UTILIZATION OF OVARIAN CANCER SCREENING, RISK-REDUCING SALPINGO-OOPHORECTOMY, AND POST-RRSO HEALTH PRACTICES IN FEMALE BRCA1/BRC2 MUTATION CARRIERS

A Thesis Presented to the Faculty of California State University, Stanislaus

In Partial Fulfillment of the Requirements for the Degree of Master of Science in Genetic Counseling

By Jennifer E. Jones May 2013
CERTIFICATION OF APPROVAL

UTILIZATION OF OVARIAN CANCER SCREENING, RISK-REDUCING SALPINGO-OOPHORETOMY, AND POST-RRSO HEALTH PRACTICES IN FEMALE BRCA1/BRCA2 MUTATION CARRIERS

by
Jennifer E. Jones

Janey Youngblom, Ph.D.
Professor of Genetics
California State University, Stanislaus

Leslie Manace Brenman, M.D., MPhil
Kaiser Permanente Oakland Genetics Department

Karen Ahn, M.S., LCGC
Kaiser Permanente Oakland Genetics Department

Bethan Powell, M.D.
Gynecologic Oncology
Kaiser Permanente San Francisco

Signed Certification of Approval Page is on file with the University Library
DEDICATION

For those families whose lives have been irrevocably altered by cancer and whose stories inspire our work every day. This is also dedicated to my family members, colleagues, classmates, friends, and mentors who supported me throughout this process.
ACKNOWLEDGEMENTS

Data for this thesis has been made possible by the Kaiser Permanente Community Benefit grant, 2012 PI: Catherine Bethan Powell, MD, Evaluation of utilization of ovarian cancer screening, risk reducing surgery, and post risk reducing salpingo-oophrectomy health practices in female BRCA 1 or 2 mutation carrier members of Kaiser Permanente Northern California.

I would also like to acknowledge and thank the Kaiser Permanente Northern California Division of Research (DOR), the Breast Cancer Tracking System (BCTS) team and my wonderful research committee: Catherine Bethan Powell, M.D., Janey Youngblom, Ph.D., Karen Ahn, M.S., LCGC, and Leslie Manace Brenmen, M.D., M.Phil, who brought this project to my attention.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dedication</td>
<td>iv</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>v</td>
</tr>
<tr>
<td>List of Tables</td>
<td>vi</td>
</tr>
<tr>
<td>Abstract</td>
<td>viii</td>
</tr>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>Literature Review</td>
<td>2</td>
</tr>
<tr>
<td>Methods</td>
<td>17</td>
</tr>
<tr>
<td>Overview of Study</td>
<td>17</td>
</tr>
<tr>
<td>Study Population</td>
<td>17</td>
</tr>
<tr>
<td>Data Collection</td>
<td>19</td>
</tr>
<tr>
<td>Statistical Analysis</td>
<td>20</td>
</tr>
<tr>
<td>Results</td>
<td>23</td>
</tr>
<tr>
<td>Characteristics by BRCA1/2 Test Result</td>
<td>23</td>
</tr>
<tr>
<td>RRSO versus No RRSO</td>
<td>25</td>
</tr>
<tr>
<td>Post–RRSO Health Monitoring Practices and Outcomes</td>
<td>27</td>
</tr>
<tr>
<td>Breast and Ovarian Cancer Screening Adherence</td>
<td>30</td>
</tr>
<tr>
<td>Discussion</td>
<td>32</td>
</tr>
<tr>
<td>Conclusion</td>
<td>40</td>
</tr>
<tr>
<td>References</td>
<td>44</td>
</tr>
<tr>
<td>Appendix</td>
<td>55</td>
</tr>
</tbody>
</table>
LIST OF TABLES

<table>
<thead>
<tr>
<th>TABLE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Characteristics of Study Population by ( BRCA1/2 ) Test Result</td>
<td>24</td>
</tr>
<tr>
<td>2. Characteristics of Study Population by RRSO</td>
<td>26</td>
</tr>
<tr>
<td>5. Proposed Recommendations for Post–RRSO Health Maintenance</td>
<td>39</td>
</tr>
</tbody>
</table>
ABSTRACT

This retrospective study aims to determine the uptake of ovarian cancer screening and RRSO as well as health outcomes and monitoring practices among female \textit{BRCA1/2} carrier members of Kaiser Permanente Northern California (KPNC). Currently, \textit{BRCA1/2} test results are followed by a regional tracking system within KPNC and all health-related information is available in electronic health records. The results presented here are based on the preliminary analysis of data from women identified in the Breast Cancer Tracking System (BCTS) from 1Jan1995 to 1Jan2012. In 305 female carriers (170 \textit{BRCA1} and 135 \textit{BRCA2}), 228 (74.8\%) underwent RRSO at a median age of 49.7 years and 17\% by age 40 years. 50\% of women had RRSO within 6 months of genetic testing, with a mean of 11.6 months ($SD = 17$ months, range 1–105 months). RRSO was associated with having at least one DEXA scan ($p < .0001$), lipid panel ($p < .0001$), and blood glucose level ($p < .0001$) documented in the electronic medical chart. Premenopausal RRSO ($n = 81$) was not significantly associated with a diagnosis of stroke, venous thromboembolism, or osteoporosis/osteopenia. Diagnosis of CAD or MI was near significant ($p = .06$). In those eligible for screening, 143 (46.9\%) got CA-125 serum screening and 139 (45.6\%) got a transvaginal ultrasound (TVUS) within the first year of genetic testing. By year five, 6 (1.9\%) got serum CA-125 and 7 (2.3\%) got a TVUS. Our results are consistent with previous studies that show a high uptake of RRSO; however, the majority did not have RRSO prior to age 40 years. Overall, premenopausal RRSO
was not associated with increased incidences of related health problems. Adherence
to ovarian cancer screening is low and declines rapidly over a five-year period.
INTRODUCTION

In the United States, women in the general population face a 12% chance of developing breast cancer and a 1.4% chance of developing ovarian cancer by the age of 90 years (National Cancer Institute SEER data, 2012). The overall incidence of breast cancer in 2012 was 124.3 per 100,000 women. Put another way, 1 in 8 women will be diagnosed with breast cancer in their lifetimes, making it the most common cancer in women (NCI SEER data, 2012). Ovarian cancer is less common, with an overall incidence 12.7 per 100,000 women in 2012 (NCI SEER data, 2012).

The discovery of BRCA1 on chromosome 17 in 1994 and BRCA2 on chromosome 13 in 1996 made it possible to describe the genetic cause underlying families who seemed to be at increased risks for breast and ovarian cancer. BRCA1 and BRCA2 are tumor suppressor genes that encode proteins essential to the DNA repair process. Approximately 3–5% of breast cancer and 10–15% of ovarian cancer are due to germline mutations in BRCA1 and BRCA2 (Schneider, 2012). BRCA1 and BRCA2-related Hereditary Breast and Ovarian Cancer (HBOC) syndrome families are characterized by multiple members with breast and/or ovarian cancer at younger ages at diagnosis than expected. Women with deleterious germline mutations in BRCA1/2 have an 82% lifetime risk of developing breast cancer and a 54% and a 24% lifetime risk of developing ovarian cancer, respectively (King, 2003). Additionally, in the 10 years following the first diagnosis of breast cancer, women
with BRCA1/2 mutations have approximately a 30% risk of developing contralateral breast cancer (Gronwald et al., 2005).

