1% and 11.7% of all patients with OS, respectively. However, the second most repeated diagnostic code in the TL group was excessive and abnormal bleeding (N92.X-N93.X), which was coded for in 3.5% of the patients.

Table 3.2 Frequency of Diagnostic Codes/Diseases Across Different Surgery Groups					
	Hysterectomy n = 21 287			Tubal sterilization n = 4 356	
	Alone n = 17 676	With OS n = 1 309	With BSO n= 2 302	Tubal ligation n = 4 134	OS n = 222
ICD-10 diagnostic codes	**Cases to which codes assigned, n (%)[a]**				
Inflammatory diseases of female pelvic organs (N70.X-N77.X)	963 (5.4)	457 (34.9)	1072 (46.6)	78 (1.9)	29 (13.1)
Endometriosis (N80.X)	1133 (6.4)	649 (49.6)	1693 (73.5)	26 (0.6)	26 (11.7)
Menopause (N95.X)	3095 (17.4)	21 (1.6)	451 (19.6)	0 (0.0)	0 (0.0)
Female genital prolapse (N81.X)	2152 (12.2)	156 (11.9)	376 (16.3)	4 (0.1)	0 (0.0)
Noninflammatory disorders of ovary, fallopian tube and broad ligament (N83.X)	274 (1.6)	429 (32.8)	2061 (89.5)	49 (1.2)	45 (20.3)
Polyp of female genital tract (N84.X)	4991 (28.2)	151 (11.5)	708 (30.8)	4 (0.1)	1 (0.5)
Dysplasia of cervix uteri (N87.X)	411 (2.3)	62 (4.7)	78 (3.4)	16 (0.4)	0 (0.0)
Other noninflammatory disorders of uterus, cervix uteri, vagina, vulva, and perineum	2399 (13.6)	333 (25.4)	1330 (57.8)	21 (0.5)	1 (0.5)

(N85.X, N88.X-N90.X)					
Excessive and abnormal bleeding (N92.X-N93.X)	10656 (60.3)	1943 (148.4)	1425 (61.9)	145 (3.5)	10 (4.5)
Sterilization (Z30.X)	1667 (9.4)	348 (26.6)	45 (2.0)	3936 (95.2)	157 (70.7)
Leiomyoma of uterus (D25.X)	2267 (12.8)	1025 (78.3)	1911 (83.0)	19 (0.5)	1 (0.5)

Abbreviations: ICD-10 = *International Statistical Classification of Diseases and Related Health Problem* (10th revision)

[a]Each patient could have more than one diagnostic code

3.3.4. Cancer Diagnoses

The average follow-up period was shortest for the hysterectomy with OS group at 71.5 ± 30.5 months. In comparison, the follow-up periods for the hysterectomy with BSO and without BSO groups were similar, averaging 85.3 and 87.4 months, respectively.

Patients could have multiple cancer diagnoses, explaining the discrepancy between the total number of cancer patients and the total cancers diagnosed per group. Within the hysterectomy group, 975 cases were diagnosed with at least one type of cancer after their surgery. The lowest post-surgery cancer incidence was in the hysterectomy with OS group at 2.6%, and the highest was in the hysterectomy with bilateral BSO group at 6.3% (Table 1. supplemental).

Breast cancer was the most common diagnosis across all hysterectomy cohorts, affecting around 30% of patients, followed by cancers of the digestive organs, with slightly higher occurrences in

the BSO groups, 18.2% vs 17.3% (Table 1. supplemental). For the hysterectomy with OS group, thyroid and other endocrine cancers were the second most frequent diagnoses.

In the tubal sterilization cohorts, 62 cases of cancer were diagnosed post-operatively, constituting 1.5% of the TL group and 0.9% of the OS group. Follow-up for the TL group was longer by 33 months compared to the OS group (94.6 vs 61.3 months). Breast cancer remained the predominant diagnosis in the TL group, while the only cancers diagnosed in the OS group were in the skin and urinary tract.

