Sexual Function in Women Undergoing Risk Reducing Salpingo-Oophorectomy With or Without Hysterectomy

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SEXUAL FUNCTION IN WOMEN UNDERGOING RISK REDUCING SALPINGO-OOPHORECTOMY WITH OR WITHOUT HYSTERECTOMY

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree of
Master of Medical Science

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LIST OF ABBREVIATIONS

ACOG American College of Obstetricians and Gynecologists
AH Abdominal Hysterectomy
BC Breast Cancer
BRCA Breast Cancer Susceptibility Gene
BRCA+ Breast Cancer Gene Positive
BSO Bilateral Salpingo-Oophorectomy
E Estrogen
E+P Estrogen plus progesterone
FSDS Female Sexual Distress Score
FSFI Female Sexual Function Index
FSH Follicle-stimulating Hormone
GLM Generalized Linear Model
HBOC Hereditary Breast and Ovarian Cancer
HRT Hormone Replacement Therapy
LASH Laparoscopic Supracervical Hysterectomy
MENQOL Menopause-Specific Quality of Life
MENQOL-I Menopause-Specific Quality of Life Intervention
NCCN National Comprehensive Cancer Network
NORM Norm Sample
QOL Quality of Life
RCTs Randomized Controlled Trials
RRBSO Risk-Reducing Bilateral Salpingo-Oophorectomy
SAQ Sexual Activity Questionnaire
TAH Total Abdominal Hysterectomy
VH Vaginal Hysterectomy

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Table 1. Female Sexual Function Index (FSFI) scores and domain coefficients

Table 2. Descriptive Characteristics of Study Variables
ABSTRACT

Bilateral Salpingo-Oophorectomies are offered to women with hereditary breast and ovarian cancer syndromes as prophylaxis to reduce the incidence of ovarian cancer. These surgeries induce acute surgical menopause and often result in compromised sexual function including decreased desire, sexual discomfort, and diminished sexual satisfaction. However, little is known about the differences in sexual function in women who undergo surgery with hysterectomy versus those that leave their uterus intact. Using a prospective cohort study, we will compare the effects of Bilateral Salpingo-Oophorectomy alone versus Bilateral Salpingo-Oophorectomy plus hysterectomy on sexual function in premenopausal women with breast cancer gene mutations. We will evaluate sexual function using several well-validated surveys including the Female Sexual Function Index. These insights will arm medical professionals and their patients with data on sexual outcomes and will help patients decide whether to include a hysterectomy in their cancer prevention plan.
CHAPTER 1: INTRODUCTION
1.1 Background
1.1.1 Hereditary Breast and Ovarian Cancer Syndrome and RRBSO

Hereditary breast and ovarian cancer (HBOC) syndrome is an autosomal dominant cancer-predisposition syndrome that is most often associated with mutations in the BRCA1 gene and the BRCA2 gene. HBOC predisposes affected individuals to an elevated lifetime risk of ovarian cancer in women, and breast cancer in both men and women. Women carrying the BRCA1 and BRCA2 mutations have an increased lifetime risk of developing breast (72% and 69%) and ovarian cancer (44% and 17%) compared to the general population who have a 12.8% lifetime risk of breast cancer and 1%-5% lifetime risk of ovarian cancer. Recent literature has also suggested that there may be an increased risk of uterine serous and serous-like endometrial carcinomas in women with BRCA gene mutations, especially those with BRCA1 mutations.

The excessive risk of ovarian cancer among women with BRCA mutations warrants consideration of more intensive screening and prevention strategies. Ovarian cancer is the deadliest gynecological malignancy, causing more deaths than any other cancer of the female reproductive system. It has a poor prognosis with 47% survival at 5 years, and in the United States, 70% of women diagnosed with ovarian cancer will die from this disease. Given the lack of effective early detection methods for ovarian cancer, and the increased lifetime risk of ovarian cancer women with BRCA mutations face, preemptive surgical removal of the bilateral fallopian tubes and ovaries is currently recommended. In the medical community, this procedure is referred to as Prophylactic Risk-Reducing Bilateral Salpingo-Oophorectomy (RRBSO), and has been adopted as the gold standard and the most effective option for ovarian cancer risk reduction.
study, this procedure was shown to reduce the incidence of ovarian cancer in high-risk women by up to 95% and leads to an overall survival benefit.\textsuperscript{10} A meta-analysis of 10 studies of BRCA1 and 2 mutation carriers showed an approximate 80% reduction in the risk of ovarian or fallopian tube cancer following an RRBSO\textsuperscript{11} as well as a potential reduction in breast cancer incidence.\textsuperscript{12,13} Despite varying estimates of risk reduction, the benefits of RRBSO are clear, and increased awareness of surgical options to reduce risk has led to an increase in uptake of RRBSO of 75% among women with BRCA mutations\textsuperscript{14}.

\textbf{1.1.2 RRBSO and Surgical Menopause}

Current NCCN guidelines recommend BRCA1 women undergo RRBSO at age 35–40 and BRCA2 women at age 40–45 or upon completion of child bearing, whichever is sooner.\textsuperscript{2} Although RRBSO is highly effective in preventing cancer, it is associated with significant short-term and long-term morbidity\textsuperscript{15,16}, including increased risk of cardiovascular disease, accelerated osteoporosis, neurocognitive decline and a host of other chronic conditions.\textsuperscript{15,17-19}

Another significant consequence of RRBSO is surgical menopause, which is both common and a cause for concern among many women undergoing this procedure.\textsuperscript{20} Since RRBSO is undergone prior to the average age of natural menopause which, in the United States, occurs at age 51,\textsuperscript{21} it usually induces acute surgical menopause. Among women with BRCA mutations, the majority of whom are young and premenopausal at the time of surgery, this abrupt transition into surgical menopause is severe, and concerns about early menopause are a common reason for deferring or declining the procedure.\textsuperscript{20} Natural menopause transition is a normal physiologic condition where the decline of ovarian
hormone synthesis happens gradually over time. In contrast, surgical menopause results in the abrupt decrease in sex hormones circulating such as estrogen, testosterone, and progesterone and is more severe than what is seen in natural menopause. In pre-menopausal women, like many BRCA patients, surgical menopause is associated with increased severity of sexuality, intimacy, and menopause symptoms such as hot flashes, night sweats, vaginal dryness, loss of sexual desire, and dyspareunia (painful intercourse). Women who undergo surgical menopause also have higher rates of hypossexual desire disorder (deficiency/absence of sexual thoughts and desires) than women who undergo natural menopause. These symptoms negatively affect the quality of life of these women and their longevity.

1.1.3 The Role of Hormone Replacement Therapy in Sexual Function

The occurrence of early menopause and decline in sexual function after RRBSO are some of the most feared consequences by both patient and physician. Luckily, hormone replacement therapy (HRT), has shown broad benefits in women who undergo RRBSO, and can partially mitigate these symptoms. Since sexual dysfunctions after RRBSO are primarily the result of decreased sex hormones, the administration of hormone replacement therapy (HRT) until the average age of natural menopause plays a critical role in this population. In addition to decreasing the risk of coronary artery disease, osteoporosis, vasomotor symptoms and neurocognitive decline, HRT use in the first year after RRBSO has demonstrated beneficial effects in reducing endocrine and sexual dysfunctions among women with BRCA mutations. When comparing pre- and post-surgical sexual functioning of women who have undergone RRBSO with control women, women with RRBSO have worse sexual functioning. Sexual functioning is improved
with administration of HRT, but not to pre-surgical levels.\textsuperscript{23} Due to the loss of circulating testosterone and androstenedione which are also produced by the ovaries but often not a part of HRT, HRT does not improve all aspects of sexual dysfunction.\textsuperscript{31}

In the early 2000s, hesitancy about HRT in the general population arose because of data released on the negative effects of long-term HRT use including risk of breast cancer.\textsuperscript{32} However, it has been repeatedly demonstrated that short-term use of HRT does not have any influence on the protective effect of RRBSO on breast cancer incidence,\textsuperscript{33,34} is a safe therapeutic option for BRCA mutation carriers undergoing RRBSO,\textsuperscript{25} and that some types of HRT, such as estrogen therapy alone, may even have a protective effect on breast cancer.\textsuperscript{34} For women who choose to undergo a concurrent hysterectomy, estrogen alone HRT seems to be the safest and most reasonable choice.\textsuperscript{25} BRCA mutation carriers can be reassured that HRT short-term usage does not substantially diminish the breast cancer risk reduction gained from RRBSO.\textsuperscript{25} It should be noted however, that HRT is contraindicated in women with a prior diagnosis of breast cancer.\textsuperscript{35}

1.1.4 Hysterectomy at the time of risk-reducing surgery

Total hysterectomy is defined as the removal of the uterine corpus with the cervix. Hysterectomy remains the most common major gynecological surgery in the United States after cesarean section.\textsuperscript{36} In the United States, oophorectomy is performed in conjunction with hysterectomy about 40-50\% of the time.\textsuperscript{37} The lifetime risk of ovarian cancer is low in the general population (about 1.4\%), and the benefits of concomitant hysterectomy and BSO may not outweigh the risks. However, among women with BRCA mutations, this risk/benefit tradeoff is very different, and the decision to perform hysterectomy at the time of RRBSO should be individualized.\textsuperscript{38}
Many clinicians recommend that women with BRCA mutations undergo RRBSO with concurrent hysterectomy. In a study of 339 BRCA women, 55.8% (N=185) underwent a concomitant hysterectomy with their RRBSO\(^\text{39}\) despite the fact that the NCCN Guidelines, last updated in November 2020, do not specifically recommend a hysterectomy as part of the care offered to BRCA women.\(^\text{2,40}\) In this study, the reasons most commonly cited for concurrent hysterectomy were provider recommendation (38.9%) and personal desire to remove the uterus to prevent uterine cancer (27.6%).\(^\text{39}\) Over half of the women in the study decided to undergo RRBSO with hysterectomy, and most did so because of the recommendation of their providers.\(^\text{39}\) It has been proposed that providers may be making this recommendation because some literature supports the association between uterine serous carcinomas among women with BRCA mutations,\(^\text{6,39,41-43}\) especially BRCA1 mutation carriers.\(^\text{6}\)

Although hysterectomy is not thought to be justified for cancer prevention, women with BRCA mutations should be made aware that they face a non-negligible risk of endometrial cancers that can be eliminated through hysterectomy.\(^\text{44}\) Uterine serous carcinoma is an aggressive disease with a high rate of recurrence, and although it accounts for around 10% of cases of uterine cancer, it makes up 39% of uterine cancer deaths.\(^\text{45}\) Multiple studies have suggested an increased risk specifically of uterine serous carcinoma in BRCA mutation carriers\(^\text{6,41-43}\); however, some have shown no association.\(^\text{46-48}\) A 2016 study by Shu et al. has suggested there is an increased risk of uterine serous and serous-like endometrial carcinomas in women with BRCA gene mutations, especially those with BRCA1 mutations.\(^\text{6}\) Additionally, there is some evidence that performing a
hysterectomy at the time of prophylactic surgery in BRCA1 carriers is cost-effective and could lead to decreased mortality against serous or serous like uterine cancers.\textsuperscript{38}

Women who undergo hysterectomy at the time of RRBSO are candidates for estrogen alone hormone replacement therapy which is associated with a decreased risk of breast cancer (and is considered safe) compared to combined estrogen and progesterone which is required when the uterus is left in situ.\textsuperscript{34,49} However, estrogen alone HRT in BRCA carriers increases the risk of more aggressive uterine serous carcinoma.\textsuperscript{25} Women who have not undergone a hysterectomy in addition to RRBSO are not able to take unopposed estrogen because of the increased risk of endometrial hyperplasia/cancer in an intact uterus.\textsuperscript{50,51} They are given estrogen with progesterone HRT, but the potential adverse effect of progestin containing HRT warrants further studies because there is some evidence that progestin-containing HRT has adverse health risks. One study reported an increase breast cancer risk by 8% for every year of progestin therapy administered.\textsuperscript{34}

There are a few surgical risks associated with performing RRBSO with concurrent hysterectomy. In one study of 257 women, RRBSO with concurrent hysterectomy was associated with longer mean hospital stay compared to RRBSO alone. There was one bowel and three bladder injuries which occurred in patients who underwent concurrent hysterectomy, however there was not found to be a statistically significant increase (p=.14) in surgical complications compared to RRBSO alone.\textsuperscript{52} This study concluded that because all bladder and bowel injuries occurred in the hysterectomy group as well as the lack of convincing evidence that the BRCA mutation is associated with endometrial cancer, that they could not endorse concurrent hysterectomy at time of RRBSO sorely for cancer risk reduction.\textsuperscript{52} In summary, although there is the potential
for surgical complications,\textsuperscript{52} higher morbidity with concurrent hysterectomy,\textsuperscript{53,54} and impact on quality of life,\textsuperscript{55} hysterectomies offer numerous benefits BRCA women should consider. As previously discussed, hysterectomy at the time of RRBSO can simplify future HRT by avoiding the use of combined progesterone-containing HRT,\textsuperscript{34,56} making it possible to use estrogen alone to manage symptoms of acute surgical menopause which does not alter the risk of breast cancer.\textsuperscript{16} Women should also consider the increased risk of serous and serous-like endometrial carcinoma\textsuperscript{6} (especially BRCA1 women) when discussing the advantages of hysterectomy at the time of RRBSO. More research is needed on quality of life for women with and without hysterectomy in order to better inform women with a hereditary predisposition to breast and ovarian cancers\textsuperscript{44} and debates amongst members of the scientific community continue.