Inherited mutations in BRCA1/2 are relatively uncommon. The estimated carrier frequency in the general population is 1 in 800 (Schneider, 2012). The carrier frequency within the Ashkenazi Jewish population is much higher, at approximately 1 in 40, due to three common founder mutations; two in BRCA1 and one in BRCA2 (Roa et al., 1996).

As a result of the discovery of BRCA1/2, subsequent delineation of cancer risks, and a storm of media attention, utilization of BRCA1/2 testing is increasing. Risk-reducing surgeries have been shown to reduce the incidence of breast and ovarian cancer and overall mortality in this high risk population (Domchek et al., 2010). There is, however, variable follow-up and outcomes for patients with BRCA1/2 mutations regarding organ surveillance and risk-reduction procedures, particularly regarding ovarian cancer screening and management. In this study, the HBOC syndrome cancer screening and care of patients testing positive for a BRCA1 or BRCA2 deleterious mutation within a managed care setting over 17 years is evaluated.

**Literature Review**

The National Comprehensive Cancer Network (NCCN) provides evidence-based guidelines and resources that are used by many cancer health care providers, including gynecologic oncologists and genetic counselors. The NCCN recommends that women with germline BRCA1/2 mutations initiate self-breast exams at 18 years
of age and at 25 years of age begin clinical breast exams (CBE) every 6-12 months. Annual mammogram and breast magnetic resonance imaging (MRI) are also recommended to begin at age 25 years, or earlier if the family has members with very young age of onset of breast cancer (NCCN HBOC management guidelines v2.2013). MRI is a more sensitive modality for the detection of breast lesions than mammography; the combination of MRI, mammography, and CBE has the highest sensitivity for detection of breast cancer in high-risk \textit{BRCA}1/2 mutation carriers (Kriege et al., 2004). This strategy of combined screening is effective at detecting breast cancer at earlier stages. Early stage detection is important because the 5-year survival rate for breast cancer confined to the primary site is 98.4% and 83.9% if confined to regional lymph nodes (NCI SEER data, 2012).

The NCCN guidelines also recommend that risk-reducing mastectomy (RRM) be discussed on a case-by-case basis with review of benefits, risks, and reconstruction options. It has been well-documented that RRM reduces the risk of breast cancer by greater than 90-95% (Meijers-Heijboer et al., 2001). Recent studies in North America have examined the uptake of RRM from 3 to 5 years after \textit{BRCA}1/2 testing. They have found that 48% of carriers previously affected with breast cancer and 20-36% of unaffected carriers choose RRM (Beattie et al., 2009; Friebel et al., 2007; Metcalfe et al., 2008).

In addition, chemoprevention with medications including tamoxifen and raloxifene has been offered as an option for breast cancer risk-reduction. However, because of the hormone receptor profiles of \textit{BRCA}1/2 breast cancers, determination of
benefit within this group is less straightforward. The NCCN recommends
consideration of the risk and benefits of chemoprevention but does not give specifics
for who would be an ideal candidate. Studies have suggested that chemoprevention
may reduce breast cancer risk by 62% in *BRCA2* mutation carriers but offers no
protective benefit in *BRCA1* mutation carriers due to the low prevalence of estrogen
receptor positive breast cancers in this group (King et al., 2001). Tamoxifen use has
been shown to reduce the risk of contralateral breast cancer in *BRCA1/2* mutation
carriers independent of the risk benefit provided by oophorectomy (Narod et al.,
2000).

Along with management of increased risk of breast cancer, women with
deleterious *BRCA1/2* mutations face the challenge of managing ovarian cancer risk.
When compared to breast cancer screening guidelines, the ovarian cancer picture is
less clear. This is of particular concern because ovarian cancer is the leading cause of
death from gynecologic malignancy. The overall 5-year survival rate is approximately
40% with the majority of ovarian cancer presenting at advanced stages (NCI SEER
data, 2012). The current NCCN guidelines recommend risk-reducing salpingo-
oophorectomy (RRSO), the surgical removal of the ovaries and the Fallopian tubes,
ideally between 35 and 40 years or upon completion of childbearing or individualized
based on the earliest age of onset of ovarian cancer in the family.

For female carriers of *BRCA1/2* mutations who have not elected risk-reducing
surgery, ovarian cancer screening is offered including concurrent transvaginal
ultrasound and serum CA-125 (cancer antigen 125) determination every 6 months.
starting at age 35 years or 5-10 years earlier than the earliest age of first diagnosis of ovarian cancer in the family. Serum level of CA-125 is frequently used as a biomarker because it is often elevated in patients with ovarian carcinoma. The CA-125 test has an 80% chance of being abnormal in stage II, III, and IV ovarian cancer patients; however, it is elevated in only 50% of stage I ovarian cancer patients. Furthermore, CA-125 levels can be elevated in a variety of other benign conditions such as endometriosis, fibroids, menstruation, and pregnancy (“Ovarian Cancer: diagnosis and treatment,” n.d.).

There are retrospective data indicating that annual ovarian screening using transvaginal ultrasound and serum CA-125 are neither an effective strategy for early detection of ovarian tumors nor a reasonable substitute for RRSO (NCCN guidelines v 2.2013). Even with regular screening the diagnosis of early stage ovarian cancer is rarely made and false positives lead to unnecessary anxiety and invasive procedures (Berliner & Fay, 2007). Thus, the American College Obstetricians and Gynecologists (ACOG) recommends that patients not undergoing RRSO consider transvaginal ultrasound and CA-125 every 6 months with the caution that there is no evidence to support that ovarian cancer screening reduces mortality or improves survival in high risk populations (ACOG, 2009). Given the limitations of current ovarian cancer screening approaches, RRSO, particularly after a woman’s childbearing is concluded, is highly accepted by BRCA1/2 mutation carriers. A study by Rhiem et al., (2011) revealed a high acceptance rate of 57% (175/306) for RRSO in BRCA1/2 mutation carriers. Additional studies in the US have found that long-term uptake of RRSO has
ranged from 51% to 71% (Schwartz et al., 2012). As a result, it is now considered standard of practice for gynecologic oncologists and genetic counselors to discuss RRSO upon completion of childbearing and not to wait until after menopause to maximize risk reduction (Berliner & Fay, 2007).

The efficacy of RRSO for the prevention of ovarian and fallopian tube cancer in BRCA1/2 mutation carriers has been well established in the literature (Kauff et al., 2002). In a study by Rebbeck et al. in 2002, RRSO reduced ovarian cancer risk by 96% in BRCA 1 and BRCA 2 mutation carriers. Additionally, RRSO has also been shown to confer a 50% reduction of risk for developing breast cancer if performed premenopausally (Kauff et al., 2002; Rebbeck et al., 1999). A multi-center prospective study by Kauff et al. (2008) showed that during a 3-year follow up, RRSO was associated with an 85% reduction in BRCA1-associated gynecologic cancer risk and a 72% reduction in BRCA2-associated breast cancer risk. Studies have also shown that serial sectioning of RRSO specimens have detected clinically occult fallopian tube and ovarian carcinomas, highlighting that ovarian cancers can be detected at the time of RRSO (Powell et al., 2004). However, RRSO does not eliminate the risks of ovarian cancer completely, as there is a 2-4% risk of subsequent peritoneal cancer which is clinically and histologically indistinguishable from ovarian cancer (Rebbeck, Kauff & Domchek, 2009; Finch et al., 2006).