3.3.5. Gynecologic Cancers Occurrence Post-Surgery

Given the study's focus on gynecologic cancer, the incidence of all gynecologic cancer types was evaluated and presented in Table 3.3 In the hysterectomy group, the proportion of patients diagnosed with a type of cancer in female genital organs (C51-C58) was comparable between hysterectomy alone and hysterectomy with BSO groups, at 06% and 07%, respectively. The occurrence of female genital cancer in hysterectomy with OS was the lowest, with only 0.3% of all patients diagnosed with cancer after the surgery. Within the category of female genital organ cancers, the total number of fallopian tube (C57.0) and ovarian (C56.9) cancers diagnosed was 20 in hysterectomy alone, 10 in hysterectomy with BSO, and none in hysterectomy with OS group.

In the hysterectomy alone group, corpus uteri (C54.x), with 56 diagnoses, was the most frequent gynecologic cancer. Furthermore, 13 cases were diagnosed with ovarian cancer, including two cases diagnosed within three months post-surgery. Seven fallopian tube cancer cases were identified, of which four also had additional gynecologic malignancies; one patient had a

concurrent unspecified malignancy of female genital organs (C57.9), and another was diagnosed with endometrial cancer (C54.1). Notably, two patients had synchronous ovarian and fallopian tube cancers, with one patient's diagnosis occurring immediately post-surgery, indicative of pre-existing cancer. For the remaining six cases, the mean time interval from the date of hysterectomy to the diagnosis of fallopian tube cancer was 50.2 months, with the time intervals ranging from 25 to 126 months. The histology of the neoplasm was STIC (8441/2) in four cases, serous adenocarcinoma (8441/3) in one case, and serous surface papillary carcinoma (8461/3) in one case.

Nine out of 18 diagnosed gynecologic cancers in hysterectomy with BSO group were ovarian primary (C56.9). However, eight of these nine cases were diagnosed within three months following surgery, suggesting a pre-existing condition. Likewise, the only case with fallopian tube cancer with histology of STIC (C57.0/8441/2) and synchronous ovarian cancer (C56.9) was diagnosed shortly after the surgery.

The mean age at the time of diagnosis was reflective of the population's mean age at the time of each surgery, with the hysterectomy with BSO having the highest mean age (62.7 ± 9.9) and hysterectomy with OS having the lowest (42.5 ± 4.9). Geographically, the distribution of cancer diagnoses mirrored the surgical locations; however, there was a slight deviation in the hysterectomy with OS group. In this group, the central health authority accounted for the second-highest number of cases, following the eastern region, which contrasts with the pattern seen in surgical distributions.

In the tubal sterilization group, only seven cases were diagnosed with a type of gynecologic cancer, and all of them were in the tubal ligation group. The mean age of diagnosis was 42 ± 3.7 years old. Only one case was diagnosed with ovarian cancer with the histology of mucinous adenocarcinoma, which was 127 months after tubal ligation. No cancers in female genital organs were observed in the OS group.

Table 3.3 Post-surgery Cancer Profile of Patients with a Relevant Surgery					
	Hysterectomy n = 21 287			Tubal sterilization n = 4 356	
	Alone n = 17 676	With OS n = 1 309	With BSO n= 2 302	Tubal ligation n = 4 134	OS n = 222
Counts, n (%)					
Total number of people diagnosed with a cancer in female genital organs (C51-C58)	113 (0.6)	4 (0.3)	17 (0.7)	7 (0.2)	0 (0.0)
Total number of cancers diagnosed in female genital organs (C51-C58)	117	4	18	7	0
Age at diagnosis, yr, mean ± SD	59.4 ± 12.0	42.5 ± 4.9	62.7 ± 9.9	42 ± 3.7	0
RHA, n (%)					
Eastern	58 (51.3)	3 (75.0)	13 (72.2)	4 (57.1)	0 (0.0)
Central	33 (29.2)	1 (25.0)	0 (0.0)	3 (42.9)	0 (0.0)
Western	10 (8.8)	0 (0.0)	4 (22.2)	0 (0.0)	0 (0.0)
Labrador-Grenfell	11 (9.7)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)
Missing	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Female genital organs sites, n (%)[a]					
Uterus, NOS (C55)	0 (0.0)	0 (0.0)	2 (11.1)	1 (14.3)	0 (0.0)
Ovary (C56.9)	13 (11.1)	0 (0.0)	9 (50.0)	1 (14.3)	0 (0.0)
Fallopian tube (C57.0)	7 (6.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)
Other and Unspecified female genital	5 (4.3)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)