\textbf{1.1.5 Hysterectomy and Sexual Function}

Postoperative sexual function after hysterectomy is a major cause of anxiety and concern for many women undergoing hysterectomy.\textsuperscript{57} Indeed, it has been noted that nearly one half of the women undergoing hysterectomy for benign pathology fear postoperative changes in sexuality.\textsuperscript{58} While little is known about change in sexual function among women who undergo elective hysterectomy without presence of benign pathology (which we anticipate in the majority of our study population), there is a wealth of data comparing sexual function after varying types of hysterectomies, and in women undergoing hysterectomy for benign pathology and bothersome symptoms such as fibroids or somatic symptoms.

Research has been conducted to understand whether hysterectomy type (total versus subtotal [cervix sparing]) affects sexual function. In a recent 2018 prospective
study, sexual functioning in women undergoing total laparoscopic hysterectomies versus subtotal hysterectomies was evaluated. The conclusion was that preservation of the cervix does not show an advantage in improving sexual function.59 Other studies have also revealed no differences concerning postoperative female sexual function comparing total with subtotal hysterectomy.60-64 However, a few studies found supracervical hysterectomy to have superior post-operative sexual function.65-67 The results of one of these papers should be interpreted with caution because of the use of a retrospective study design and use of a questionnaire65 that has not been validated. A 2012 Cochrane Review using only RCTS in their meta-analysis comparing subtotal and total hysterectomy examined 6 RTCs between 2002 and 2010 with a follow up time of 2 years that included outcomes related to sexual function.68 They found no difference in sexual satisfaction or patient-reported painful intercourse in their metaanalysis.44 An observational study of 788 women reported sooner resumption of sexual activity in subtotal laparoscopic hysterectomy versus total laparoscopic hysterectomy, although FSFI scores did not differ between the two groups.65 In summary, no sound evidence exists to support the idea that retaining a part of the uterus (subtotal) versus total hysterectomy results in better sexual function.

According to reviews within the last decade, hysterectomy performed to alleviate symptoms based on somatic conditions improves female sexual function and quality of life.69-71 In patients with impaired sexuality pre-surgery, hysterectomy for benign reasons such as uterine fibroids, endometriosis, and abnormal uterine bleeding may improve sexual function.

Studies on sexual function post-hysterectomy vary with regards to results because the study populations have varied greatly. Populations studied include premenopausal
women, postmenopausal women, women undergoing concomitant bilateral salpingo-oophorectomy and women not undergoing BSO. We expect varying sexual functioning in these groups at baseline, leading to difficulty comparing post-surgery results.

In conclusion, after allowing appropriate time to heal from surgery, there is no good evidence to support the idea that keeping all or part of the uterus will result in better postoperative sexual function compared with a total hysterectomy.\textsuperscript{72} Despite some concerns that femininity has been diminished, or concern of injury to nerve endings in the uterovaginal plexus, the predominant evidence is that hysterectomy has no negative effects on sexual function\textsuperscript{73} and that hysterectomy for benign conditions improves sexual function.\textsuperscript{74} Whether or not sexual function in premenopausal women changes more after RRBSO with or RRBSO without hysterectomy remains to be seen, because previous studies on hysterectomy among women with BRCA mutations have primarily focused on cancer risk reduction and general health issues rather than sexual function.\textsuperscript{72}

1.2 Statement of the problem

To date there have been few prospective studies among women with BRCA mutations, a group that faces unique challenges because of the early age they undergo RRBSO and surgical menopause.\textsuperscript{29,75} Specifically, there is an unmet need for data on the non-cancer consequences of RRBSO in this population.\textsuperscript{1} Given the fact that many women choose to include hysterectomy as part of their cancer prevention plan, more research is needed to compare non-cancer outcomes between these two surgeries, especially those outcomes that matter most to women, including sexual function.\textsuperscript{20}

Women often cite menopausal symptoms, including sexual side effects, as one of their greatest concerns about undergoing RRBSO.\textsuperscript{20} We found a few studies evaluating
sexual function in premenopausal women who undergo RRBSO compared to a control population who did not undergo surgery. For example, Johansen\textsuperscript{76} examined pre- and post-surgical decline in sexual function, but failed to differentiate between premenopausal women who undergo RRBSO with and without hysterectomy. This deficit of research has resulted in a gap in the literature and deficit of knowledge of important surgical results. This prospective study will assess if there is a significant difference in change in sexual function between the two groups, which has been shown to be a concern in this group of women.

Therefore, we propose a prospective study to evaluate the degree of change in sexual function that premenopausal American women experience after RRBSO alone compared with a sample of women who undergo RRBSO with hysterectomy. The results gained by this novel study have the potential to assist BRCA women in tailoring a cancer prevention plan to their individual needs.

\textbf{1.3 Goals and Objectives}

Choosing between a RRBSO with or without a hysterectomy is a difficult and important decision. The overall goal of this study is to support informed decision making by providing more information for premenopausal BRCA+ women choosing between RRBSO with and without hysterectomy on what they can expect after surgery with regards to the change in sexual function from their baseline. Our objective is to examine the primary outcome, mean change in sexual function as measured by the Female Sexual Function Index (FSFI), and secondary outcomes as measured by the Menopause Related Quality of Life (MENQOL) scale in pre-menopausal women with BRCA mutations from a pre-surgical baseline (defined as 3 weeks prior to surgery) to 6 months after surgery.
The results of this study will determine the relationship between sexual function and RRBSO with or without hysterectomy.

1.4 Hypothesis

Among premenopausal BRCA+ women, we hypothesize that the mean change in sexual function scores when measured by FSFI questionnaire from baseline to 6 months will be statistically significantly difference between women who undergo RRBSO with hysterectomy as opposed to women who undergo RRBSO alone after accounting for confounding variables.

1.5 References


CHAPTER 2: REVIEW OF THE LITERATURE

2.1 Introduction

We performed a thorough review of the literature between December 2020- July 2021 using The Cochrane Library, Ovid (Medline), Pubmed, Scopus, and Web of Science. The following (MeSH) terms and key terms were used and combined to extract articles pertaining to the study population of BRCA + women at high inherited risk of breast and ovarian cancer: BRCA1, BRCA2, HBOC syndromes, ovarian neoplasms, breast neoplasms, fallopian tube neoplasms. Terms used to search the intervention RRBSO with and without hysterectomy were: prophylactic, preventative, risk-reducing, salpingectomy, ovariectomy, salpingo-oophorectomy, tubectomy, hysterectomy, prophylactic salpingo-oophorectomy, and risk reducing surgery. Terms used to search the outcome of sexual function were: female sexual dysfunction, sexual function, and sexuality. Within Scopus we also searched for intervention terms salpingectomy, ovariectomy, salpingo-oophorectomy, tubectomy, hysterectomy combined with adjacent words prophylactic, preventative, risk-reducing within a 2-word proximity. We used combinations of key terms to find studies that applied to HRT in the BRCA population. Only articles in English were evaluated. Titles and abstracts of search results were screened for relevance to the proposed study, and full-text versions of potentially relevant articles were obtained and assessed for inclusion. This literature review explores the current body of evidence while highlighting the limitations of the data, thus justifying the need for our proposed study.
2.2 Review of Empirical Studies
2.2.1 Overview of literature on studies focusing on non-cancer outcomes among premenopausal women at risk for ovarian cancer

There are few existing studies that examine the impact of risk-reducing salpingo-oophorectomy on non-cancer outcomes in premenopausal women. In 2017, Vermeulen et al. conducted a systematic review of studies amongst premenopausal women at high risk for ovarian cancer. Women with BRCA mutations were included, and women with other hereditary syndromes like Lynch syndrome, Peutz-Jeghers syndrome, and women undergoing surgery for benign reasons were excluded. Primary outcomes were physical, physiological, psychological, or functional consequences of RRBSO including quality of life, endocrine symptoms, sexual function, osteoporosis, cardiovascular health, lipid profile, metabolic syndrome, cognitive impairment.

Vermeulen’s overall conclusion after reviewing articles on sexual function and HRT was that sexual dysfunction was more prevalent after RRBSO. HRT gives a significant reduction of vasomotor complaints after RRBSO, but that symptom levels remain well above those of premenopausal women without RRBSO and sexual discomfort is not always alleviated by HRT.

In Vermeulen’s search, only 22 studies pertaining to quality of life, endocrine symptoms, sexual function, or effect of HRT after RRBSO were identified. Of these, the majority (10) were retrospective. Retrospective studies were at times problematic and were found to have threats to study validity. For example, in a retrospective study of menopausal symptoms, RRBSO was sometimes completed 20 years prior to the study questionnaires administration (median 60 months) which introduces the potential for recall or misclassification bias, and potentially confounding results. These retrospective studies were
limited in that they failed to determine causation and provided an inferior level of evidence compared to prospective studies.

Prospective studies provide a superior level of evidence, but 6 out of 8 studies identified by Vermeulen have limitations in the context of our study. Four studies failed to identify the number of premenopausal women involved in the study. Of the studies that did note the number of premenopausal women, only 2 included 100% BRCA women. The other two studies involved limited or unknown numbers of BRCA carriers: one had 28 premenopausal women of which 39.5% were reported BRCA carriers\(^9\) and the other 35 premenopausal women with an unknown number of mutation carriers.\(^{10}\)

Few studies have directly measured how RRBSO with and without hysterectomy affect changes in sexual functioning in premenopausal women. The prospective studies identified in Vermeulen’s review that 1) clearly stated the number of premenopausal women and 2) contained a high percentage of BRCA carriers, were only 2 out of 22 studies. Both of these were conducted by author Finch et al., with 65 premenopausal women\(^{11}\) and 75 premenopausal women\(^7\) respectively. However, neither study focused exclusively on premenopausal women (both included post-menopausal women), or used the FSFI questionnaire.

In the remainder of our literature review, we expand on this systematic review by including more recent literature, and will examine pertinent retrospective and prospective studies (one of which was listed above by Finch et al. and a later study which was published after Vermeulen’s review in 2019 by Hall et al.\(^{12}\)). In addition, we will discuss papers that utilized FSFI as a primary dependent variable after gynecologic surgery. The first is a prospective study comparing baseline to post-surgical changes in women undergoing
hysterectomies, and the second a prospective study observing changes after varying hysterectomy types with RRBSO for benign reasons.

**2.2.2 Sexual function after gynecological surgery in both premenopausal and postmenopausal women**

**RETROSPECTIVE DESIGN**

Of the retrospective studies in the Vermeulen review, one key study by Johansen et al. is particularly relevant and related. It is one of few studies we identified that observes sexual function in sizable group of premenopausal women undergoing RRBSO (N=128). Only a few studies we found had larger numbers of premenopausal women\(^ {13-15}\). Focal points of the Johansen et al. study are primarily sexual function outcomes and HRT, whereas other studies focus on quality of life (QOL), relationship satisfaction, cardiovascular health and other outcomes.