Optimal timing of RRSO takes into account several factors including reproductive desires, timing of breast cancer risk, timing of gynecologic cancer risk and other risk-reducing strategies. The mean age at diagnosis of ovarian cancer was
found to be 50.8 years in a study by Rebbeck et al. in 2002. Female carriers of a
*BRCA1* mutation have a 2–3% risk of developing gynecologic cancer by age 40 years
and should consider RRSO by the late 30s to early 40s. Female carriers of a *BRCA2*
mutation approach the 2–3% risk of gynecologic cancer by age 50 years but may still
want to consider RRSO to reduce the 26% to 34% breast cancer risk (Kauff &
Barakat, 2007). Studies have shown that the greatest proportion of risk reduction is
conferred when RRSO is performed prior to age 40 years or before the age of natural
menopause (Meijer & van Lindert, 1992).

There has historically been a high acceptance rate of RRSO among *BRCA1/2*
mutation carriers. A few studies have looked at factors that influence whether a
woman chooses to have RRSO. Friebel et al. (2007) found that age greater than 40
years and presence of ovarian cancer in first degree relatives were significant
predictors of RRSO. Schwartz et al. (2012) prospectively examined long-term risk
management outcomes and predictors after *BRCA1/2* testing. They followed patients
for a mean time of 5.3 years after testing and found that by the end of follow-up, 37%
of *BRCA1/2* carriers opted for RRM and 65% opted for RRSO. They also reported
that age (being 40 years or older) was the only predictor of RRSO among carriers,
reflecting current guidelines recommending RRSO by age 40 years. Risk-reducing
mastectomy was associated with having intact ovaries and higher anxiety at the time
of genetic counseling.

If female *BRCA1/2* mutation carriers follow the NCCN guidelines and opt for
RRSO prior to age 40 years, they would experience acute surgical menopause 10-15
years ahead of the expected age of natural menopause. The surgical inducement of menopause can raise quality of life concerns within this group (Rebbeck et al., 2005). Tubal ligation (without oophorectomy), another potential surgical intervention, has been found to reduce the risk of ovarian cancer by approximately 50% in the general population and among retrospectively studied BRCA1 mutation carriers (Narod et al., 2001). Although not widely used, it has been suggested that salpingectomy (removal of the entire fallopian tube) may represent a short-term risk-reducing strategy for selected young women who have completed childbearing but who prefer to delay removal of the ovaries until closer to natural menopause (Greene et al., 2008).

For young women who have not completed childbearing, chemoprevention may be discussed as a risk-reduction strategy (ACOG, 2009). Studies have reported a reduction in risk of ovarian cancer among women who have ever used oral contraceptive pills (OCPs) and among those who have used OCPs for a longer duration. Narod et al. in 1998 found that OCP use was associated with a 60% reduction in ovarian cancer for both BRCA1 and BRCA2 carriers. However, in 2002, Narod et al. found that OCPs increased the risk of breast cancer for BRCA1 mutation carriers, especially if they were used prior to 1975, prior to age 30 years, and for 5 or more years. OCPs did not appear to increase the risk of breast cancer among BRCA2 mutation carriers. Overall, it appears that the most effective risk-reducing strategy for ovarian cancer is RRSO.

Studies in the general population have found that premature menopause or early menopause, whether spontaneous or induced, is associated with long-term
health risks including premature death, cardiovascular disease, neurological disease, osteoporosis, psychosexual dysfunction, and mood disorders such as depression. (Shuster et al., 2010). Results from the Mayo Clinic Cohort of Oophorectomy and Aging found an increased risk of cognitive impairment or dementia later in life in women who underwent oophorectomy before menopause compared to women who did not (Rocca et al., 2007). This cohort also showed that bilateral oophorectomy before age 45 years increased mortality due to cardiovascular disease (Rocca et al., 2006). In addition, surgical menopause in young women can result in severe hot flashes, vaginal dryness, sexual dysfunction, sleep disturbances and cognitive changes that may affect quality of life (Rebbeck et al., 2005). In 2003, Robson et al. surveyed 59 women at risk for ovarian cancer (22 had a germline mutation in BRCA1/2 or MLH1) who underwent RRSO and found that vaginal dryness and dyspareunia were the most bothersome symptoms of estrogen deprivation. Pointedly, vaginal symptoms and the occurrence of coital problems were the strongest predictors of dissatisfaction with the decision to undergo RRSO. Finch and Narod reviewed the current literature (as of 2011) regarding quality of life and health status after RRSO. Overall, they found that in the short term (<5 years), quality of life appears to be similar before and after surgery and that changes in sexual functioning are common. Despite the general consensus within the gynecologic oncology and genetic counseling communities that it is appropriate to recommend RRSO by age 40 years to BRCA1/2 mutation carriers, few studies have examined the effects of surgical menopause in this population.
Investigation of health maintenance practices of surgically induced menopause is important for female $BRCA1/2$ mutation carriers who have elected to pursue RRSO. The NCCN guidelines do recommend addressing topics such as increased risk for osteoporosis and cardiovascular disease associated with premature menopause, but offers no clear standard for how to diagnose and follow these conditions in this post-RRSO population. In fact, there are no clear standard national guidelines for post-RRSO care. A recent survey in 2011 of women undergoing RRSO at the University of California, San Francisco found that the use of CA-125 for subsequent cancer screening, bone mineral density (DEXA) scans and calcium supplementation, hormone replacement therapy use and heart disease prevention as health monitoring and maintenance practices for surgically induced menopause was inconsistent among physicians. A lack of firm national guidelines and individual physician preferences were suggested to be the most likely reasons for inconsistency (Chapman et al, 2011).

Estrogen therapy (HRT) may reduce RRSO induced menopausal symptoms but hormone use is often contraindicated in women with a personal history of breast cancer. Thus, these women have limited options for the management of vasomotor and sexual symptoms related to menopause (Finch and Narod, 2011). As a result, some high risk women may defer RRSO because of concerns about hormone replacement therapy and breast cancer risk, while remaining at risk for ovarian cancer (Rebbeck et al., 2005). However, HRT is not contraindicated for women with intact breasts and who have no previous history of breast cancer (Finch and Narod, 2011).
The PROSE study group found that short-term HRT following RRSO did not alter the substantial reduction in breast cancer risk associated with RRSO. Furthermore, women who had undergone RRSO and took HRT had a greater reduction in breast cancer risk than women who did not undergo RRSO and did not take HRT (Rebbeck et al., 2005). Madalinska et al. (2006) compared premenopausal women who underwent RRSO with those who underwent screening and found that among those who had RRSO, individuals on HRT reported fewer menopausal symptoms. Future studies on this data will further evaluate the proportion of menopause-related symptoms. The safety of HRT in BRCA1/2 mutation carrier is still under debate (Chapman et al., 2011).