organs (C57.x) except fallopian tube (C57.0)[b]					
Corpus Uteri (C54.X)	57 (48.7)	0 (0.0)	1 (5.6)	2 (28.6)	0 (0.0)
Combined lower genital tract (C51.X -C53.X)[c]	35 (29.9)	4 (100)	4 (22.2)	3 (42.9)	0 (0.0)

Abbreviations: BSO = bilateral salpingo-oophorectomy, OS = opportunistic salpingectomy, RHA= regional health authority, ICD-O = *International Statistical Classification of Diseases for Oncology* (third edition), NOS: Not otherwise specified

[a]Each patient could have more than one diagnostic code

[b]The count for fallopian tube cancer (C.57.0) is reported separately although it falls into C57.X category

[C]Cancers in lower genital tract includes the vulva, vagina, and cervix uteri

3.4. Discussion

The study demonstrates a significant evolution in gynecological surgical practices in Newfoundland and Labrador (NL) Canada, evidenced by a marked increase in the adaptation of OS during the study period. The 10.3-fold increase in the uptake of OS at the time of hysterectomy from 2010 to 2019 reflects a change in clinical practice within NL. In 2010, 86.5% of all hysterectomies were hysterectomy alone, which decreased to 80.4% in 2019. Despite the promising trend, a substantial majority of hysterectomy cases in 2019 did not have OS, highlighting a continued opportunity to expand the practice. Compared to the average uptake of OS during hysterectomy across Canada (excluding Quebec), which was reported at 35.5% of all hysterectomies in 2016, NL shows a slower adoption of this procedure, with only 16.1% of hysterectomies including OS in 2019 (27). Analyses of the US Nationwide Inpatient sample dataset

showed that in 2015, 60% of women undergoing hysterectomy also had opportunistic salpingectomy (28). The significant rise in the U.S. reflects a more aggressive shift in clinical practice than in Canada. While NL has shown a promising trend toward OS adoption, there remains substantial room for alignment with the more pronounced change observed in the U.S. and the rest of Canada, especially the province of BC, where uptake rates were reported as 35% of all hysterectomies (29).

While the adoption of opportunistic salpingectomy (OS) for tubal sterilization in this province has experienced a considerable increase, with a 28.1-fold rise from 2010 to 2019, tubal ligation continues to be the preferred method, accounting for 83.1% of all sterilizations in 2019. A notable finding is the sharp rise in the uptake of OS in 2017. 9.6% of all tubal sterilizations were performed as OS in 2017 compared to 3.6% in 2016. This may be attributable to the issue of the American College of Obstetricians and Gynecologists (ACOG) guidelines in 2015, suggesting a positive influence on the practice of OS (30). Comparatively, in 2016, the national average for OS adoption during tubal sterilization in Canada was 35.5% (27). This gap highlights the potential for further implementation of OS for tubal sterilization in NL.

The analysis of diagnostic codes indicates that OS was more frequently performed in the presence of other gynecological health issues. Specifically, 11 to 20% of OS cases were associated with diagnoses like endometriosis, inflammatory diseases of pelvic organs, and noninflammatory disorders of the ovary, fallopian tube, and broad ligaments. In contrast, tubal ligation was predominantly performed for sterilization alone, with only 0.5 to 3.5% of cases linked to additional health complications. This variation may reflect some gynecologists' reluctance in NL to conduct OS for sterilization alone, without other gynecological indications, possibly due to concerns about

its irreversibility and the absence of local IVF services. Such hesitancy may be a factor in the procedure's limited adoption. Furthermore, the average age of patients undergoing OS was 37, compared to 33.8 for those receiving tubal ligation, suggesting that decisions regarding sterilization methods may also be influenced by patient age.