This 2016 Norwegian retrospective cohort study examined sexual activity and functioning in 294 women after RRBSO and the impact of hormone replacement compared to a control group of 1228 women from the general population.\(^ 4\) They identified women who underwent RRBSO between 1978 and 2005 through surgical records from three Norwegian hospitals because of an increased risk of breast and ovarian cancer. The sample was invited to participate in the study via a mailed questionnaire. Responders were classified as being sexually active if they had answered yes to the question “Are you engaged in a sexual relation at the moment?” and answered all 10 questions concerning sexual functioning. All data were self-reported in the questionnaires by both the NORM (the norm sample collected by the Norwegian Radium Hospital) and the RRBSO group, with the exception of the date of birth and date of surgery in the RRBSO group. The SAQ-F, which evaluates sexual pleasure and discomfort, was completed by both groups.
The statistical analysis of this study involved linear regression rather than matched controls to adjust for confounders, as the regression technique has been shown to strengthen the statistical power and provide almost identical outcomes by comparison of the two adjustment methods. Sexual functioning scores were best described as means. Among the sexually active women, the RRSO group reported significantly lower pleasure scores compared with women in the NORM group [10.5 vs 11.9; p=0.009] and higher discomfort scores [1.9 vs 0.83; p<0.001] after adjusting for age, history of cancer, and use of HRT. These findings are also supported by findings in other studies. Among the 201 sexually active women in the RRBSO group, 77 were current HRT users that reported on preparation type. The majority used systemic preparations exclusively (N=66), and 11 women reported the use of local applications only. Among the 66 users of systemic HRT, 25 women used estrogen preparations, 20 women used combination (estrogen and progesterin) preparations, and 21 women used tibolone (an agonist of estrogen, progesterone, androgen receptors, which is not available in the United States). In subgroup analyses of the RRBSO group, users of systemic HRT had significantly less discomfort than nonusers (1.2 versus 2.4, p=0.001). Furthermore, there were no significant differences in sexual pleasure (p=0.12) between HRT users and nonusers in the RRBSO group, which was similar to findings in other studies.

This study has a number of limitations in the context of our proposed intervention. First, it did not incorporate RRBSO with hysterectomy. Second, the comparison NORM group had a low survey response rate (42%) compared with the response rate of the RRBSO population (72%). Low response is a common problem in surveys of sensitive matters such as sexual activity and functioning, and the responders in the NORM groups
many not have been representative of the general population. This non-response bias may have led to non-random deviation of survey answers away from their true value. An advantage of our study is that we will not be comparing our women to a NORM group. Instead, we will be comparing two surgery types amongst similar groups of BRCA women and anticipate similar response rate in both groups. A third disadvantage of this study is that the SAQ questionnaire does not evaluate orgasmic function or sexual drive, which are two important components of sexual function. In contrast the FSFI, a questionnaire used in our proposed study, evaluates both of these outcomes (with the orgasm and desire domains). Finally, the results of this study should be interpreted with caution due to the retrospective study design. The design did not allow for examination of the differences in sexual activity and functioning at baseline between RRBSO and NORM groups and it was unknown if the RRBSO women had lower or higher levels of discomfort scores at baseline compared to the controls. Regardless, the RRBSO group reported more discomfort and less sexual pleasure than did the controls, which is supported by other studies.7,16

**PROSPECTIVE DESIGN**

We identified two important prospective studies which investigated changes in sexual functioning due to RRBSO. They are Finch et al. and an extension by Hall et al. In 2019, Hall et al. conducted a prospective study on the effects of bilateral salpingo-oophorectomy on menopausal symptoms and sexual functioning among Canadian women with BRCA1 or BRCA2 mutations.12 This study is among the few we identified with a prospective design, and was an extension of a 2011 study by colleagues Finch et al. who reported on the experiences of 114 BRCA mutation carriers before and one year following prophylactic oophorectomy.7 Hall revisited this cohort of previously surveyed BRCA
mutation carriers (N=114) and expanded to sample size (N=140) with an average follow up of 3.5 years (range 2.9-6.4 years) following BSO. The extended post-surgical follow up allowed for trending sexual functioning over a longer period of time.

Hall et al. included 93 (66.4%) premenopausal women and 47 (33.6%) postmenopausal women who reported being sexually active at baseline and follow up. The assessment tools were the following three questionnaires, which were administered before surgery, and two times post-surgery: 1) Medical History Questionnaire, designed especially for the study including questions on reproductive history, cancer history, medication use including HRT, and menopausal status 2) Menopause-Specific Quality of Life Questionnaire 3) Sexual Activity Questionnaire. Eligibility criteria was 1) a documented BRCA1 or BRCA2 mutation 2) at least one ovary intact and 3) no personal history of cancer other than breast cancer.

Changes between the baseline and second follow-up questionnaire were analyzed using a paired t-test for all domains evaluated by the questionnaires. For analysis stratified by menopausal status and HRT use following surgery, the students t-test was used to evaluate differences in the scores between the subgroups. Generalized linear regression was used to adjust the baseline scores for age at time of surgery, previous breast cancer diagnosis, and time between surgery and baseline questionnaire completion. The follow up scores were further adjusted for HRT use, baseline score and time between surgery and follow up questionnaire.

Hall found that, at baseline, post-menopausal women (N=47) reported worse sexual functioning (sexual desire, vaginal dryness, and avoidance of intimacy) on the MENQOL-I compared to premenopausal women (N=93) although this was not statistically significant.
Among women who were premenopausal at time of surgery, they found surgery was associated with a significant (P<0.001) increase in menopausal symptoms [vasomotor: change 1.34, and physical: change .48]. Using the SAQ (a decrease in score indicates a decline in sexual functioning) Hall found that premenopausal women showed a significant (P<0.0001) decline in sexual functioning (less pleasure: change -2.07, and more discomfort: change -1.73), but this had no impact on overall QOL (P=0.31). A significant change in sexual function (p<0.0001) was also seen in premenopausal women in the 2011 study by Finch (less pleasure: change -2.13 and more discomfort: change -1.26).

Comparing SAQ domain score changes between baseline and follow up, the evidence is convincing that change in sexual function experienced by women in Finch et al. shortly after surgery (years between baseline and first follow up: mean 1.21 years; range .59-3.14 years) is similar to the what is observed in the longer follow up period in Hall et al. (years between baseline and second follow up: mean 3.49 years; range 2.86-6.38 years) with less pleasure (change in 1 year -2.13 vs change in 3.5 years -2.07) and more discomfort (change in one year -1.26 vs change in 3.5 years -1.73). There was a similar pattern in all domains of the MENQOL-I. This data supports the concept of immediate and sustained effects of surgical menopause (P change overtime ≥0.08) with little to no worsening of sexual functioning over the first few years after surgery.¹² Notably, this was true for all study groups including our proposed study population of premenopausal women with and without HRT. Hall’s study suggests that changes observed from baseline to 6 months post-surgery in our proposed study may also be generalizable to longer term effects of surgery.

HRT in premenopausal women mitigated but did not eliminate the adverse effects in both studies. Finch’s study reported differences in changes between these groups (with HRT
pleasure score: change 1.92; p for change=0.010 and without HRT change 2.29; p for change=0.004) though the probability for change was not significantly different between the two groups (p=0.498). It should be noted that there were only 29 (39.7%) premenopausal women in Finch’s study that used HRT and 37 (42.5%) in Hall’s study, which is a limitation in extrapolating results of this subgroup analysis. With increased acceptance and knowledge among providers of appropriate HRT use after surgery, it is reasonable to expect that we will see more participants in our study population use HRT.

Strengths of these studies includes the choice of widely used questionnaires with demonstrated test-retest reliability, including the MENQOL-I which we are including as a secondary outcome in our study. Scoring of questionnaires and exclusion of women who reported no sexual activity at baseline and at follow up was appropriate. The prospective design with long follow up period is unique and allows for assessment of temporal relationships and a superior level of evidence compared to previous retrospective studies.

Both Finch’s and Hall’s studies were limited by the small sample size. Inclusion of a small number of women with a history of breast cancer precluded robust subgroup analysis. Given that HRT is currently contraindicated in this population, that chemotherapy regimens have been shown to impact sexual functioning and menopausal symptoms, and the small sample size (N=50, 35.7%) with multiple comparisons, the authors could not evaluate the impact of HRT on symptoms in an analysis stratified by personal history of breast cancer. Additional limitations include non-randomization of subjects to hormone replacement therapy and results may be subject to confounding by indication. Furthermore, the classification of women as premenopausal if they reported having a menstrual cycle in the past year is problematic. It is difficult to determine if women were classified as
premenopausal correctly, as reporting may be subject to recall bias because women may not have been able to recollect the exact date of their last menstrual cycle.

Hall et al. and Finch et al. are highly applicable to our study, although they differ in a few key ways. Our choice in questionnaire types differ, our study includes only premenopausal women, and the duration between surgery and questionnaire administration in our planned study is 6 months, versus 3.5 years in Hall’s study. Additionally, our study will recruit equal numbers of women undergoing RRBSO and RRBSO with hysterectomy, allowing robust subgroup analysis.

Finally, although the authors did make note of surgery type [Finch study BSO only (N=5), BSO with prior TAH (N=5), TAH BSO (N=104) and Hall study Oophorectomy (N=23) Oophorectomy and hysterectomy (N=117)] neither paper conducted subgroup analysis between these groups due to limited sample sizes, and we cannot draw any conclusions about effects of additional hysterectomy with oophorectomy. For analysis, all surgeries were simply compiled into one category, which was referred to as “oophorectomy.” The question remains unanswered then, if surgery type contributes to differences in changes in sexual function.

2.2.3 Use of FSFI scoring tool: Effects of hysterectomy on Sexual Function

We did not identify any prospective studies that utilized the FSFI scoring tool after RRBSO with and without hysterectomy for prophylactic reasons. However, we did find studies that used the FSFI to answer questions on sexual function changes after hysterectomy, and after various hysterectomy types and concurrent bilateral salpingo-oophorectomy for benign pathology in non-BRCA women.
Berlit et al. conducted a prospective study on 120 women undergoing total hysterectomy (removal of the entire uterus) versus subtotal hysterectomy (removal of the body of the uterus while leaving the cervix in place) to evaluate postoperative sexual functioning. At baseline, 3-, 6-, and 12-months post-surgery, women were asked to assess their level of sexual functioning using the FSFI questionnaire. Indications for surgery included fibroids, endometriosis, prophylactic hysterectomy, and endometrial hyperplasia.

Difference scores were calculated between baseline and each of the 3 follow-ups. Difference scores were compared between the two groups in separate one-factorial analysis of variance, while taking baseline level of sexual functioning into account by entering baseline FSFI scores as covariate into the analysis. To test for statistically significant changes in scores from baseline, FSFI difference scores were tested against 0 by means of a one sample t-test. At baseline, there were no statistically significant differences in the FSFI total score, or any of the domain scores between the two groups (total score $p=0.392$; desire $p=0.914$; arousal $p=0.245$; lubrication $p=0.298$, orgasm $p=0.290$; satisfaction $p=0.606$, pain $p=0.181$). FSFI scores were expressed as means ± standard deviation.

The researchers postulated that sexual function would be worse in the total hysterectomy group versus the cervix sparing group. However, after allowing time for women to heal from both surgeries, they found no significant difference in sexual function between these groups in surveys 6 months ($p=0.663$), and 12 months ($p=0.326$) post-surgery. Similarly, the results of a Cochrane review comparing sexual function after both surgery types found no differences in sexual satisfaction or dyspareunia. There was a significant difference at 3 months ($p=0.006$), which the authors hypothesized was due to faster healing time in the cervix sparing hysterectomy. For both surgery types, surgery
improved sexual function. These results are similar to finding from literature reviews on hysterectomy performed to alleviate symptoms of somatic conditions. In these cases, hysterectomy in general improved sexual function and quality of life. In addition, for both surgery types, the baseline sexual function predicted the strength of change at each of the follow-ups. A lower level of baseline sexual function was linked to stronger improvement post-surgery (p<0.001). Interestingly, they found that sexuality in general ([measured with a 5-point Likert scale with rating scores ranging from 0(unimportant) to 4 (very important)]) was significantly more important for women who underwent LASH/subtotal hysterectomy (LASH 2.98 ±0.80, TLH 2.57±.86; p=0.009). They also found that across groups, statistical analyses did not reveal significant improvement of sexual functioning 6 months after surgery (t=1.25, p=0.216).

The strengths of this study include use of the most widely utilized screening tool for sexual function (FSFI) which entails reproducibility of results and fulfills the psychometric quality criteria. Although the surgery types in our proposed study differ from Berlit et al., we utilize the same questionnaire and the same dependent variable. Portions of our statistical analysis are based off of what was conducted in Berlit’s study.