Utilization of BRCA1/2 genetic testing and risk-reducing practices has been a focus of a number of studies. However, few studies have looked at long-term outcomes. Botkin et al. (2003) evaluated uptake of genetic testing and cancer risk management strategies up to two years following genetic test results. They reported a relatively high level of utilization of genetic testing among their sample: 52% of at-risk men and 55% of at risk-women. When looking at management strategies, they found that carrier women clearly preferred risk-reducing strategies over early detection measures to manage their risk of ovarian cancer. Forty-six percent of carrier women had obtained an oophorectomy 2 years after genetic testing, including 78% of women 40 years of age or older. They looked at screening practices over two years and reported that 26% of carrier women had transvaginal ultrasound in the first year and 11% in the second year. For CA-125, the same drop-off was not observed: 32%
obtained a CA-125 measurement in the first year and 37% in the second year. For mammography, 59% of carriers had a mammogram in both of the two years following testing. Twenty-nine percent had not obtained a mammogram in both years following testing. Breast MRI was not a standard recommendation at the time and was not assessed. In 2012, Schwartz et al. prospectively examined risk-reducing strategies among participants for 5.3 years. To date, this is the longest follow-up duration of any study. They reported that among participants with intact breasts and/or ovaries at the time of genetic testing, 37% opted for RRM and 65% opted for RRSO. When the investigators examined screening adherence after receipt of \( BRCA1/2 \) results and reported that use of mammography was high (92%) and use of breast MRI was strongly associated with test results. Forty-six percent of unaffected carriers reported at least one breast MRI. When they evaluated ovarian cancer screening, they found that rates of CA-125 and transvaginal ultrasound were lower than rates of breast cancer screening, 56% and 42% respectively.

Campitelli et al. (2011) did not exclusively study \( BRCA1/2 \) mutation positive carriers but examined adherence to breast and ovarian cancer screening recommendations in females from high, moderate, and low risk families in Canada. Risk was characterized based on a family history questionnaire and criteria included having two or more first degree relatives with breast and/or ovarian cancer. Their study demonstrated that women from the high risk family groups had the highest adherence to screening recommendations but that the numbers were still suboptimal. For women aged 40-49 years at a high or moderate risk, 56.3% had mammogram
within the last 12 months. Of the women with high familial risk, 2.8% had received a transvaginal ultrasound and 3.3% had CA-125 test.

Published studies have examined factors influencing adherence to breast and ovarian screening recommendations. Tinley et al. (2004) assessed adherence to \( BRCA1/2 \) screening guidelines in individuals who are carriers of a deleterious mutation and individuals at 50% risk of being carriers (i.e. first-degree relatives of known carriers). They reported that adherence rates were 72% for annual mammography, 19% for transvaginal ultrasound, and only one patient was adherent to semi-annual CA-125. Investigators found that a more satisfactory experience with healthcare providers and perceived confidence in the utility and effectiveness of breast cancer screening were variables associated with mammography adherence. For participants whose physicians recommended yearly mammograms, the odds of adherence were 211 times higher than the odds among women whose physicians did not recommend yearly mammogram. Those who were adherent to transvaginal ultrasound had a higher perception of their numerical risk of ovarian cancer and were more likely to intend RRSO. Again, physician recommendation was associated with transvaginal ultrasound adherence. Wainberg and Husted (2004) found that the proportion of unaffected \( BRCA1/2 \) carriers who chose surgery (risk-reducing mastectomy and RRSO) varied across studies, ranging from 0% to 54% and 13% to 53% respectively. Adherence to ovarian cancer screening was relatively low across three studies (<43%). The authors hypothesize that study location, healthcare coverage, cultural differences and values surrounding body image and femininity,
sociodemographic differences, and greater uncertainty surrounding the efficacy of ovarian cancer screening influence surgical and screening decisions. Loescher et al. (2009) investigated cancer surveillance behaviors of women at risk for hereditary breast and ovarian cancer who presented for clinical *BRCA1/2* testing. More than 87% of participants reported at least a yearly clinical breast exam, mammogram, or pelvic examination. Forty-six percent reported having had a transvaginal ultrasound and 47% reported having had a CA-125 test. Some participants confused the CA-125 test with the *BRCA* test. The investigators found that approximately 50% stated they did not engage in screening because their physicians did not recommend the procedures. Dhar et al. (2011) found significant differences among physician specialties in management recommendations of *BRCA1* mutation carriers. They reported that physicians clearly recommended more intense screening for mutation positive than for mutation negative women but only 16% of physicians made recommendations consistent with NCCN guidelines. There was significant variation among specialists who recommended breast MRI and RRSO with 76% and 78% of general surgery and obstetrics and gynecology recommending RRSO and 38% of internal medicine. One explanation for the differences among specialties in risk management recommendations may relate to lack of physician experience with genetic testing in their practice. They suggest that targeted education of physicians is needed.

Increasing uptake of *BRCA1/2* testing will lead to greater numbers of women identified as being carriers of deleterious mutations. If it is the hope to recommend
risk reducing measures such as RRSO through genetic counseling and molecular genetic testing, it seems logical to be able to effectively track ovarian cancer surveillance and post-RRSO health maintenance. The ultimate goal of tracking would be for healthcare providers to make recommendations that reduce BRCA1/2 cancer-related mortality and morbidity associated with premature menopause. Additionally, in women who do not choose RRSO, more effective follow-up to ensure adherence to screening recommendations is warranted.

The current study aims to address the following questions: how often are female carriers of a BRCA1/2 mutation undergoing transvaginal ultrasound and CA-125 tests for ovarian cancer screening versus electing risk-reducing salpingo-oophorectomy? What other strategies, if any, are these women electing to reduce their risks? If RRSO is performed, what is the rate of post-RRSO usage of hormone replacement therapy (HRT), DEXA bone scans, calcium, vitamin D, CA-125, and lipid profiles to manage morbidity related medical problems like diabetes, hypertension, heart disease, osteoporosis, dementia, and mood disorders? And finally, what is the BRCA1/2 cancer rate in women who underwent screening versus RRSO? By evaluating these questions, the study aims to establish the baseline of what this at-risk population is currently practicing for ovarian cancer screening, prevention, and risk reduction as well as early menopause health outcomes and maintenance practices in a managed healthcare setting. The data from this study will add to the limited literature examining the long-term outcomes of RRSO. Our study also aims to be the
first to report NCCN guideline breast and ovarian cancer screening adherence for five years following BRCA1/2 testing.
METHODS

Overview of the Study

The present study examines the utilization of screening, chemoprevention, prophylactic ovarian surgery and early menopause health monitoring practices and outcomes in female BRCA1/2 mutation carrier members of Kaiser Permanente Northern California (KPNC). Kaiser Permanente is an integrated managed care consortium based in Oakland, California. KPNC includes all Kaiser Permanente affiliated centers in the northern California region. Currently, KPNC identifies patients with BRCA1/2 mutations in the Integrated Regional Genetic System (IRGS) and the KP Regional Breast Cancer Tracking System (BCTS). The BCTS sends patient and physician reminders for scheduling screening tests at appropriate time intervals based on published cancer care guidelines. The BCTS also follows outcomes, correlates mammogram findings with biopsy, surgery, and survival. The BCTS currently provides this service only for breast cancer risk and does not address ovarian cancer screening, management, or outcomes in this select BRCA1/2 mutation positive population. A secondary outcome of this study is to determine if sufficient data exists to recommend the inclusion of ovarian cancer screening to the BCTS to improve adherence.

Study Population

A flow chart detailing how we obtained our study population can be found in the Appendix. Female KPNC members were identified in BCTS and IRGS as diagnosed carriers of a BRCA1 or BRCA2 mutation. Between January 1, 1995 and
January 1, 2012, BCTS and IRGS identified 563 female patients who received BRCA1/2 testing and were found to be mutation carriers. Of the 563 identified, 34 were excluded who left Kaiser within 1 year of testing, 2 died within 1 year of testing, and 67 were excluded for a diagnosis of ovarian, peritoneal, or tubal cancer prior to testing or who had undergone RRSo prior to testing for an independent diagnosis. During a comprehensive chart review, 92 women were also excluded because they received a variant of uncertain significance (VUS). Sixty-three were excluded from final statistical analysis due to insufficient information extracted from the electronic medical record. Our final sample (N = 305) represents those patients who were at least 18 years of age or older at the time of testing and who have a documented BRCA1 or BRCA2 mutation in BCTS and IRGS.