The low rate of opportunistic salpingectomy might also be explained by the fact that this is a relatively new strategy, and there has not been clear evidence until 2022 to support the efficacy of this surgery (20). This could lead to not prioritizing this surgery due to concerns regarding the operation duration and other peri-operative complications. Moreover, the Eastern Regional Health Authority, which serves more than 50% of our study population, is an academic centre. Adding another nonpriority procedure to the hysterectomy in the limited OR time is challenging in a teaching environment. The low uptake of OS could also be explained by the concerns of provincial gynecologists about the difficulties of surgeries and complications in obese patients. In 2022, 41.9% of adults in NL had a BMI of 30 or greater, making it the second-highest rate of obesity among provinces of Canada (31). Adding another procedure, which might increase the OR time and, therefore, the duration of anesthesia, is high-risk in these patients. Usually, obese patients are placed in the Trendelenburg position for the surgery for better visualization of the pelvis. However, there are physiological risks associated with this position, including increased ventilation requirements and increasing OR time, which can jeopardize the patient’s safety (32,33). Additionally, the addition of OS to hysterectomy could potentially influence the choice of surgical approach, particularly in patients with obesity where the decision between vaginal surgery, minimally invasive, and abdominal is crucial.

With respect to cancer incidence in the hysterectomy group, 1% of hysterectomy alone group and hysterectomy with OS group were diagnosed with breast cancer, indicating the similarity between the populations. However, the total number of cases with a diagnosis of ovarian cancer or fallopian tube cancer more than three months after the surgery was 18 in the hysterectomy group (0.1% of all cases) compared to none in hysterectomy with OS. However, it should be noted that the hysterectomy with OS group had a shorter follow-up time of 14 months compared to the hysterectomy alone group. When comparing tubal ligation with OS, one OC case with the cell type of mucinous adenocarcinoma was identified 127 months post tubal ligation, compared to none in the OS group.

It is important to recognize that the mean age across the five surgical groups was relatively young, ranging from 33.8 years in the tubal ligation group to 52.5 years in the hysterectomy with BSO group. This is particularly significant considering the median age for ovarian cancer diagnosis in Canada is 63 years (34). Even the hysterectomy with BSO group, which had the highest average age at surgery and the longest follow-up, did not reach this median age by the end of the study period. These age differences are crucial for interpreting the observed cancer incidences within our cohorts. We recognize the study is underpowered to make any inferences about the relationship between OS and OC, but the trends in the descriptive data suggest that including OS during hysterectomy procedures could potentially have prevented the development of subsequent ovarian and/or fallopian tube cancers observed in the follow-up period. Specifically, in the hysterectomy alone group, there were 11 cases of ovarian cancer and six cases of fallopian tube cancer that emerged postoperatively, which may have been preventable had OS been performed. Similarly, among those who had tubal ligation, one case of ovarian cancer might have been averted with the

uptake of OS instead of tubal ligation. This observation aligns with findings from Giannaakeas et al., who also found no statistically significant association between salpingectomy and reduced ovarian cancer risk in Ontario despite observing a lower incidence of ovarian cancer in the OS group compared to no surgery group, likely due to the rarity of ovarian cancer and the limited follow-up duration (35).

3.4.1. Limitations

There are inherent limitations in the use of secondary data. We cannot ensure that the coding in the source database had been done entirely accurately. We also assumed that in the surgery of partial salpingectomy, the fimbriated ends of the fallopian tubes were removed and, therefore, included them in the OS groups. In addition, the small population of NL, the short follow-up period, the young population and the low absolute numbers of cancer limited study power. There is a need for longer-term studies and/or pooled data from multiple studies to establish a definitive protective effect and benefits of this procedure. However, this project was the first research on the uptake of gynecologic surgery and cancer outcomes in the province of NL and provides useful preliminary descriptive data.

3.4.2. Future Research Direction

Given the relatively short time since the implementation of OS globally, there are still unexplored questions. Retrospective longitudinal study over an extended follow-up period will allow a more sophisticated exploration of cancer outcomes through time-to-event analyses with larger cohorts.