The results of this study are important. Women who rated their sexuality as more important choose to retain part of their uterus (LASH surgery), presumably in an effort to preserve sexuality. FSFI improved after surgery in both groups and there were no significant differences in FSFI scores after surgery at 6- and 12-month time points. Based off of this study and one other, we have chosen to administer our post-surgical questionnaires at 6 months. This will allow our hysterectomy group to heal from surgery, avoiding confounding results from potential post-surgical pain or discomfort. Strengths of this study also included
additional exploratory analysis comparing groups of women who a) only completed the baseline survey (loss to follow up), versus women who b) completed all surveys. Analysis demonstrated that these findings were not influenced by selection effects of women dropping out of the study. In addition, this study’s results were similar to other studies which reported that hysterectomy alone does not have a negative effect on sexual function, and may even provide significant improvement.28

There were a few limitations of Berlit’s study. First, the authors failed to publish a table breaking down the FSFI domain scores (desire, arousal, lubrication, orgasm, satisfaction, and pain) at the 3-, 6-, and 12-month post-operative time points. They printed the FSFI domain scores only for the baseline questionnaire. Second, the authors neglected to adjust for age at time of surgery in their analyses, which is uncommon compared to other studies. However, other studies had a much wider age range of participants, and whereas Berlit’s participants had little age variation, an no significant age variation between groups (LASH mean age 46.7±5.2, and TLH mean age 46.8±7.3 p=0.935).

2.2.4 Use of FSFI scoring tool: Effects of hysterectomy and BSO on Sexual Function for benign causes

Studies on hysterectomy and elective bilateral oophorectomy have mainly focused on cancer risk reduction,28 however we identified a study utilizing the FSFI to evaluate sexual function changes. In 2008, a study on the effect of abdominal versus vaginal hysterectomy with BSO on sexual function in post-menopausal women was conducted by Celik and colleagues.27 This Turkish prospective study was completed on 92 sexually active women who had an BSO with either abdominal hysterectomy or vaginal hysterectomy for benign reasons, and excluded women who underwent hysterectomy due
to malignancy. In addition, they excluded women who had diagnoses of diabetes, hypertension, hyperlipidemia, smoking, and obesity (BMI >30).

Celik et al. found that hysterectomy and BSO, through either vaginal or abdominal route, significantly reduced total FSFI scores in post-menopausal women (p<0.01, and p<0.001). Vaginal hysterectomy with BSO (n=37) FSFI total score was 24.11 ± 4.83 preoperative compared to postoperative 22.44 ± 4.64. Abdominal hysterectomy with BSO (N=55) total FSFI score was 24.86 ± 4.40 preoperative compared to post-operative 22.07 ± 4.77. Significant decreases in FSFI domains were observed in the following categories: orgasm (p=0.006) for the vaginal group, and desire (p =0.001), arousal (p =0.0001), lubrication (p =0.0001), orgasm (p =0.03), and satisfaction (p =0.0001) for the abdominal group. Celik et al. reasoned that post-menopausal ovaries are not inactive, have a significant place in testosterone and estrogen production, and therefore BSO in these postmenopausal women further reduced hormonal values, producing a negative effect on sexual functions. Overall, study results revealed that surgery causes significant unfavorable effects on sexual functions in at least the first 6 months in terms of FSFI scores. These results are similar to another study on post-menopausal women, which showed that FSFI scores and overall sexual function decreases after oophorectomy. With concomitant BSO and removal of the ovaries which produce hormones important for sexual function, it is not surprising that these women experienced a decrease in sexual functioning.

A major limitation of this study in terms of our proposed study is that the participants were post-menopausal women. Pre-menopausal women in our study may experience a different magnitude of change in FSFI scores after surgery, and results from
this study must be generalized with caution. A unique strength of this study is the randomization of women to surgery type, which is rare in the literature.

2.3 Review of Studies to Identifying Possible Confounding Variables

Sexual function is a vital component of women’s lives, and it involves complicated multidimensional interactions between relationships, sociocultural, psychological and biological factors. While reviewing previous studies, we noted multiple confounding variables affecting female sexual function and surgery type that we will attempt to address with the proposed study design. Factors negatively affecting sexual function include menopausal, mental, and emotional status, aging, and chronic medical problems. Our subjects self-select their surgery type (not randomized), and it will be necessary to adjust all analyses for potential confounders that might relate to both arm and outcome.

Age and Menopausal Status at times of surgery

A woman’s age is highly relevant to her risk of sexual dysfunction. As patients age, the FSFI score markedly declines and sexual dysfunction increases. In one study of 518 Italian women ages 40-55 in the menopausal period, it was found that sexual dysfunction increases by about 30%, from 55% from age 40 to 45, and to 82% in the years 52-55 (p<0.01). Mean FSFI scores also decrease significantly from ages 40 to 45 compared with ages 46 to 48 (23.13± 9.76 vs 19±9.88; p<0.05). All studies discussed in our literature review with the exception of one adjusted FSFI scores for age at time of surgery. Due to the potential confounding impact that age can have on sexual function and in particular FSFI scores, we will adjust for age in our study.

Baseline FSFI Score
Sexual dysfunction (FSFI scores <26.55)\(^3\) is highly prevalent in the global community with a range of 35.9 to up to 86.5\(^%\)\(^\,\)\(^\,\)\(^\,\)\(^4\) and it is critical for our study to identify women with low total FSFI scores at baseline. Domain scores at baseline are also of great importance; a longitudinal study of FSFI scores in pre and postmenopausal women indicated that baseline scores of the FSFI domains of desire and arousal were the main predictors of changes in sexual function.\(^4\)

The prospective design our proposed study will provide FSFI domain and total scores at baseline, and will allow us to uncover if differences between our groups exist at baseline. Previous cross-sectional and retrospective studies have been limited in that there is an unknown rate of sexual dysfunction in the study cohort prior to surgery\(^6\). In a previous study, women who ranked sexuality as more important opted to undergo a surgery that preserved more of their uterus\(^2\). It is possible that women who have higher sexual functioning at baseline may opt for preservation of the uterus (RRBSO alone group) because of the belief that it may preserve sexual function. This higher baseline sexual functioning may in turn affect follow up FSFI scores, or the magnitude of change in scores. To prevent confounding due to baseline FSFI scores, we will compare FSFI scores before and after surgery, use the difference in scores as comparison indexes, and adjust follow up scores for the baseline score as was done in other studies\(^7,12\).

**Gynecologic Symptomatology**

Other confounders that must be considered include presence of gynecologic symptomatology. This includes symptoms of pelvic pain, heavy vaginal bleeding (a side effect of combined estrogen and progesterone HRT which is given only to the RRBSO alone group to protect the uterus), or painful periods. In a study of women with chronic
pelvic pain, FSFI scores in most domains (desire, arousal, lubrication, orgasm, and pain) were lower in women with pain than in control groups. In addition to altering FSFI scores, gynecological symptomatology may also influence choice of including a hysterectomy with surgery. Therefore, it is crucial to identify these women with symptomatology in our Participant Questionnaire (Appendix E).

2.4 Review of Relevant Methodology
2.4.1 Study Design and Setting

This observational study describes a 36-week, multi-site prospective cohort study with forward directionality analyzing the impact of RRBSO with hysterectomy versus RRBSO alone in premenopausal BRCA + women on sexual function.

Our proposed study will be a prospective study for two key reasons. First, the choice of our prospective longitudinal design is a response to the deficit of prospective studies of surgical menopause in the BRCA population. As discussed previously there are few prospective studies of surgical menopause and sexual function among women with BRCA mutations and no studies we know of directly compare sexual function in RRSBO with or without hysterectomy like the proposed study does. Secondly, our prospective design is a response to the limitations of other study designs, namely retrospective and cross-sectional studies, that do not allow determination of causality or incidence. The retrospective studies lack baseline measurement of sexual outcomes and are subject to confounding due to the unknown pre-surgical sexual functioning scores of women.

2.4.2 Recruitment Techniques and Sampling
Previous studies determining the association between sexual function and gynecological surgeries in BRCA mutation carriers have used convenience sampling to recruit participants from this unique group who are rare in the general population (a BRCA mutation occurs in an estimated 1/400 people). For retrospective studies, women were selected if they had undergone surgery in a specific time frame because of increased risk of breast and ovarian cancer and were invited to participate via a mailed questionnaire. Convenience sampling can continue to be utilized in future studies investigating sexual function and gynecological surgeries among women with BRCA mutations.

To reach appropriate number of study subjects, previous study recruitment often involved multiple sites, enrolling women from a variety of private and public hospitals. Our study is designed to recruit from multiple online platforms and clinical sites, improving upon previous small sample sizes, increasing the heterogeneity of our population, and expanding our generalizability compared to other studies. We are also designing our study to capture results from women across the United States as opposed to previous studies focused on results in Australian, Canadian, and Norwegian women.

2.4.3 Selection Criteria

Age and Menopausal Status

Our proposed study will include women aged 30-55. Review of the literature illustrated that many women undergo RRBSO at a wider range of ages than what is recommended by the NCCN guidelines (recommended ages 35-45). It is common practice and beneficial for recruitment if studies expand inclusion criteria to reflect this. For example, both younger and older women who underwent RRBSO at ages 31-76 were
included in a study of sexual activity and functioning after risk-reducing salpingooophorectomy, and the median age of RRBSO (n=249) was 48\textsuperscript{4}. In a study by Finch et al., ages 35-69 were included, and only 47% of the study subjects underwent prophylactic RRBSO in the NCCN recommended age range 35-44\textsuperscript{7}.

Our proposed study will include women in the premenopausal and perimenopausal periods to capture a sufficient sample size for our study. Hall et al.\textsuperscript{12} used self-reporting techniques to determine women’s menopausal status at baseline by asking women if they had a menstrual period in the year prior to surgery. While self-reporting may be accurate, answers may be subject to reporting bias. For this reason, our study will require more criteria in addition to self-reporting a menstrual cycle in the last year. In other studies of exclusively pre-menopausal women, FSH cutoffs are used \textsuperscript{42}. To ensure study subjects are pre-menopausal at baseline (who are expected to undergo more dramatic and severe effects of surgical menopause) Hickey et al. implemented the following criteria: hormone level of <15 IU/L on days 2-6 of the menstrual cycle, at least one period in the last year, and absence of vasomotor symptoms\textsuperscript{42}. Another study used FSH <40 IU/L as a cutoff\textsuperscript{27}. Because our study seeks to exclude post-menopausal women, and includes pre and perimenopausal women, our study cut off is FSH <40 IU/L.

It should be noted that FSH alone is not an effective predictor of transition in to the postmenopausal period, and a FSH cutoff of 40 IU/L is inappropriate by itself for clinical determination of post-menopausal status\textsuperscript{45}, thus we will also require that participants have had a period in the last year to confirm pre-menopausal status.

Other inclusion criteria will be modeled in part after the study by Hall et al. which requires: 1) a documented BRCA1 or BRCA2 mutation 2) at least one ovary intact and 3)
no personal history of cancer other than breast cancer. Exclusions were based off of a variety of studies\textsuperscript{1,42}: <3 months since pregnancy and lactation, abnormal uterine bleeding, women with other hereditary cancer syndromes like Lynch, Peutz-Jeghers syndrome, women undergoing surgery for benign reasons, those using antiestrogens such as tamoxifen, and those with history of breast cancer requiring antiestrogens. We have chosen to exclude subjects with history of breast cancer for a number of reasons. In studies where breast cancer survivors were included, the small numbers of these patients precluded robust subgroup analysis\textsuperscript{7,12}. Additionally, in these women, HRT is contraindicated\textsuperscript{19,20}. Excluding this group will also decrease potential loss to follow up from breast cancer deaths.

2.4.4 Survey Instruments Used to ascertain Primary and Secondary Outcome Measures

Medical History Questionnaires

Our study will model its medical history questionnaire after the questionnaire used in the study by Hall et al\textsuperscript{12}. Their custom form, designed specifically for that study, asked details on patient reproductive history, height, weight, menopausal status, personal history of cancer, medication use including HRT, lifestyle factors including smoking status, alcohol intake, frequency and intensity of physical activity, and vitamin and supplement use. Our medical history questionnaire is devised to provide us the ability to compare differences in study variables between our two groups and determine presence of potential confounding factors not addressed in other studies, such as gynecologic symptomatology.