**Inclusion Criteria**

Female KPNC members with:

- *BRCA1* deleterious mutation documented in medical record
- *BRCA2* deleterious mutation documented in medical record
- *BRCA1/2* testing done between 01Jan1995 and 01Jan2012
- Medical records available within Kaiser Permanente for at least one year after diagnosis of *BRCA1/2* mutation
- Age ≥18 years

**Exclusion Criteria**

Female KPNC members with:

- Non-*BRCA1/2* hereditary risk for ovarian cancer
- *BRCA1/2* variant of uncertain significance (VUS)
- Died or left Kaiser within one year of diagnosis of *BRCA1/2* mutation
- Diagnosed with ovarian, primary peritoneal or tubal cancer prior to their diagnosis of *BRCA1/2* mutation
- Underwent RRSO for an independent diagnosis prior to diagnosis of *BRCA1/2* mutation

**Counseling Protocol**

At Kaiser Permanente Northern California, women with deleterious mutations in *BRCA1/2* receive genetic counseling according to the most recently published “Genetic/Familial High–Risk Assessment: Breast and Ovarian” NCCN guidelines.

**Data Collection**

HealthConnect (Epic Systems Corporation), implemented in 2002, is Kaiser Permanente’s comprehensive electronic medical chart system. The majority of this study’s retrospective chart review process utilized HealthConnect. Medical record information prior to 2002 utilized CIPS, an earlier electronic charting system. All relevant data were retrieved from the patients’ electronic medical record in HealthConnect or CIPS. Physician’s and genetic counselor’s letters, pathology reports, pedigrees, and imaging reports were used to collect detailed information about variables included in the study. Information on date of testing, age at testing, mutation status, personal oncologic history, date of RRSO, date of bilateral mastectomy, gravity and parity, ethnicity (Ashkenazi/non-Ashkenazi), pathology, menopause, chemoprevention, and HRT use were collected for all eligible
participants. In our study, menopause is defined as the cessation of menstruation for 12 consecutive months. Early menopause is defined as menopause prior to age 46.

Chemoprevention includes tamoxifen/raloxifene and OCPs. HRT includes estrogen or progesterone therapy or both. We measured the proportion of KPNC female BRCA1/2 mutation carriers who are in compliance with NCCN guidelines for breast and ovarian cancer screening (transvaginal ultrasound and serum CA-125 measurement every 6-12 months). The study also quantified and calculated the proportion of BRCA1/2 carriers who currently use or have used chemoprevention and/or tubal ligation for risk-reduction, RRSO for ovarian/breast cancer risk-reduction, and post-RRSO early menopause health maintenance usage of DEXA scans, calcium and vitamin D supplementation, HRT, and lipid profiles. The study also calculated the incidence of BRCA1/2 related cancers with or without RRSO and incidence of menopausal related health problems in BRCA1/2 carriers (menopausal symptoms, hypertension, heart disease, venous thromboembolism, diabetes, osteoporosis/osteopenia, depression, and dementia). All data was stored in KP network computers on a restricted access drive. Data was then entered into a secure, password protected Microsoft Excel spreadsheet accessible only by the study investigators.

**Statistical Analysis**

The study utilized SAS correlational and descriptive statistics (frequencies, means, medians, proportions) of demographic (age at BRCA testing, race/ethnicity, etc.) and clinical characteristics (osteoporosis, heart disease, etc.). To measure the
proportion of participants in compliance with ovarian cancer screening recommendations, individuals without RRSO with at least one transvaginal ultrasound or CA-125 measurement within 12 month intervals following testing were calculated over a denominator of total eligible participants (BRCA1/2 positive and no RRSO). Participants who underwent RRSO during the 5 year follow-up were censored along with patients who left Kaiser. Similarly, we calculated the proportion of women in compliance with breast cancer screening recommendations for comparison. We calculated the proportions of BRCA 1/2 carriers that use OCPs, tamoxifen/raloxifene, and tubal ligation for risk reduction, RRSO for ovarian/breast cancer risk reduction, post RRSO, early menopause health maintenance usage of DEXA scans, calcium and vitamin D supplementation, HRT, and lipid profiles. We calculated the incidence of BRCA-related cancers after RRSO for the length of patient follow up in Kaiser Permanente and calculated the incidence of menopausal related health problems post RRSO and compared that with the incidence in the cohort who did not undergo RRSO. Health related problems associated with menopause include osteoporosis, heart disease, hyperlipidemia, hypertension, diabetes, depression, and hot flashes. These values were calculated using Chi-squared tests. Fishers exact tests were used for tables with small cells ($n < 5$).

**Institutional Review Board Approval**

The study protocol was a grant project approved by KPNC’s Division of Research Institutional Review Board (Protocol #CN-11CPowe-03-H) and the
Institutional Review Board at the California State University, Stanislaus (Protocol #1213-044).
RESULTS

Characteristics by BRCA1/2 Test Result

Characteristics of our study population by BRCA1/2 positive test result are summarized in Table 1. The majority of our sample was white (n = 216) which comprised 70.8% of the total. Twenty-nine percent were non-white (African American, Hispanic, Asian, or other). Sixty (19.7%) were of Ashkenazi Jewish decent; 38 BRCA1 mutation carriers and 22 BRCA2 mutation carriers. One hundred seventy (55.7%) women in our sample had (unilateral or bilateral) breast cancer prior to testing; 99 (32.5%) were BRCA1 mutation carriers and 71 (23.3%) were BRCA2 mutation carriers. A diagnosis of breast cancer includes DCIS and LCIS in addition to invasive carcinoma. The mean age at testing of BRCA1 mutation carriers (M = 45.9, SD = 11.7) was significantly younger than the mean age at testing of BRCA2 mutation carriers (M = 49, SD = 12.7), t(303) = -2.17, p = .030, 95% CI [11.3, 13.2]. Of the 305 women who tested positive for BRCA1 (n = 170) or BRCA2 (n = 135) deleterious mutations, 228 (74.8%) elected to undergo RRSO, 131 BRCA1 mutation carriers (77.1% of the BRCA1 mutation carriers) and 97 BRCA2 mutation carriers (71.9% of BRCA2 mutation carriers). Thirty-one (10.2%) BRCA1 mutation carriers underwent bilateral mastectomies and 20 (6.6%) BRCA2 mutation carriers underwent bilateral mastectomies. Twenty-three (9 BRCA1 and 14 BRCA2) members of our study population had tubal ligation prior to BRCA1/2 testing and 4 (0 BRCA1 and 4 BRCA2) had hysterectomy without removing the fallopian tubes and ovaries prior to BRCA1/2
testing. There was a significant difference between BRCA1 and BRCA2 mutation carriers and hysterectomy.