Patient- and clinician-reported outcomes can also help us understand the underlying reasons for the low uptake of this surgery in our province and strategize future planning. Moreover, qualitative patient-oriented research can help to identify the areas that need improvement and the barriers that need to be overcome, such as awareness in the general population about OS as a contraception method or its addition to the hysterectomy.

3.4.3. Conclusion

This article offers foundational insights that can help identify key research priorities, involve clinicians and researchers, and initiate discussions among clinical practice and policy leaders regarding the feasibility and benefits of OS within Canadian regions. While data suggest the use of OS increased over the last decade, the uptake is not as high as BC or the national average. Baseline data such as these are necessary for tracking change over time, and future research is needed to better establish the efficacy of OS as a cancer prevention strategy.

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Chapter 4: Discussion

4.1. Overall Thesis Summary

OC is the most lethal gynecological cancer, with over 3000 new cases in Canada every year. Despite efforts to identify effective screening, the survival rate has not improved significantly over the past decades for this silent killer. Current screening tests have low sensitivity for early-stage OCs, which is crucial for a better prognosis. Opportunistic salpingectomy was first introduced in 2010 as a preventative measure for the general population, following the discovery that the origin of OC is the distal end of fallopian tubes.

The narrative review revealed that opportunistic salpingectomy is a feasible and safe preventative strategy for patients undergoing hysterectomy for benign reasons or those seeking permanent contraception. Robust evidence revealed the cost-effectiveness and efficacy of this surgery, supporting its broader implementation in the general population. Despite the compelling evidence supporting the benefits of this surgery, the adoption rate of opportunistic salpingectomy in Canada is variable across provinces and remains lower than in the United States.

An analysis of chart reviews and registry data indicates that while the uptake of OS in NL, Canada, increased significantly from 2010 to 2019, tubal ligation rather than salpingectomy continues to be the predominant method of tubal sterilization. Furthermore, a significant number of women (80%) undergoing hysterectomy do not undergo fallopian tube removal, missing a critical opportunity for cancer prevention.

Moreover, although OS is recognized for its promising role in the prevention of OC, the data suggest there remains significant room for increasing its acceptance and altering practice patterns

among obstetricians and gynecologists in NL, Canada. The reluctance or slow pace in adopting this practice could be attributed to various factors, including the lack of awareness about the benefits, resistance to change in surgical routines in an academic center, or perceived risks associated with the procedure.

4.2. Contribution to the literature

This is the first study to examine the uptake of OS in the general population of NL at the time of hysterectomy for benign reasons or as a contraceptive method and to report the cancer outcome following the surgery. The results of this research add to the broader Canadian data landscape, potentially contributing to more statistically powerful outcomes in future research.

Moreover, the research conducted for this thesis is vital in laying the groundwork for enhanced adoption of OS in NL, Canada. Insights from this study provide essential baseline metrics that not only help in articulating future research directions but also assist in strategizing more effective implementations of this preventive measure. It is imperative that continuing education and policy-making efforts are directed towards promoting the benefits of OS to both healthcare providers and patients, ensuring that this preventive strategy is more widely utilized to improve women's health outcomes in NL and across Canada as the evidence base grows.

4.3. Future Research Direction

Future work should involve:

1. Prospective research on ovarian reserve to better understand the long-term effects of OS on ovarian function.
2. Chart review studies from various healthcare centers across Canada to gather diverse data on the use of OS and OC outcomes.
3. Pooled data analysis to provide comprehensive reporting on OC prevention.
4. Prospective studies with extended follow-up periods to assess the long-term efficacy of OS in the prevention of OC.
5. Clinician-centred studies to yield valuable insights into several aspects, including:

    - Barriers to adoption
    - Effectiveness and safety
    - Patient follow-up and satisfaction
    - Limitations from the perspective of both clinicians and health systems

6. Patient-focused qualitative studies to understand the subjective experiences, attitudes, and concerns of patients to further inform and enhance clinical practices, decision-making processes, and patient education.