Sexual Function Scoring and timing for Measuring Outcomes
Throughout our literature search, we found that self-reported questionnaires and face-to-face surveys were the most common ways to measure sexual function in patient populations. Previous studies have used questionnaires such as the FSFI, MENQOL-I, MENQOL, and SAQ-F to examine a variety of gynecological surgeries including RRBSO, RRBSO plus hysterectomy and hysterectomy alone. These scales have been well studied in women across the menopausal time line from premenopausal to perimenopausal to postmenopausal and have been used for women who undergo surgery for a wide range of reasons.

Our study will utilize the FSFI. The FSFI is the most widely used screening tool to measure female sexual function\textsuperscript{26}. It is convenient and quick to complete; information can be gathered through patient interviews or questionnaires and takes less than five minutes to complete. The FSFI has demonstrated a high level of acceptability, test-retest reliability, internal consistency, and validity in cancer and non-cancer populations and is also perceived as easy to use and relevant\textsuperscript{46,47}. It has also been validated in women with sexual arousal disorders\textsuperscript{48}. Previous studies observing change in sexual function before and after gynecological surgeries have administered the FSFI at a variety of time points. In Berlit et al., participants completed the FSFI and other questionnaires before surgery, and 3-, 6-, and 12-months following surgery\textsuperscript{21}. The proposed study will adapt this model and administer the FSFI before surgery and at 6 months. We have excluded the 3-month questionnaire to allow women sufficient time to heal after surgery, and omitted the 12-month questionnaire due to time limitations of our study.

The FSFI consists of 19 items in six domains: desire (two items), arousal (four items) lubrication (four items), orgasm (three items), satisfaction (three items) and pain
(three items). Each item is scored using a 5-point Likert scale ranging from zero (or one) to five, and higher scores indicate greater levels of sexual function\textsuperscript{48}. The total score is calculated as the sum of the scores in these six domains after multiplying a specific weight factor for each domain to place all domains on a comparable scale (0.6 for desire, 0.4 for arousal and lubrication and 0.3 for orgasm, satisfaction and pain) for a possible score from 2 to 36\textsuperscript{48}. The validity and reliability of this questionnaire have been confirmed by Rosen et al\textsuperscript{48}.

Meston et al. identified errors researchers make in interpreting and scoring the FSFI. One common mistake is administering the FSFI to women who are not sexually active and have not attempted vaginal penetration in the last 4 weeks, or using a reference point other than the past 4 weeks to determine current sexual activity status\textsuperscript{26}. Another problem is researchers publishing FSFI scores without also publishing individual domain scores\textsuperscript{26}. To ensure incorrect biasing towards dysfunctional scores, it has been found that implementing exclusion criteria for women who have not been sexually active in the past 4 weeks is an acceptable option, which excludes erroneous scores of 0 which correlate to either “did not attempt intercourse” or “no sexual activity”\textsuperscript{26}. This is the approach we will take in our study, utilizing the exclusion criteria to remove this group of women at baseline, and the participant questionnaire to exclude at 6 months.

It should be noted that alone, low FSFI scores cannot be used to make a diagnosis of female sexual dysfunction. However, in combination with another tool, the FSDS\textsuperscript{49}, the persistence of the symptoms for over 6 months, and ruling out other causes of sexual dysfunction, the diagnosis of sexual dysfunction may be made.

\textit{Menopausal Related Quality of Life}
The MENQOL-Intervention questionnaire consists of 32 items in four domains: vasomotor (three items), psychosocial (seven items), physical (nineteen items), and sexual (three items). Each item is scored using a 7-point Likert scale ranging from zero to six, and higher scores indicate a worsening in symptoms. For scoring, each item is transferred to an 8-point scale from 1 (the patient did not experience the symptom) to 8 (extremely bothered). The total score is calculated as the sum of the scores in these domains. For each domain, an increase in score represents a worsening of symptoms. The MENQOL recall time is one month, but the MENQOL-I has shortened this to one week. The MENQOL-I has been adapted from the MENQOL to capture areas that may negatively affect quality of life related to hormone replacement therapy with the addition of 3 questions in the physical domain which is pertinent to our study and has been used in previous studies. The MENQOL-I has a test-retest reliability of .83 for the sexual domain.

2.4.5 Sample Size

Sample sizes can be calculated based on the anticipated change in score for the Female Sexual Function Index. There are no studies that disclose a minimally clinically significant difference for the FSFI scale. We will use a recent study that published figures of changes in FSFI scores before and 6 months after gynecologic surgery for our calculations. We extrapolated that the mean change from the pre- to post-surgical time point after bilateral salpingo-oophorectomy with hysterectomy was 2.23 with a standard deviation of 4.66. Although we found no data on FSFI changes in pre-menopausal women from pre-surgical to 6 months post-surgical in RRBSO alone, we will assume a 2-
point mean change in FSFI. Given that our two surgery types have never been directly compared and the novelty of the proposed study, we will opt for a two tailed test.

2.5 Conclusion

In this literature review, we summarized a number of research papers examining the effects of RRBSO and hysterectomies on women across the menopausal timeline from premenopausal to perimenopausal to postmenopausal. We included studies on women undergoing surgery for a variety of reasons, from benign pathology to prophylaxis, and critically evaluated a number of retrospective and prospective studies that employed a variety of questionnaires including the FSFI, SAQ-F, and MENQOL to observe sexual function outcomes after gynecologic surgery.

The overall findings of the current evidence reviewed in our literature search are as follows. Studies on the effects of hysterectomy have yielded mixed results. The majority report that hysterectomy alone does not have a negative effect on sexual functions, and that hysterectomy for benign disease is usually associated with improved quality of life and beneficial effects on sexual function\textsuperscript{23-25,51,52}, irrespective of the surgical approach or removal of the cervix\textsuperscript{28,53}. However, some studies reported that sexual function was affected negatively\textsuperscript{54}. Preventative bilateral oophorectomy and concurrent hysterectomy for benign disease has detrimental effects on sexual functioning, and sexual dysfunction is more prevalent after RRBSO\textsuperscript{2-4}. HRT after preventative bilateral oophorectomy significantly reduces vasomotor complaints, however, symptom levels remain well above those of premenopausal women without RRBSO\textsuperscript{4-7}. Finally, sexual discomfort is not always alleviated by HRT\textsuperscript{4-7}. 
There are a few limitations of the existing body of literature. While several studies have measured menopausal symptoms and sexual functioning in high-risk women after oophorectomy\textsuperscript{2,3,6,16,55}, it is optimal to compare symptoms before and after surgery in a prospective fashion\textsuperscript{7}. Our prospective design is pivotal in identifying confounding factors and decline in sexual function from baseline, and is a strength of the proposed study. In this literature review, we noted an absence of randomized controlled trials assessing non-cancer impacts of risk-reducing salpingo-oophorectomy in premenopausal women. This nonexistence of RTCs was also observed in a 2017 systematic review by Vermeulen et al\textsuperscript{1}. Given that many ethical issues arise in a study that randomizes surgery types or hormonal therapies to patients, the lack of RCTs is not surprising and limits the generalizability of the existing studies. We also found it problematic that numerous studies treated RRBSO and RRBSO with hysterectomy, which are two distinct surgery types, as one entity. Studies did not provide justification or explanation for this decision, and often, the only way we discovered that these two distinct surgeries were being studied together was upon review of Table 1 comparing baseline characteristics of study subjects. Failure to statistically treat these two surgeries as separate operations is a major limitation of previous studies. This distinction is necessary to answer the important question of what, if any, sexual function changes women should expect after either surgery.

The studies discussed in this literature review are high quality sources of literature from a range of peer-reviewed journals that have attempted to determine sexual function after gynecological surgeries, including RRBSO and hysterectomy. While no study exists on sexual function changes after RRBSO with and without hysterectomy in premenopausal women to date, the studies above demonstrate that our proposed study
design is feasible in this group of pre-menopausal BRCA mutation carriers with justified rationale. Our proposed study will integrate successful elements of previous studies into its’ design to evaluate changes in FSFI after surgery.

2.6 References


CHAPTER 3: STUDY METHODS

3.1 Study Design

This observational study proposal describes a 36-week, multi-site prospective cohort study analyzing the impact of RRBSO with hysterectomy versus RRBSO alone in premenopausal BRCA + women on sexual function. Study participants will be electing to undergo their preferred surgery type prior to the study, and thus will not blinded to the surgery type. However, researchers entering and analyzing data will be blinded to surgery type. This study provides a safe clinical study setting with stringent protocols, proper consent, monitoring and independent oversight that we will utilize during the entirety of our study.

3.2 Study Population and Sampling Type

Our source population will be BRCA + women in the United States, who are at high inherited risk of breast and ovarian cancer. Women enrolled will be pre-menopausal, aged 30-55, planning to undergo RRBSO with or without hysterectomy, and have a surgery scheduled within our study period. Participants must agree to provide written information based on mailed questionnaires 3 weeks prior to surgery and 6 months post-surgery. Our sampling method will be consecutive sampling, enrolling participants until the required sample size is achieved. Our study population may be heavily skewed towards women in Connecticut because of substantial recruitment at Yale Health sites, and thus the study population’s generalizability to our source population may be limited.

3.3 Inclusion and Exclusion Criteria

Inclusion criteria include being English-speaking, pre-menopausal, aged 30-55, and sexually active in the past month; electing to undergo RRBSO with/without
hysterectomy to reduce the risks of tubo-ovarian cancer; having surgery scheduled within our study period, a documented BRCA mutation, at least one functioning ovary, uterus in place, and no personal history of cancer. Sexually active women will have responded yes to the question “Are you engaged in a sexual relationship at the moment (in the past 4 weeks)?” which has been adapted from previous studies. Pre-menopausal status will be confirmed prior to surgery with follicle stimulating hormone <40 IU/L, and at least one menstrual cycle in the past 12 months. Planned total hysterectomy type may be either abdominal or vaginal.

Exclusion criteria include undergoing RRBSO or hysterectomy for benign reasons, other hereditary cancer syndromes like Peutz-Jeghers syndrome and Lynch syndrome, being post-menopausal (follicle stimulating hormone >40 IU/L), having undergone previous bilateral salpingectomy/bilateral oophorectomy/hysterectomy, clinical suspicion of tubo-ovarian cancer at baseline or history of cancer, being <3 weeks since pregnancy and lactation, using anti-estrogen medications, not being sexually active in the last 4 weeks, and being unable to provide informed consent.

3.3 Subject Protection and Confidentiality

This study will seek ethical review and Yale Institutional Review Board (IRB) approval prior to recruitment. Once approved by the IRB, study subjects will be recruited and given the Consent for Participation in Research Project form 200 FR 1 form (Appendix A). All study participants will provide written informed consent, including consent to access medical records, which we will use to confirm eligibility and gather study data. To ensure that the personal information of all participants is kept private and confidential, each study participant’s data will be protected under HIPAA compliance.
Subjects will be assigned a unique subject identifier to be used on all data collection forms and in the statistical analysis. Paper records collected during our study will be secured in a locked box and entered in a de-identified, password protected data management system, only accessible to approved researchers. The link to personal information will be kept for 5 years, after which the link will be destroyed and the data will be anonymous. Paper records including questionnaires will be destroyed 12 months after the end of the study period.

3.4 Recruitment

Women planning RRBSO with and without hysterectomy will be recruited via flyer posted at clinical sites within the Yale New Haven Hospital System, through an online marketing campaign targeting popular BRCA support sites, and, for women on the Yale BRCA list maintained by Johanna D’Addario PA-C, directly contacted by our research assistant. The proposed study has a multi-centered design to ensure adequate recruitment and expand our generalizability to women across the United States.

At Yale, we will post recruitment flyers at the Sexuality, Intimacy, and Menopause Clinic, the Yale Cancer Genetics and Prevention Clinic, gynecological oncology, gynecological surgery and general gynecology outpatient clinics. In these clinics, women interested in participating in the study will scan the flyer’s QR code on their phone, which will link them to a brief online survey to determine study eligibility. At the end of the survey, eligible women will be prompted to enter their contact information. Within one week, a research assistant will contact the eligible women to confirm interest, provide an explanation of the study, requirements for participation, and answer any questions. Interested women will receive an email with a PDF version of the
Consent for Participation in Research Project form (Appendix A) to obtain written consent, and medical records release consent. After both are signed and returned electronically, we will request access to patients’ medical records to confirm eligibility. $25 USD will be mailed to the study participants upon successful completion of the pre- and post-surgery surveys. The recruitment flyer may be found in Appendix B.