**Table 1**

*Characteristics of Study Population by BRCA1/2 Test Result (%)*

<table>
<thead>
<tr>
<th></th>
<th>BRCA1 (n=170)</th>
<th>BRCA2 (n=135)</th>
<th>Total (N=305)</th>
<th>$\chi^2$</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at dx of BRCA 1/2$^a$</td>
<td>$M = 45.9$</td>
<td>$M = 49$</td>
<td>($N = 305$)</td>
<td>.03*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$SD = \pm 11.7$</td>
<td>$SD = \pm 12.7$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td>.12</td>
<td>.72</td>
</tr>
<tr>
<td>White</td>
<td>119 (39.0)</td>
<td>97 (31.8)</td>
<td>216 (70.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-white/unknown</td>
<td>51 (16.7)</td>
<td>38 (12.5)</td>
<td>89 (29.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td>2.55</td>
<td>.28</td>
</tr>
<tr>
<td>Ashkenazi</td>
<td>38 (12.5)</td>
<td>22 (7.2)</td>
<td>60 (19.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Ashkenazi</td>
<td>112 (36.7)</td>
<td>91 (29.8)</td>
<td>203 (66.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>20 (6.6)</td>
<td>22 (7.2)</td>
<td>42 (13.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer prior to testing</td>
<td>99 (32.5)</td>
<td>71 (23.3)</td>
<td>170 (55.7)</td>
<td>.97</td>
<td>.32</td>
</tr>
<tr>
<td>Other cancer prior to testing</td>
<td>4 (1.3)</td>
<td>7 (2.3)</td>
<td>11 (3.6)</td>
<td>1.74</td>
<td>.22</td>
</tr>
<tr>
<td>Surgery prior to testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral mastectomy</td>
<td>31 (10.2)</td>
<td>20 (6.6)</td>
<td>51 (16.7)</td>
<td>.63</td>
<td>.43</td>
</tr>
<tr>
<td>Tubal Ligation</td>
<td>0 (0.0)</td>
<td>4 (1.3)</td>
<td>4 (1.3)</td>
<td>5.22</td>
<td>.04*</td>
</tr>
</tbody>
</table>

Note. $M$ = mean; $SD$ = standard deviation; RRSO = risk-reducing salpingo-oophorectomy; Fisher’s exact test used for table values less than 5.

$^a t(303) = -2.17$

$^b \text{BRCA1 (n=170); BRCA2 (n=132); Total (N=302).}$

*p < .05.
RRSO versus No RRSO

Characteristics of our study population who underwent RRSO versus those who did not are summarized in Table 2. Our mean follow-up duration was 53 months (approximately 4.4 years). Mean time to RRSO after receipt of positive BRCA1/2 test results was 11.6 months (SD = ±17 months, range = 1 – 105 months). Fifty percent of women in our study had RRSO within 6 months. The median age at the time of RRSO was 49.7 years and the mean age was 50.2 years. Seventeen percent of our study population had RRSO by age 40 years. There was a significant difference between RRSO and race (p = .01). Twenty-three (7.5%) women who underwent RRSO used OCPs prior to RRSO or menopause whereas 205 (67.2%) women who underwent RRSO did not use OCPs prior to RRSO or menopause; this difference was significant (p = <.0001). In our sample, there was a significant association between HRT use and RRSO/menopause, χ² (2, N = 305) = 79.1, p = <.0001, ϕ = .51. When comparing women with a breast cancer diagnosis (prior to testing or during follow-up) and women without a breast cancer diagnosis, significantly more women with breast cancer did not use HRT, χ² (2, N = 305) = 30.1, p = <.0001, ϕ = .31. Parity and RRSO was also found to be statistically significant; women who underwent RRSO tended to have had children, χ² (3, N = 296) = 32.3, p = <.0001, ϕ = .33. We also found a significant association between prior breast cancer and RRSO, χ² (1, N = 305) = 10.0, p = .002, ϕ = .18 and race and RRSO, χ² (1, N = 305) = 6.12, p = .01, ϕ = .14. Of the women who underwent RRSO, (n = 228), 7 (2.3%) were diagnosed with breast cancer during follow-up (on or after the test date), 4 (1.3%) were diagnosed with
ovarian cancer during follow-up, and 7 (2.3%) were diagnosed with a cancer other than breast or ovarian (lung, pancreas, melanoma).

Table 2

**Characteristics of Study Population by RRSO (%)**

<table>
<thead>
<tr>
<th></th>
<th>RRSO (n = 228)</th>
<th>No RRSO (n = 77)</th>
<th>Total (N = 305)</th>
<th>χ²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean time to RRSO&lt;sup&gt;a&lt;/sup&gt;</td>
<td>M = 11.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SD = ± 17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age at RRSO&lt;sup&gt;b&lt;/sup&gt;</td>
<td>M = 50.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SD = ± 9.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test result</td>
<td></td>
<td></td>
<td></td>
<td>1.08</td>
<td>.30</td>
</tr>
<tr>
<td>BRCA1</td>
<td>131 (43.0)</td>
<td>39 (12.8)</td>
<td>170 (55.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA2</td>
<td>97 (31.8)</td>
<td>38 (12.4)</td>
<td>135 (44.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td>6.12</td>
<td>.01*</td>
</tr>
<tr>
<td>White</td>
<td>170 (55.7)</td>
<td>46 (15.1)</td>
<td>216 (70.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-white/unknown</td>
<td>58 (19.0)</td>
<td>31 (10.2)</td>
<td>89 (29.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td>3.26</td>
<td>.20</td>
</tr>
<tr>
<td>Ashkenazi</td>
<td>45 (14.6)</td>
<td>15 (4.9)</td>
<td>60 (19.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Ashkenazi</td>
<td>147 (48.2)</td>
<td>56 (18.4)</td>
<td>203 (66.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>36 (11.8)</td>
<td>6 (2.0)</td>
<td>42 (13.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI at testing&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>3.84</td>
<td>.28</td>
</tr>
<tr>
<td>Normal</td>
<td>75 (24.6)</td>
<td>34 (11.2)</td>
<td>109 (35.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>60 (19.7)</td>
<td>14 (4.6)</td>
<td>74 (24.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>51 (16.7)</td>
<td>15 (4.9)</td>
<td>66 (21.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>42 (13.8)</td>
<td>14 (4.6)</td>
<td>56 (18.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCPs prior to RRSO/menopause</td>
<td>23 (7.5)</td>
<td>25 (8.2)</td>
<td>48 (15.7)</td>
<td>21.74</td>
<td>&lt;.0001**</td>
</tr>
<tr>
<td>HRT after RRSO/menopause</td>
<td>53 (17.4)</td>
<td>5 (1.6)</td>
<td>58 (19.0)</td>
<td>79.08</td>
<td>&lt;.0001**</td>
</tr>
<tr>
<td>Breast cancer prior to testing</td>
<td>139 (45.6)</td>
<td>31 (10.2)</td>
<td>170 (55.7)</td>
<td>10.00</td>
<td>.002*</td>
</tr>
</tbody>
</table>
Breast cancer \textit{after} testing & 7 & (2.3) & 1 & (0.3) & 8 & (2.6) & 0.71 & .68 \\
Ovarian cancer \textit{after} testing & 4 & (1.3) & 1 & (0.3) & 5 & (1.6) & 0.07 & 1.00 \\
Other cancer \textit{prior} to testing & 7 & (2.3) & 4 & (1.3) & 11 & (3.6) & 0.75 & .48 \\

<table>
<thead>
<tr>
<th>Parity$^d$</th>
<th>RRSO ($n=223$)</th>
<th>No RRSO ($n=73$)</th>
<th>Total ($N=296$)</th>
<th>$\chi^2$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>40 (13.5)</td>
<td>37 (12.5)</td>
<td>77 (26.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>47 (15.8)</td>
<td>6 (2.0)</td>
<td>53 (17.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>93 (31.4)</td>
<td>18 (6.1)</td>
<td>111 (37.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GE3</td>
<td>43 (14.5)</td>
<td>12 (4.1)</td>
<td>55 (18.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. RRSO = risk-reducing salpingo-oophorectomy; OCPs = oral contraceptive pills; HRT = hormone replacement therapy; BMI = body mass index; Parity = total number of live births; GE = three or more.