4.4. Conclusion

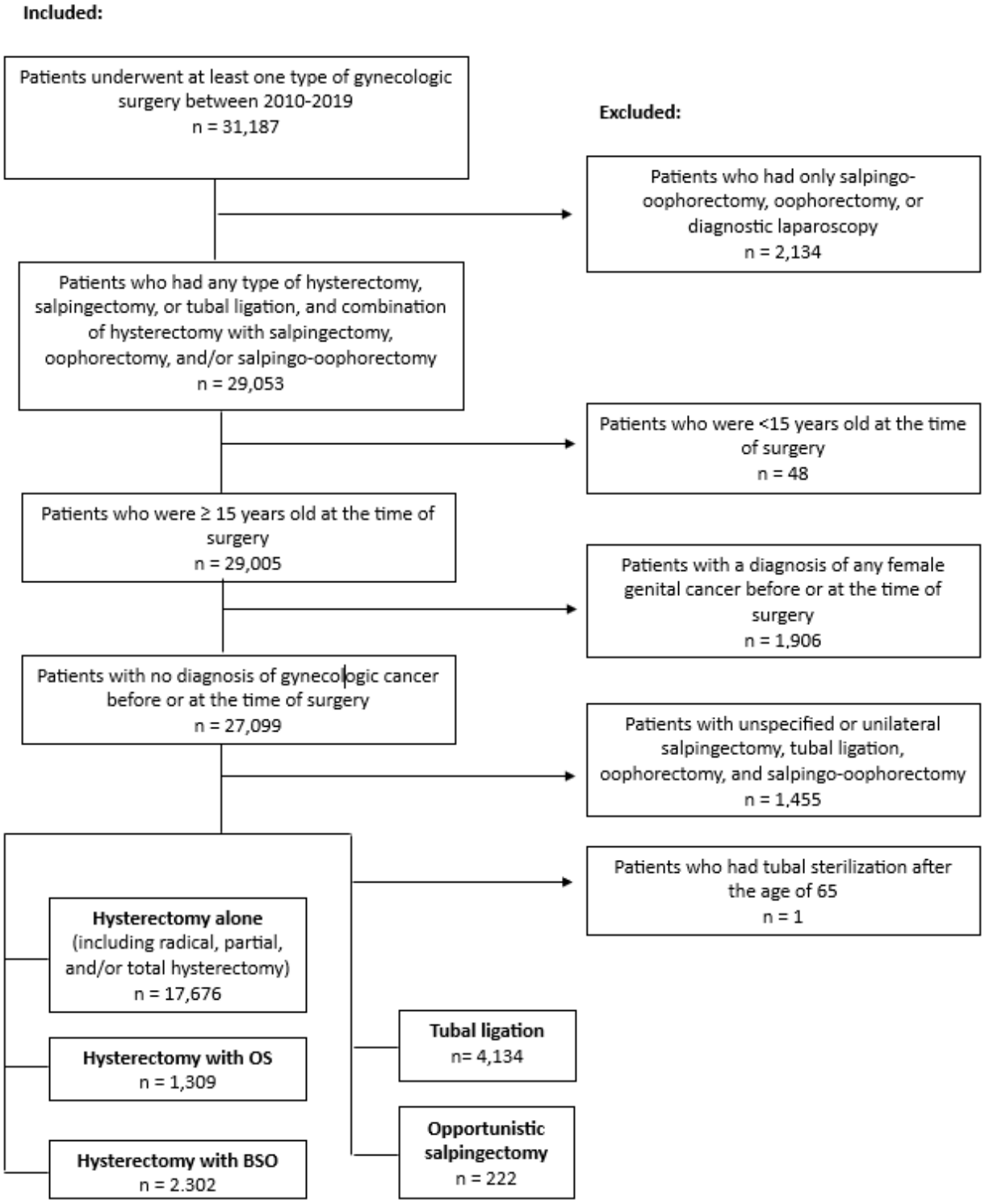
The findings from this study not only enrich the Canadian data landscape but also provide a model that can be replicated and expanded in other regions. By demonstrating the feasibility, safety, and efficacy of OS, this research supports its broader adoption as a standard practice in gynecologic surgery, thereby extending its benefits to a wider population.