Online advertising targeted to both patients and providers will be posted on the following websites: FORCE (Facing Our Risk of Cancer Empowered) https://www.facingourrisk.org/, the Women’s Sexual Health Cancer Registry, and Scientific Network on Female Sexual Health and Cancer https://www.cancersexnetwork.org/. Interested women will click on the online advertisement’s link to the eligibility survey. After survey completion, the same recruitment protocol will be followed as noted above.

Lastly, the research assistant will utilize Yale’s BRCA patient database maintained by Johanna D’Addario PA-C, coordinator of the Sexuality, Intimacy, and Menopause Clinic to contact patients by phone to determine study interest. As of 7/14/2021 this database contained 327 BRCA + patients. If women indicate their interest participating in this study, preferred cell phone numbers will be confirmed and women will be sent a text message link to the online eligibility survey. After survey completion, the same recruitment protocol will be followed as noted above. Equal numbers of women will be recruited for each surgery type until required sample size is met.

3.5 Study Variables and Measures
3.5.1 Independent Variable

The independent variable is Risk Reducing Bilateral Salpingo-Oophorectomy with hysterectomy versus Risk Reducing Bilateral Salpingo-Oophorectomy without
hysterectomy. Hysterectomy is removal of the entirety of the uterus, either vaginally or abdominally. Surgery type, date, and surgeon will be confirmed by medical record review following surgery by the study research coordinator.

3.5.2 Dependent Variables

The dependent variable and primary outcome is change in sexual function scores, which will be measured and operationalized by the mean change after 6 months in the self-administered FSFI scores (Appendix C). Change in scores will be reported as a continuous variable and described using means and standard deviations if normally distributed, and median and nonparametric test if not normally distributed.

Secondary outcomes of interest include change in menopause related quality of life, which will be operationalized by the mean change after 6 months in the self-administered MENQOL-I questionnaire (Appendix D) scores. Both questionnaires will be administered at baseline and 6 months post-surgery. These secondary outcomes will be reported as continuous variables and will be described using the same tests as noted above. For both primary and secondary outcomes, we will use bivariate and multivariate analyses to assess changes over time between our two groups (RRBSO alone and RRBSO with hysterectomy) after measuring and controlling for confounders.

3.5.3 Potential Confounding Variables

Sexual function can be affected by many factors. Because women in this study self-select their surgery type (not randomized), it will be necessary to adjust all tests for potential confounders that might relate to both study arm and outcome. The known confounders that we will adjust for are age at time of surgery\(^{2-7}\), baseline FSFI score, and presence of gynecologic symptomatology. Other potential confounders include
pathogenic-variant type, gravida, parity, method of contraception, race, ethnicity, sexual orientation, relationship status, HRT use and HRT type, sexual dysfunction at baseline, body mass index, exercise, education level, smoking status, and alcohol use. These descriptive and confounding factors will be assessed in our participant survey.

Presence of gynecologic symptomatology is described as presence of painful vaginal bleeding, heavy vaginal bleeding, or pelvic pain. Pathogenic variant type is one of the following categories: BRCA1, BRCA2, or BRCA1 and 2. Age at time of surgery is a continuous variable. Exercise is described as five sessions of moderate aerobic session per week, lasting at least 30 minutes per session. HRT use after surgery will be stratified into yes or no categories, with further division of the yes category into systemic or local HRT type. Sexual dysfunction is an FSFI score of less than 26.55.

3.6 Monitoring Adverse Events

No serious adverse events are anticipated, although there is the possibility of minor phlebotomy related issues, including bruising at the draw site, and negative psychological responses to questionnaires. For any negative psychological responses or low scoring FSFI forms (scores <26.55), we will provide patients with a Resources form (Appendix F) which includes a list of counseling and sexual health resources in addition to the contact information for the Yale Sexuality, Intimacy, and Menopause (SIM) Clinic. Patients will be encouraged ask their primary care clinicians for a referral to the SIM clinic if they are interested. Women recruited from outside of Yale may seek counseling resources from the Sexual Health Network. This Resources form will be provided to women with low FSFI scores after the submission and scoring of the patients 6-month
post-surgery FSFI, when a patient chooses to withdrawal from the study, or at the end of the study if requested by participants (regardless of FSFI score).

3.7 Data Collection

Baseline (3 weeks prior to surgery) and 6-month post-surgery self-administered questionnaires and surveys will be collected for all study participants. The Participant Survey (Appendix E) will gather demographic and medical information used to analyze descriptive factors and confounding factors. The FSFI and MENQOL questionnaires will collect information on primary and secondary outcomes (sexual function and menopause related quality of life). The FSFI and MENQOL will be scored according to published guidelines\(^8\) and FSFI domain scores are multiplied by the respective domain coefficient to calculate total and domain scores (Table 1). If a study participant is visually impaired or identifies barriers to written completion of the surveys, surveys will be administered over the phone. Medical records will be reviewed to confirm surgery adherence, type, and date of procedure. This will easily be done in EPIC if the patient’s care is Yale-affiliated. If an outside institution or hospital is used, records will be requested by secure fax. In order to minimize missing data, the research coordinators will contact the participants on a weekly basis by phone to encourage completion of forms if they have not been received at baseline or 6 months post-surgery. In order to prevent data entry error, the questionnaires will be independently scored on two separate occasions before data entry. The research analyst assigned to data entry will be blinded to patient surgery type.

3.8 Sample Size calculation

We conducted a power calculation using t-test Power and Precision Software to determine the probability of finding a difference in FSFI scores between the two groups
under comparison at an 80% level. With 86 subjects in each group, we will detect a statistically significant mean difference of 2 points in sexual functioning after 6 months as measured with the FSFI tool (effect size). This is based on evidence of mean changes of $2.23 \pm 4.6$ in FSFI pre-post RRBSO and hysterectomy based on the study by Celik et al.\textsuperscript{9} Other assumptions for this calculation included a 2-sided hypothesis, a significance level of 5%, and a 2-point mean change in FSFI score for RRBSO alone group based on theoretical considerations.

Factoring in an expected 25% of women who do not complete the questionnaires and are lost to follow up as reported in a similar study by E. Hall et al\textsuperscript{10}, the total sample size will be 216 with 108 participants in each group. Calculations have been included in Appendix G. Given the level of uncertainty in the literature regarding this topic, and that to date, there are no studies examining our outcome of interest with our independent variables of interest, we have opted for a two-tailed test and large sample size.

\textbf{3.9 Statistical Analysis}

\textbf{3.9.1 Bivariate analysis}

A confounder is a variable associated with our independent variable of interest as well as the study outcome. A confounder is not in the causal pathway between the independent and the outcome variable. Imbalance in the distribution of a confounder between our two study groups has the potential to distort the relationship between our independent and dependent variable. To characterize the study population and determine which potential confounders we should include in our multivariate model, we will determine the association between potential confounders and our independent variable of interest as well as the association between confounders and our outcomes. If in these bivariate analyses, the association between the confounder and the independent variable
or the confounder and dependent variable is statistically significant (values that are significant will achieve p<0.1) then it will be included in the regression model as a potential confounder. A priori, age at time of surgery, existing gynecologic symptomatology, and baseline scores need to controlled for in our analysis\(^2\)\(^-\)\(^7\), so these variables will be included as potential confounders in the linear regression model regardless of whether or not we observe a lack of association.

Potential confounding factors that are categorical or dichotomous variables such as HRT use, presence of gynecologic symptomatology, and baseline sexual dysfunction (FSFI <26.55) will be analyzed using Chi Square Tests. If a potential confounder is a continuous variable that is normally distributed, a parametric test (student’s t-test) will be used, otherwise a nonparametric version will be used. Study variables can be found in Table 2. We will also compare each woman’s FSFI and MENQOL Scores pre and post-surgery to identify any confounders in surgery type. After summarizing baseline characteristics, confounding factors that are ordinal variables such as education will be analyzed using paired-t tests.

### 3.9.2 Unadjusted Bivariate Analysis

Next, using bivariate analysis, we will determine the relationship between independent and dependent variables. That is, we will observe the bivariate association between change in our outcomes between baseline and 6 months by surgery type.

Each participant’s baseline and follow-up scores for FSFI and MENQOL will be treated as paired samples and evaluated with the Student’s Paired T-Test for each domain evaluated by the questionnaires. If normally distributed, baseline and follow up scores
will be described as a mean and standard deviation; if not normally distributed, they will be described as a median and standard deviation.

### 3.9.3 Multivariable Analyses

To test our hypothesis, we will use generalized linear regression to measure the association between surgery type and changes in sexual functioning and will conduct separate GLMs for our primary and secondary outcomes. We will adjust the baseline and follow-up questionnaire scores for age at time of surgery and presence of gynecologic symptomatology. As discussed in Chapter 2, these factors are previously known to confound results and thus need to be controlled for. We will also adjust for any variables we previously identified in our analyses that are potential confounders in this data.

Subgroup analyses will be conducted to determine if the effect varies 1) between women who do or do not use HRT and 2) among those using HRT, whether the effect varies by type of HRT (local or systemic). For these analyses, the students t-test will be used to evaluate differences in scores between the subgroups. All analysis will be conducted in SAS program. P-values <.05 will be considered statistically significant.

### 3.10 Timeline and resources

This study will be completed in a two-year time frame. We will allocate two months for IRB approval, after which all research coordinators will attend a four-hour mandatory training to review inclusion and exclusion criteria for study enrollment. Participant recruitment and enrollment will begin at Month 3 and will continue through Month 13 on a rolling basis until sufficient study participants have been recruited. Equal numbers of women undergoing each surgery type will be recruited. After Month 13, enrollment will not be allowed to allow adequate time for surgery and receipt of the 6-
month post-surgery questionnaires. Survey responses will be entered within one week of receipt. Months 19-24 will be used for data collection, entry, patient follow-up, and statistical analysis.

Research personnel needed are a research coordinator to enroll subjects and request and review medical records to confirm surgery date, type and surgeon, a research assistant to follow up with patients on the phone if surveys are not received, a second research assistant to enter data, identify any post-surgical FSFI questionnaires with very low scores (<26.55), and offer patients’ a list of counseling resources (Appendix F), a research analyst to conduct statistical calculations, an independent data administrator to monitor all data entry, and a Principal Investigator to oversee all phases of the research study. Desk space, computer software, a secure fax machine, and lock box will be required at the Yale School of Medicine. Funding for patient transportation to laboratory sites for FSH blood test will be required, and if insurance does not cover cost of blood draw and FSH test this will be required as well. Funding will be required to cover cost of designing the online eligibility survey, online advertisements, and paper advertisements posted in clinics. Mailing questionnaires, with prepaid return postage for questionnaires will also be required. All participants will receive USD $25 for completion of baseline and post-surgery questionnaires (USD $50 for both), which will be included in our study budget.

3.11 References


CHAPTER 4: CONCLUSION
4.1 Advantages

This novel study has multiple advantages over studies in the existing body of literature. It addresses an urgent need for prospective research on sexual function outcomes among pre-menopausal women with BRCA mutations and compares RRBSO with and without hysterectomy. Our prospective design allows for interpretation of causal relationships and detection of changes in sexual functioning over time with administration of our baseline (pre-surgical) and follow up (post-surgical) questionnaires. With the exception of a few studies, the existing body of literature relies heavily on retrospective and cross-sectional studies.

Methodological strengths include use of the FSFI, a broadly accepted standardized questionnaire that has been validated in populations of women with hypoactive sexual desire disorder \(^{1-4}\) to assess sexual functioning. Utilizing valid outcome measures allows reproducibility of the proposed study’s findings to future studies. Additional advantages include design to encourage high response rate and retention of study subjects. Our short length of participation for study subjects (approximately 7 months), weekly reminder calls, and financial incentives lend themselves to decreased loss to follow up and high questionnaire completion rate. Previous studies had significantly longer follow-up periods (some surveyed women up to 3.5 years after surgery) and did not use reminder calls or financial incentives to encourage questionnaire completion. Finally, our custom Participant Questionnaire obtains important participant characteristics, such as presence of gynecologic symptomatology, that were not recorded in other studies.
4.2 Disadvantages

Although our proposed study addresses several disadvantages of past studies, certain limitations persist. The main limitation of our study is that women are not randomized to surgery type. The choice of surgery type is based on informed consent and shared decision making between women and their providers, and ultimately, participating women decide their own surgery. In addition, our participants elect whether or not to take HRT. It is possible that the decision to initiate HRT in women after surgery may be linked to our outcome of interest (i.e., women that opt to take HRT post-surgery may experience more severe sexual or menopausal effects of surgery). Throughout our analyses, we will take steps to identify, examine, and control for potential confounders to mitigate confounding, and will conduct sub-group analyses based on HRT use and type. The goal of future studies may be to investigate a similar study in a randomized clinical trial setting; however, it is unethical and unlikely that eligible women would want to be randomly assigned to a surgery type (or hormone replacement therapy).