$^a$Time in months

$^b$Age in years

$^c$Body mass index uses height and weight to determine amount of body fat. 18.5-24.9 = normal; 25.0-29.9 = overweight; 30.0 and above = obese.

$^d$$N=296$. Excludes participants whose parity values were not included in the medical chart.

$^*p<0.05$.

$^**p<0.01$.

\textbf{Post–RRSO Health Monitoring Practices and Outcomes}

Post-RRSO health monitoring practices and health outcomes are described in Table 3. Significantly more women who had RRSO had at least one DEXA scan, $\chi^2 (1, N=305) = 24.8, p = <.0001, \phi = .29$, at least one lipid panel, $\chi^2 (1, N=305) = 24.6, p = <.0001, \phi = .28$, and at least one blood glucose level, $\chi^2 (1, N=305) = 28.7, p = <.0001, \phi = .31$. 
Table 3


<table>
<thead>
<tr>
<th></th>
<th>RRSO (n = 228)</th>
<th>No RRSO (n = 77)</th>
<th>Total (N = 305)</th>
<th>$\chi^2$</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one DEXA</td>
<td>125 (41.0)</td>
<td>17 (5.6)</td>
<td>142 (46.6)</td>
<td>24.81</td>
<td>&lt;.0001**</td>
</tr>
<tr>
<td>At least one lipid panel</td>
<td>161 (52.8)</td>
<td>30 (9.8)</td>
<td>191 (62.6)</td>
<td>24.64</td>
<td>&lt;.0001**</td>
</tr>
<tr>
<td>after age 45 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one blood glucose</td>
<td>166 (54.4)</td>
<td>30 (9.8)</td>
<td>196 (64.3)</td>
<td>28.71</td>
<td>&lt;.0001**</td>
</tr>
<tr>
<td>level after age 45 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCTS listed cause of death</td>
<td>3.16</td>
<td>.26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>2 (1.9)</td>
<td>1 (0.9)</td>
<td>3 (2.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other cancer</td>
<td>0 (0.0)</td>
<td>1 (0.9)</td>
<td>1 (0.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>79 (73.2)</td>
<td>25 (23.2)</td>
<td>104 (96.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. DEXA = bone mineral density scan; BCTS = breast cancer tracking system.

Table 4 describes health outcomes in women who elected RRSO premenopausally (surgically induced menopause). In women who underwent premenopausal RRSO, we did not find a significant association with diagnoses of venous thromboembolism, stroke, and osteopenia/osteoporosis and premenopausal RRSO. We found a near significant ($p = .06$) association between diagnosis of coronary artery disease and myocardial infarction. We did not find a significant association with premenopausal RRSO and use of calcium, vitamin D, bisphosphonates, or tamoxifen.
### Table 4

**Menopause Related Health Practices and Outcomes in Study Population Who Elect RRSO premenopausally (%)**

<table>
<thead>
<tr>
<th>Health Practice</th>
<th>RR SO $(n = 81)^a$</th>
<th>No RR SO $(n = 27)$</th>
<th>Total $(N = 108)$</th>
<th>$\chi^2$</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer after testing</td>
<td>4 $(3.7)$</td>
<td>0 $(0.0)$</td>
<td>4 $(3.7)$</td>
<td>1.38</td>
<td>.57</td>
</tr>
<tr>
<td>Ovarian cancer after testing</td>
<td>1 $(0.9)$</td>
<td>1 $(0.9)$</td>
<td>2 $(1.9)$</td>
<td>0.67</td>
<td>.44</td>
</tr>
<tr>
<td>Diagnosis of CAD/MI after RRSO/menopause</td>
<td>0 $(0.0)$</td>
<td>2 $(1.9)$</td>
<td>2 $(1.9)$</td>
<td>6.11</td>
<td>.06</td>
</tr>
<tr>
<td>Diagnosis of stroke after RRSO/menopause</td>
<td>1 $(0.9)$</td>
<td>0 $(0.0)$</td>
<td>1 $(0.9)$</td>
<td>0.34</td>
<td>1.00</td>
</tr>
<tr>
<td>Diagnosis of VT after RRSO/menopause</td>
<td>0 $(0.0)$</td>
<td>0 $(0.0)$</td>
<td>0 $(0.0)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis of osteopenia/osteoporosis after RRSO/menopause</td>
<td>1 $(0.9)$</td>
<td>0 $(0.0)$</td>
<td>1 $(0.9)$</td>
<td>0.34</td>
<td>1.00</td>
</tr>
<tr>
<td>Ever used calcium</td>
<td>39 $(36.1)$</td>
<td>15 $(13.9)$</td>
<td>54 $(50.0)$</td>
<td>0.44</td>
<td>.51</td>
</tr>
<tr>
<td>Ever used vitamin D</td>
<td>40 $(37.0)$</td>
<td>15 $(13.9)$</td>
<td>55 $(50.9)$</td>
<td>0.31</td>
<td>.58</td>
</tr>
<tr>
<td>Ever used bisphosphonates</td>
<td>2 $(1.9)$</td>
<td>1 $(0.9)$</td>
<td>3 $(2.8)$</td>
<td>0.11</td>
<td>1.00</td>
</tr>
<tr>
<td>Ever used tamoxifen</td>
<td>16 $(14.8)$</td>
<td>8 $(7.4)$</td>
<td>24 $(22.2)$</td>
<td>1.14</td>
<td>.29</td>
</tr>
</tbody>
</table>

*Note. RRSO = risk-reducing salpingo-oophorectomy; CAD = coronary artery disease; MI = myocardial infarction; VT = venous thromboembolism. BCTS = breast cancer tracking system.*

*aRRSO done premenopausal.*
Breast and Ovarian Cancer Screening Adherence

Comparison of breast and ovarian cancer screening adherence among eligible women is shown in Fig. 1. *BRCA1/2* positive women are recommended to undergo ovarian cancer screening (CA-125 and transvaginal ultrasound) every six months if they do not elect RRSO (ovaries and fallopian tubes intact). *BRCA1/2* positive women are recommended to undergo breast cancer surveillance by mammogram and breast MRI every six months if one or both breasts are intact. At the end of each year of follow-up, women who elected either RRSO or bilateral mastectomy or both were censored from the screening group. The fraction of eligible women was recalculated based on the new total eligible denominator after each year. During follow-up in year one, a total of 143 (46.9%) of eligible women got the recommended CA-125 serum screening. By year two, 35 (11.5%) got the recommended screening and by the end of year five, 6 (1.9%) got the recommended screening. Similarly, 139 (45.6%) of eligible women got transvaginal ultrasounds in year one, 34 (11.2%) in year two and 7 (2.3%) in year five of follow-up. Comparatively, 131 (42.9%) eligible women got mammograms in year one, followed by 83 (27.2%) in year two, and 20 (6.6%) in year five of follow-up. For breast MRI, 108 (35.4%) of women got the recommended screening in year one, 46 (15.1%) in year two, and 9 (2.9%) in year five of follow-up.
Fig. 1. Comparison of breast and ovarian cancer screening practices in BRCA1/2 positive women in our study population. Ovarian cancer screening: CA-125 represents “cancer antigen-125” serum screening; TVUS represents transvaginal ultrasound. Eligible patients are censored for ovarian cancer screening at the time of risk-reducing salpingo-oophorectomy, end of follow-up (01Jan.2012), and end of membership. Breast cancer screening: MRI represents “magnetic resonance imaging.” Eligible patients are censored for breast cancer screening at breast cancer, bilateral mastectomy, end of follow-up and end of membership. This graph highlights the decline in adherence to recommended screening.
DISCUSSION

Our study examined the uptake and utilization of ovarian cancer biochemical and imaging screening and risk-reducing surgery in female $BRCA1/2$ mutation carrier members of Kaiser Permanente Northern California. We aimed to determine the post-RRSO health maintenance practices of these women and a subset of women who elected RRSO premenopausally. Few published studies have examined the long-term health outcomes of RRSO. Our average follow-up period was 53 months (4.4 years) which is the second longest follow-up period to date.