As the first comprehensive study of its kind in NL, the research underlines the critical need for enhanced educational programs for healthcare providers and policy-making efforts to avail the benefits of OS. This strategic approach could result in a shift in standard surgical practices, making OS a routine part of gynecological procedures, thus lowering OC incidence nationwide. Moreover, the insights gained from this research lay a solid foundation for future studies. It is essential that subsequent research explores long-term outcomes, refines patient selection criteria, and assesses the psychological impacts of OS on women. By building on this groundwork, future researchers can explore innovative strategies to enhance the prevention strategies of OC, ultimately leading to improved survival rates and quality of life for women across Canada and beyond.

In conclusion, this thesis not only fills a significant gap in our current understanding and implementation of OS but also serves as a foundation for future research endeavors on this topic in NL. By continuing to build on this foundation, we can significantly enhance ovarian cancer prevention, ensuring that more women benefit from risk-reducing salpingectomy. The potential to save lives and improve health outcomes through such preventive strategies highlights the profound importance of this research within the field of gynecologic oncology.

Appendices

Appendix 1: Flow Chart of Study Population Selection



Appendix 2: Table 1

Table 1 Cancer Incidence in Patients after gynecologic Surgery for Benign reason					
	Hysterectomy n = 21 287			Tubal sterilization n = 4 356	
	Alone n = 17 676	With OS n = 1 309	With BSO n= 2 302	Tubal ligation n = 4 134	OS n = 222
Counts, n (%)					
Total number of people with cancer diagnosed after the surgery	796 (4.5)	34 (2.6)	145 (6.3)	60 (1.5)	2 (0.9)
Total number of cancers diagnosed[a]	849	36	170	64	2
Mean follow-up duration (months)	87.4 ± 34.9	71.5 ± 30	85.3 ± 34.5	94.6 ± 34.4	61.3 ± 27.5
ICD-O topography categories, n (%)					
Bones, joints, and articular cartilage (C40-C41)	0 (0.0)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)
Breast (C50)	264 (31.1)	11 (30.6)	56 (32.9)	16 (25.0)	0 (0.0)

Connective, subcutaneous and other soft tissues (C49)	4 (0.5)	0 (0.0)	0 (0.0)	3 (4.7)	0 (0.0)
Digestive organs (C15-C26)	147 (17.3)	4 (11.1)	31 (18.2)	9 (14.1)	0 (0.0)
Eye, brain, and other parts of central nervous system (C69-C72)	19 (2.2)	1 (2.8)	5 (2.9)	2 (3.1)	0 (0.0)
Female genital organs (C51-C58)	117 (13.8)	4 (11.1)	18 (10.6)	7 (10.9)	0 (0.0)
Hematopoietic and reticuloendothelial sytems (C42)	21 (2.5)	0 (0.0)	1 (0.6)	4 (6.3)	0 (0.0)
Lip, oral cavity and pharynx (C00-C14)	16 (1.9)	0 (0.0)	3 (1.8)	0 (0.0)	0 (0.0)
Lymph nodes (C77)	24 (2.8)	1 (2.8)	8 (4.7)	3 (4.7)	0 (0.0)
Pelvis, NOS (C76.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory system and intratoractic organs (C30-C39)	68 (8.0)	2 (5.6)	10 (5.9)	3 (4.7)	0 (0.0)

Retroperitoneum and peritoneum (C48)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin (C44)	47 (5.5)	4 (11.1)	15 (8.8)	3 (6.3)	1 (50)
Thyroid and other endocrine glands (C73-C75)	67 (7.9)	6 (16.7)	6 (3.5)	8 (12.5)	0 (0.0)
Unknown primary site (C80)	8 (0.9)	0 (0.0)	3 (1.8)	0 (0.0)	0 (0.0)
Urinary tract (C64-C68)	45 (5.3)	2 (5.6)	14 (8.2)	5 (7.8)	1 (50)