An additional limitation is our sampling method. Limitations of convenience sampling include risk of selection bias and poor generalizability. The subjects who volunteer for this study may be a unique subset of individuals with inherent characteristics and therefore be less generalizable to populations of BRCA women in the United States. For example, we anticipate that our study population will be heavily skewed towards women in Connecticut because of the substantial recruitment at Yale Health sites. However, online advertising and recruitment may increase generalizability and make the proposed study more representative of the United States population.

4.3 Clinical and Public Health Significance
The public health benefits and clinical significance of this study are clear. The proposed study will detect differences in sexual functioning and menopausal quality of life outcomes between groups of women undergoing two common surgeries. These outcomes are previously unstudied and have been cited as outcomes that matter most to women\textsuperscript{5}. With these results, women with BRCA mutations can make informed surgical choices that aid and prolong their sexual life so they can spend more of their years in good sexual health. At a clinical level, health providers can offer premenopausal BRCA women deliberating between RRBSO alone and RRBSO with hysterectomy additional evidence based on this study on the non-cancer consequences of these two common surgical options. Ultimately, the results of this study will help women optimize a preventative health plan that best fits their individual needs. We anticipate that the knowledge gained will alleviate some anxiety and uncertainty for women who already faced numerous hardships because of their BRCA diagnosis.

4.4 References

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

200 FR. 1 (2016-2)

YALE UNIVERSITY SCHOOL OF MEDICINE

Study Title: Sexual Function in Women who undergo Risk-Reducing Bilateral Salpingo-Oophorectomy with or without hysterectomy

Principal Investigator: MJ Minkin, MD

Invitation to Participate and Description of Project

You are invited to participate in a research study designed to look at sexual function in BRCA+ women after Risk-Reducing Bilateral Salpingo-oophorectomy (RRBSO) with or without hysterectomy. You have been asked to participate because you have met the inclusion criteria as a BRCA+ pre-menopausal woman aged 30-55 electing to undergo one of the above surgery types. This study will include 216 participants undergoing surgery at multiple sites.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, and possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

If you agree to participate in this study, we will review your medical record to confirm eligibility. You will be contacted by a researcher to fill out a participant survey. This will include a number of medical history questions including demographic information, current medications, personal cancer history, scheduled surgery type and date, and BRCA+ status. The purpose of is to gather information that may impact sexual function outcomes. You will be assigned a unique number to identify you throughout the study.

Before Surgery: You will be asked to complete a mailed questionnaire 3 weeks prior to your scheduled surgery date. The questionnaire will require you to answer multiple choice questions on your sexual function including desire, arousal, lubrication, orgasm, satisfaction, and pain. An example question from the questionnaire is as follows:

Over the past 4 weeks how often did you feel sexual desire or interest?
Almost always or always
Most times (more than half the time)
Sometimes (about half the time)
A few times (less than half the time)
Almost never or never

Research staff will contact you by phone on a weekly basis to encourage completion of the questionnaire and return by mail if it has not been received. One month prior to surgery a small sample of your venous blood will be drawn from your arm (about 3 teaspoons) to check follicle-stimulating hormone (FSH) levels to confirm your premenopausal status.

After Surgery: Six months after surgery you will be asked to complete the same questionnaire and an additional questionnaire reporting medical information including current hormonal therapy if any. Research staff will contact you by phone on a weekly basis to encourage completion of the questionnaire and return by mail if it has not been received. The length of time of participation in this study is approximately 7 months. Your participation in this study will end after the 6 month post-surgery questionnaires are obtained.

A description of this clinical study will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate.

Risks and Inconveniences

There are few physical risks and discomforts identified in this study. Having a venous blood draw is a very safe procedure. There is a slight chance that multiple needle-sticks will be needed to make sure adequate blood is obtained. You might feel a small amount of pain with the needle stick but it does not last very long. A bruise or a minor infection might develop where the blood is drawn. A bruise will go away by itself and it might help if you wrap a warm towel around your arm. Infections can also be treated if necessary.

The sexual function questionnaires ask for personal information that may make you feel uncomfortable and there is the possible risk of loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed. All researchers are trained in research privacy. If any of the questions concern you or cause you to feel distress you may request to speak privately with the research Principal Investigator of this study who will be available by phone or in-person at the Yale School of Medicine research offices.
Filling out participant surveys and returning them by mail may come as a small inconvenience to you.

There is a federal law called the Genetic Information Nondiscrimination Act (GINA) that, in general, makes it illegal for health insurance companies, group health plans, and most employers, except those with fewer than 15 employees, to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

**Benefits**

There are a few direct benefits to you from your participation in this study, including learning more about your sexual function and menopause related quality of life. In addition, this study will likely benefit the population of BRCA+ women choosing between prophylactic RRBSO alone and RRBSO with hysterectomy by advancing understanding of post-surgical sexual function. We do hope the research results will help BRCA women in the future.

**Economic Considerations**

FSH test should be covered by your health insurance, but if not, our study will cover the cost of the test and transport to and from your nearest laboratory site. Surveys will be mailed to your preferred address with return postage pre-paid at no cost to you. We do not anticipate any costs that might result from participating in the study, and there will be no financial burden of participation. You will be compensated after study completion of the study with USD $50 cash. According to the rules of the Internal Revenue Service (IRS), payments that are made to you as a result of your participation in a study may be considered taxable income.

**Confidentiality**

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. Methods used to safeguard the confidentiality of your data include using only your identification number on mailed questionnaires, storing completed forms in a locked cabinet, and password protecting data stored on a computer. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained. When the results of the study are discussed or published no information will be included to reveal your identity unless specific permission for this activity is obtained.

Representatives from the Yale Human Research Protection Program, the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on
human subjects) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

The link to your personal information will be kept for 5 years, after which time the link will be destroyed and the data will be anonymous. The data will be kept in this anonymous form indefinitely.

In Case of Injury

If you are injured while on study, seek treatment and contact the study doctor as soon as you are able.
If you become ill or are physically injured due to the study venous blood draw or any investigational procedure specifically required by the plan for this study, you will not be responsible for the costs required to diagnose or treat such injury. The costs of diagnosis and medical care for any complication, injury, or illness caused by the study venous blood draw or properly performed non-standard of care investigational procedure required by the study will be covered by the Sponsor as long as you have followed the directions of the study doctor.

If you receive a bill for any costs related to the diagnosis or treatment of your injury, please contact the study doctor.

You will not receive any other kind of payment. There are no plans to pay you for such things as lost wages, disability, or discomfort as part of this study. You do not give up any of your legal rights by signing this consent form.

If you are injured while on study, seek treatment and contact the study doctor as soon as you are able.

Yale School of Medicine does not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study. You will not have the ability to withdraw your data from the research once it is collected. Unlike tissue samples, which
often can be withdrawn and destroyed, data derived as part of the research will not be covered by an option for withdrawal. Data will be unable to be withdrawn because it has been de-identified.

**Withdrawing From the Study**

If you do become a subject, you are free to stop and withdraw from this study at any time during its course.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part.

The researchers may withdraw you from participating in the research if necessary. The conditions under which a subject might be withdrawn include subject non-compliance with surgery.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with Yale-New Haven Hospital.

When you withdraw from the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to ensure the integrity of the study and/or study oversight.

**Questions**

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

**Authorization**

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name of Subject: __________________________

Signature: ________________________________

Relationship: ____________________________
Date:______________________________________

___________________________________________

Signature of Principal Investigator

Date

or

___________________________________________

Signature of Person Obtaining Consent

Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator, MJ Minkin at 40 Temple St, Suite 7A, New Haven, CT 06510

If, after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.
Appendix B: Recruitment Flyer

BRCA + Volunteers Needed for a Research Study

If you are a BRCA + woman planning a Risk Reducing Surgery (Bilateral Oophorectomy with or without hysterectomy), you may be eligible to participate in a research study

You may be eligible to participate if you are:

- 30-55 years old
- Sexually active
- Premenopausal
- Planning to undergo Risk Reducing Surgery (Bilateral Salpingo-Oophorectomy with or without hysterectomy)
- Have a documented BRCA mutation

Participation involves:

- Completing questionnaires regarding your sexual function, sexual distress, and menopausal symptoms before and after surgery
- A one-time blood draw
- All study related materials will be provided at no cost to you
- You will be compensated $25 for each questionnaire you complete

Scan the QR code below to take the eligibility survey now!

For further questions or if you are unsure if you meet the requirements, please contact a member of the study team at [email@gmail.com]
Appendix C: FSFI Questionnaire

Female Sexual Function Index (FSFI) ©

Subject Identifier __________________________ Date ______________

INSTRUCTIONS: These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation and vaginal intercourse. Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CHECK ONLY ONE BOX PER QUESTION.

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner’s sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how often did you feel sexual desire or interest?

☐ Almost always or always
☐ Most times (more than half the time)
☐ Sometimes (about half the time)
☐ A few times (less than half the time)
☐ Almost never or never

2. Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?

☐ Very high
☐ High
☐ Moderate
☐ Low
☐ Very low or none at all
Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how often did you feel sexually aroused ("turned on") during sexual activity or intercourse?

☐ No sexual activity
☐ Almost always or always
☐ Most times (more than half the time)
☐ Sometimes (about half the time)
☐ A few times (less than half the time)
☐ Almost never or never

4. Over the past 4 weeks, how would you rate your level of sexual arousal ("turn on") during sexual activity or intercourse?

☐ No sexual activity
☐ Very high
☐ High
☐ Moderate
☐ Low
☐ Very low or none at all

5. Over the past 4 weeks, how confident were you about becoming sexually aroused during sexual activity or intercourse?

☐ No sexual activity
☐ Very high confidence
☐ High confidence
☐ Moderate confidence
☐ Low confidence
☐ Very low or no confidence

6. Over the past 4 weeks, how often have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

☐ No sexual activity
☐ Almost always or always
☐ Most times (more than half the time)
☐ Sometimes (about half the time)
☐ A few times (less than half the time)
☐ Almost never or never
7. Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse?

☐ No sexual activity
☐ Almost always or always
☐ Most times (more than half the time)
☐ Sometimes (about half the time)
☐ A few times (less than half the time)
☐ Almost never or never

8. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse?

☐ No sexual activity
☐ Extremely difficult or impossible
☐ Very difficult
☐ Difficult
☐ Slightly difficult
☐ Not difficult

9. Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse?

☐ No sexual activity
☐ Almost always or always
☐ Most times (more than half the time)
☐ Sometimes (about half the time)
☐ A few times (less than half the time)
☐ Almost never or never

10. Over the past 4 weeks, how **difficult** was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

☐ No sexual activity
☐ Extremely difficult or impossible
☐ Very difficult
☐ Difficult
☐ Slightly difficult
☐ Not difficult
11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how often did you reach orgasm (climax)?

☐ No sexual activity
☐ Almost always or always
☐ Most times (more than half the time)
☐ Sometimes (about half the time)
☐ A few times (less than half the time)
☐ Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how difficult was it for you to reach orgasm (climax)?

☐ No sexual activity
☐ Extremely difficult or impossible
☐ Very difficult
☐ Difficult
☐ Slightly difficult
☐ Not difficult

13. Over the past 4 weeks, how satisfied were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

☐ No sexual activity
☐ Very satisfied
☐ Moderately satisfied
☐ About equally satisfied and dissatisfied
☐ Moderately dissatisfied
☐ Very dissatisfied

14. Over the past 4 weeks, how satisfied have you been with the amount of emotional closeness during sexual activity between you and your partner?

☐ No sexual activity
☐ Very satisfied
☐ Moderately satisfied
☐ About equally satisfied and dissatisfied
☐ Moderately dissatisfied
☐ Very dissatisfied
15. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner?

- [ ] Very satisfied
- [ ] Moderately satisfied
- [ ] About equally satisfied and dissatisfied
- [ ] Moderately dissatisfied
- [ ] Very dissatisfied

16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life?

- [ ] Very satisfied
- [ ] Moderately satisfied
- [ ] About equally satisfied and dissatisfied
- [ ] Moderately dissatisfied
- [ ] Very dissatisfied

17. Over the past 4 weeks, how **often** did you experience discomfort or pain during vaginal penetration?

- [ ] Did not attempt intercourse
- [ ] Almost always or always
- [ ] Most times (more than half the time)
- [ ] Sometimes (about half the time)
- [ ] A few times (less than half the time)
- [ ] Almost never or never

18. Over the past 4 weeks, how **often** did you experience discomfort or pain **following** vaginal penetration?

- [ ] Did not attempt intercourse
- [ ] Almost always or always
- [ ] Most times (more than half the time)
- [ ] Sometimes (about half the time)
- [ ] A few times (less than half the time)
- [ ] Almost never or never

19. Over the past 4 weeks, how would you rate your **level** (degree) of discomfort or pain during or following vaginal penetration?

- [ ] Did not attempt intercourse
- [ ] Very high
- [ ] High
- [ ] Moderate
- [ ] Low
- [ ] Very low or none at all

*Thank you for completing this questionnaire*
Appendix D: MENQOL-I Questionnaire

Menopause Related Quality of Life Intervention (MENQOL-I)

Subject Identifier____________ Date____________

For each of the following items, indicated whether you have experienced the problem in the PAST WEEK. If you have, rate how much you have been *bothered* by the problem.
<table>
<thead>
<tr>
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<td>No</td>
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<td>No</td>
<td>Yes</td>
<td>No</td>
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<td>5</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>3</td>
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</tbody>
</table>
Appendix E: Participant Survey

Participant Survey

This is a self-administered questionnaire that will be mailed to the study participant’s preferred address with prepaid return postage. We expect it to take less than 30 minutes to complete.

Date________
Subject Identifier: ________

Section 1: Baseline Demographics

Age________

Race
   A) American Indian or Alaskan Native
   B) Asian
   C) Black or African American
   D) Native Hawaiian or other Pacific Islander
   E) White
   F) Other

Ethnicity
   A) Hispanic or Latino
   B) Not Hispanic or Latino

Family History of Cancer
   G) Breast Cancer
   H) Ovarian Cancer
   I) Both
   J) Neither

Number of pregnancies
   A) 0
   B) 1
   C) 2
   D) 3
   E) 4 or more

Number of live births
   A) 0
   B) 1
   C) 2
   D) 3
   E) 4 or more
Current Menopausal Status
   A) Premenopausal (at least one menstrual period in the past year, or has IUD)
   B) Postmenopausal (no menstrual period in the past year)

Sexual Orientation
   A) Straight
   B) Gay
   C) Bisexual
   D) Decline to state

BRCA Type
   A) BRCA 1
   B) BRCA 2
   C) BRCA 1 & 2

Weight (lbs.)

Height (inches)

How many days do you engage in 30 minutes of moderate-intensity aerobic activity?
   A) 5 days or more per week
   B) Less than 5 days a week

Highest level of education completed?
   A) Did not complete high school
   B) High School of GED
   C) Higher Education/College

Do you take any prescription medications daily?
   A) Yes (please list all medication names, dosages, and frequencies)
   B) No

Do you take any supplements or vitamins daily?
   A) Yes (please list all names, dosages, and frequencies)
   B) No

Smoking Status
   A) Yes (please list years and packs per day)
   B) No
   C) Former smoker (please list quit year, years of smoking, and packs per day)

Do you drink alcohol?
   A) Yes (please list how many drinks in the past month)
   B) No
Section 2: Intervention Related Questions
PRIOR TO SURGERY/BASELINE (Please only complete this section once, prior to your surgery. Skip to the 6 month POST-SURGERY section if you have already had surgery)

Do you have a stable sexual partner?
A) Yes
B) No

Current Relationship Status
A) No paired relation (Single, Widowed, Divorced, Separated)
B) Paired relation (Married, Cohabiting, Having an Intimate relationship)

Method of contraception (birth control) prior to surgery (select all that apply)?
A) None
B) Condoms
C) Spermicide
D) Tubal Ligation
E) Vasectomy
F) IUD
G) Birth Control Pills
H) Other (please specify)_________

Have you been sexually active in the past 4 weeks?
A) Yes
B) No

If you have not been sexually active in the past 4 weeks what is the reason?
A) Too tired
B) Partner too tired
C) Not interested in sex
D) I have a physical problem
E) My partner has a physical problem
F) I do not have a partner
G) Other

Are you bothered by any of the following? (select all that apply)
A) Pelvic Pain
B) Heavy Vaginal Bleeding
C) Painful Vaginal Bleeding

Surgery Type
A) Risk Reducing Bilateral Salpingo-Oophorectomy (RRBSO)
B) Risk Reducing Bilateral Salpingo-Oophorectomy (RRBSO) with hysterectomy
Planned Surgery Date________

POST SURGERY (Please only complete this section 6 months after your surgery. Go back to the PRIOR TO SURGERY section if you have not had surgery yet)

Do you have a stable sexual partner?
A) Yes
B) No

Current Relationship Status
A) No paired relation (Single, Widowed, Divorced, Separated)
B) Paired relation (Married, Cohabiting, Having an Intimate relationship)

Have you been sexually active in the past 4 weeks?
A) Yes
B) No

If you have not been sexually active in the past 4 weeks what is the reason?
A) Too tired
B) Partner too tired
C) Not interested in sex
D) I have a physical problem
E) My partner has a physical problem
F) I do not have a partner
G) Other

Do you take any Hormonal Replacement Therapy including systemic (oral pills or transdermal patches) or local therapy (vaginal creams or suppositories)?
A) Yes, medication name, dosage, frequency and type (systemic or local):
   ________
B) No

Are you bothered by any of the following? (select all that apply)
A) Pelvic Pain
B) Heavy Vaginal Bleeding
C) Painful Vaginal Bleeding

Surgery Type
A) Risk Reducing Bilateral Salpingo-Oophorectomy (RRBSO)
B) Risk Reducing Bilateral Salpingo-Oophorectomy (RRBSO) with hysterectomy

Completed Surgery Date________
Appendix F: Resources Form

Resources Form

Yale Sexual Intimacy and Menopause Clinic
- This Yale Clinic in New Haven, Connecticut offers medical and psychological care to cancer survivors who experience a range of menopausal and sexual symptoms after surviving ovarian and breast cancer
- We encourage you to contact your primary care doctor and request a referral if interested
- [https://www.yalemedicine.org/departments/sexual-intimacy-and-menopause-program](https://www.yalemedicine.org/departments/sexual-intimacy-and-menopause-program)

FORCE Support group for BRCA women
- This website is specifically for women who carry BRCA mutations. They have an excellent resource guide and offer a hotline for women to call who have questions
- [https://www.facingourrisk.org/support/local-groups](https://www.facingourrisk.org/support/local-groups)

Better Help
- Counseling for Individuals or Couples
- [https://www.betterhelp.com/](https://www.betterhelp.com/)

Sexual Health Network
- Sexual Health Counseling for Individuals
- [https://www.drmitchelltepper.com/sexual_health_network](https://www.drmitchelltepper.com/sexual_health_network)

Previvors: Facing the Breast Cancer Gene and Making Life-Changing Decisions
- Book by Dina Roth Port

A Cancer in the Family, Take Control of Your Genetic Inheritance
- Book by Theodora Ross, MD, PhD

In the Family
- In the Family documents a BRCA positive woman’s efforts to reach out to other BRCA women while facing her BRCA diagnosis
- Film by Joanna Rudnick
- [https://www.pbs.org/pov/watch/inthefamily](https://www.pbs.org/pov/watch/inthefamily)

Pretty is What Changes: Impossible Choices, The Breast Cancer Gene, and How I Defied My Destiny
- Book by Jessica Queller
Appendix G: Sample Size Calculation

Sample size is based on the primary outcome of change in sexual function, assessed by the Female Sexual Function Index. The following calculation was made using the Power and Precision tool:

<table>
<thead>
<tr>
<th>Group</th>
<th>Population Mean</th>
<th>Standard Deviation</th>
<th>N Per Group</th>
<th>Standard Error</th>
<th>95% Lower</th>
<th>95% Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>oo + hyster (celik et al)</td>
<td>-2.23</td>
<td>4.66</td>
<td>86</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>oo alone (estimated for power)</td>
<td>-4.23</td>
<td>4.66</td>
<td>86</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean Difference 2.00 4.66 172 0.71 0.61 3.39

Alpha = 0.050, Tails = 2

Power 80%

For a given effect size (population means of -2.23 versus -4.23), SD (4.66), sample sizes (86 and 86), and alpha (0.05, two-tailed), power is .804. This means that 80% of studies would be expected to yield a significant effect, rejecting the null hypothesis that the two population means are equal.
Table 1. Female Sexual Function Index (FSFI) scores and domain coefficients
Abbreviations: Min: Minimum, Max: Maximum

<table>
<thead>
<tr>
<th>Domain</th>
<th>Questions</th>
<th>Scoring</th>
<th>Coefficient</th>
<th>Min. score</th>
<th>Max. score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desire</td>
<td>1,2</td>
<td>1–5</td>
<td>0.6</td>
<td>1.2</td>
<td>6</td>
</tr>
<tr>
<td>Arousal</td>
<td>3,4,5, 6</td>
<td>0–5</td>
<td>0.4</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Lubriction</td>
<td>7,8,9,10</td>
<td>0–5</td>
<td>0.4</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Orgasm</td>
<td>11,12,13</td>
<td>0–5</td>
<td>0.3</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>14,15,16</td>
<td>0 (or 1)–5</td>
<td>0.3</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Pain</td>
<td>17,18,19</td>
<td>0–5</td>
<td>0.3</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 2. Descriptive Characteristics of Study Variables

<table>
<thead>
<tr>
<th>Variable Description</th>
<th>Data Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at time of surgery</td>
<td>Continuous, Age in years, 30-55</td>
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<tr>
<td>Alcohol Use</td>
<td>Dichotomous, Yes, No</td>
</tr>
<tr>
<td>Baseline sexual dysfunction</td>
<td>Dichotomous, Yes, No</td>
</tr>
<tr>
<td>BMI (pre-surgery)</td>
<td>Ordinal, Underweight, Normal, Overweight, Obese</td>
</tr>
<tr>
<td>Bothersome Gynecological Symptotolgy</td>
<td>Nominal, Pelvic Pain, Heavy Vaginal Bleeding, Painful Vaginal Bleeding</td>
</tr>
<tr>
<td>BRCA Type</td>
<td>Nominal, BRCA 1, BRCA 2, BRCA 1&amp;2</td>
</tr>
<tr>
<td>Education</td>
<td>Ordinal, Completed: &lt; High School, High School or GED, Higher Education/College</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Dichotomous, Hispanic of Latino, Not Hispanic or Latino</td>
</tr>
<tr>
<td>Exercise</td>
<td>Dichotomous, Adequate (5 times or more weekly), Inadequate (less than 5 times weekly)</td>
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<td>Family History of Cancer</td>
<td>Nominal, Breast Cancer, Ovarian Cancer, Both, Neither</td>
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<td>Gravida (past pregnancies)</td>
<td>Ordinal, 0, 1, 2, 3, 4 or more</td>
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<tr>
<td>HRT Use</td>
<td>Dichotomous, Systemic, Local</td>
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<tr>
<td>Parity (past live births)</td>
<td>Ordinal, 0, 1, 2, 3, 4 or more</td>
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<tr>
<td>Post-surgical questionnaire return time</td>
<td>Ordinal, 0, 1, 2, 3, 4 or more</td>
</tr>
<tr>
<td>Race</td>
<td>Nominal, American Indian or Alaska Native, Asian, Black of African American, Native Hawaiian or Other Pacific Islander, White</td>
</tr>
<tr>
<td>Relationship Status</td>
<td>Dichotomous, No Partnered or Partnered</td>
</tr>
<tr>
<td>Sexual Orientation</td>
<td>Nominal, Straight, Gay, Bisexual, Decline to State</td>
</tr>
<tr>
<td>Smoking Status</td>
<td>Nominal, Yes, No, Former</td>
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<tr>
<td>Stable Sexual Partner</td>
<td>Dichotomous, Yes, No</td>
</tr>
<tr>
<td>Vaginal Bleeding with HRT</td>
<td>Dichotomous, Yes, No</td>
</tr>
</tbody>
</table>