Abbreviations: BSO= bilateral salpingo-oophorectomy, OS= opportunistic salpingectomy, ICD-O-3= *International Statistical Classification of Diseases for Oncology* (third edition)

[a]Each patient could have more than one diagnostic code

Appendix 2: Ethics Approval

Research Ethics Office
Suite 200, Eastern Trust Building
95 Bonaventure Avenue
St. John's, NL
A1B 2X5

February 19, 2021

Dear Tahereh Masouleh:

Researcher Portal File # 20211119
Reference # 2020.295

RE: The uptake of opportunistic salpingectomy as a benign gynecologic surgery in general population of Newfoundland and Labrador

Your application was reviewed by a subcommittee under the direction of the HREB and the following decision was rendered:

X	Approval
	Approval subject to changes
	Rejection

Ethics approval is granted for one year effective February 19, 2021. This ethics approval will be reported to the board at the next scheduled HREB meeting.

This is to confirm that the HREB reviewed and approved or acknowledged the following documents (as indicated):

- Proposal 02Feb2021, approved
- Variable List 02Feb2021, acknowledged
- Budget, acknowledged

Appendix 3: Research Proposals Approval Committee (RPAC) of Eastern Health Approval

Department of Research
5th Floor Janeway Hostel
Health Sciences Centre
300 Prince Philip Drive
St. John's, NL A1B 3V6
Tel: (709) 752-4636
Fax: (709) 752-3591

April 15, 2021

Ms. Tahereh Masouleh
300 Prince Philip Drive
St. John's, NL
A1B 3V6

Dear Ms. Masouleh,

Your research proposal *HREB Reference #: 2020.295 "The uptake of opportunistic salpingectomy as a benign gynecologic surgery in general population of NL"* was reviewed by the Research Proposals Approval Committee (RPAC) of Eastern Health April 6th, 2021, and we are pleased to inform you that the proposal has been granted full approval.

The approval of this project is subject to the following conditions:

- The project is conducted as outlined in the HREB approved protocol;
- Adequate funding is secured to support the project;
- In the case of Health Records, efforts will be made to accommodate requests based upon available resources. If you require access to records that cannot be accommodated, then additional fees may be levied to cover the cost;
- A progress report being provided upon request.

If you have any questions or comments, please contact Krista Rideout, Manager of the Patient Research Centre at 777-7283 or by email at krista.rideout@easternhealth.ca.

Sincerely,

ector, Research and Innovation
Co-Chair, RPAC

FM/rg

Appendix 4: Data Request Approval

Newfoundland & Labrador Centre for Health Information

May 17th, 2022

Tahereh Masouleh
Faculty of Medicine
Memorial University
300 Prince Philip Drive, St. John's NL A1B 3V6

Dear Ms. Masouleh:

RE: The Uptake of Opportunistic Salpingectomy as a Benign Gynecologic Surgery in the General Population of Newfoundland and Labrador
Our Reference *IM219852*

This is to advise you that the Centre's Secondary Uses Committee has reviewed your application to request Record-Level Information for Secondary Use. Having consulted with the chair, I authorize the disclosure of the requested data.

The approval of your application and use of the requested data is conditional upon the following:

- The data accessed must be used only for the purposes of this request. Future uses and/or disclosures of the data collected must have Health Research Ethics Board (HREB) approval as well as approval from the Centre;
- Cell counts or statistics based on cell counts less than 5 are not published;
- The data must be stored on a Memorial University asset and must not be places on a personal device;
- All members of the research team must comply with Memorial University's policies and procedures for privacy, security and data storage, and have signed an Oath of Confidentiality;
- At the end of the data retention period data must be disposed of by ensuring the drives on the device are appropriately sanitized (securely deleted or destroyed) prior to the disposal or repurposing of the system or any storage components;
- If there are changes with the research study and/or research team then the Centre must provide approval for these changes. Any amendments or updated HREB approval(s) will be supplied to the Centre accordingly;

Newfoundland and Labrador Centre for Health Information
www.nlchi.nl.ca
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