Our results indicated that 77.1% of $BRCA1$ mutation carriers and 71.9% of $BRCA2$ mutation carriers elected to undergo RRSO, a high rate of uptake consistent with previous studies (Beattie et al., 2009; Rheim et al., 2011; Schwartz et al., 2012). Participants completed RRSO after a mean time of 11.6 months following the receipt of positive $BRCA1/2$ results; 50% within 6 months. Previous studies have demonstrated a similar time interval between receipt of positive results and RRSO. In 2002 and 2008, Kauff et al. reported a mean time of 3.6 months and a median time of 10.3 months to RRSO, respectively. Beattie et al., (2009) found that $BRCA1/2$ positive women underwent RRSO after a median time of 4.3 months.

Although published NCCN guidelines recommend that the optimal timing for RRSO is between the ages of 35-40 years, we found that the majority of women are undergoing RRSO much later. The median age at RRSO in our study population was 49.7 ($M = 50.2$) years; only 17% had RRSO by age 40 years. This is important not
only for ovarian cancer risk but also for breast cancer risk because optimal risk reduction is achieved if RRSO is performed in the early forties. Our findings are consistent with previous studies that report that BRCA1/2 carriers typically complete RRSO after age 40 years. Robson et al. (2003) described that study participants underwent RRSO at a mean age of 51.2 years. Seventeen (28.8%) participants were pre/perimenopausal at the time of RRSO. Rhiem et al. (2011) reported a mean age of 47 years at the time of RRSO. Rebbeck et al. (2005) evaluated short-term hormone use following RRSO and found that the mean age at the time of surgery was 42.7 years.

A possible explanation for our findings is that the majority of women are not coming to clinical attention prior to the age of 40 years. The mean age at genetic testing of BRCA1 and BRCA2 mutation carriers was 46 years and 49 years, respectively. The three year difference we observed is consistent with the broader finding that BRCA2 related cancers tend to be diagnosed at a later age than BRCA1 related cancers (Finch, Evans, & Narod, 2012). Nearly 56% of women in our study population had a diagnosis of breast cancer prior to BRCA1/2 testing (32.5% of BRCA1 and 23.3% of BRCA2 mutation carriers). This shows that over half of our study population was ascertained based on a personal history of breast cancer.

BRCA1/2 mutation carriers have between a 56–87% lifetime risk of developing breast cancer and an up to 40% risk of developing ovarian cancer in the absence of risk-reducing surgical interventions (King, 2003). We analyzed how many women in our study population developed breast and/or ovarian cancer after genetic
testing. Among those who did not elect RRSO, one woman had a diagnosis of breast cancer and one woman had a diagnosis of ovarian cancer during the follow-up period. Among those who elected RRSO, seven (2.3%) were diagnosed with breast cancer during the follow-up period and of that, 4 had RRSO premenopausally. This finding was unexpected since previous studies have shown a 50% reduction in breast cancer risk if RRSO is done premenopausally (Rebbeck et al., 1999). We do not know if there are other factors (age of menarche, hormonal exposures, age at first live birth, etc.) in the personal histories of these women that may have contributed to their breast cancer risks. An additional chart review may answer some of these questions. Four (1.3%) were diagnosed with ovarian cancer during the study follow-up period. However, we did not calculate the proportion of these that were actually occult malignancies detected at the time of RRSO.

When comparing RRSO to non-RRSO groups, studies have shown a significant reduction in cancer specific mortality in the RRSO group (Domchek et al., 2006). Our study did not compare cancer mortality rates with matched controls; however, the low cancer incidence rates in our study population are similar to those previously reported (Rebbeck et al., 2002; Finch et al., 2006). A study by Rocca et al., in 2006 looked at risk of death from cancer-related and other causes within the Mayo Clinic Cohort Study of Oophorectomy and Aging. The women included in the Mayo Clinic cohort had unilateral or bilateral oophorectomy for reasons in addition to genetic predisposition including uterine fibroids and menorrhagia. They found that women who had RRSO prior to age 45 years and who were not given estrogen had an
increased risk of death. They also found increased risks of estrogen-related cancer (breast, ovarian, uterine, and vaginal) despite oophorectomy and increased risk of death due to non-cancer causes. Our study population was too small to find a significant relationship between cause of death and premenopausal RRSO.

When we examined cardiovascular health monitoring practices and outcomes, we found that RRSO was significantly associated with having had at least one lipid panel and at least one blood glucose level during the follow-up period. We were interested in looking at premenopausal RRSO and related health problems. We did not find a significant association with a diagnosis of a venous thromboembolism and/or stroke and premenopausal RRSO. Our average follow-up period was 4.4 years so it is possible that some women in our study may not have had their stroke event yet, especially if they are still relatively young. Longer follow-up is needed. However, we did find a near significant relationship between a diagnosis of coronary artery disease/myocardial infarction and premenopausal RRSO. Findings from The Mayo Clinic Cohort Study (Rivera et al., 2009) found a significantly increased risk of cardiovascular mortality in RRSO performed prior to age 45 years in the absence of estrogen therapy.

In our study, women who elected to undergo RRSO were more likely to use HRT. This factor may have mitigated cardiovascular health risks in our study population. The correlation between RRSO and HRT use probably reflects the symptomatic sequelae of RRSO surgery. Premenopausal women with intact ovaries are unlikely to require HRT for symptom management (Rebbeck et al., 2005).
Women with a diagnosis of breast cancer were also less likely to use HRT. This is consistent with the recommendation that systemic HRT is relatively contraindicated after breast cancer (Holmberg & Anderson, 2004; Chelbowski & Prentice, 2008).

Our results show that significantly more women who had RRSO had at least one DEXA scan during the follow-up period. Previous studies have reported rates of 51% had at least one bone density scan after RRSO and 61% within the last two years (Pezaro et al., 2012). In women who had RRSO premenopausally, we did not find a significant association with RRSO and a diagnosis of osteopenia/osteoporosis. Although there have been very few longitudinal studies that have examined the effect of premenopausal oophorectomy on bone health, our data contrast with results that have shown higher rates (up to 70%) of osteopenia and osteoporosis (Cohen et al., 2012) especially for women who did not take HRT (Challberg et al., 2011). One explanation for our findings could be that our sample size of women with premenopausal RRSO was relatively small. In addition, it is possible that osteopenia or osteoporosis was not coded as a diagnosis in the electronic medical chart. Lastly, we did not compare bone density measurements over time so borderline abnormalities or gradual changes on DEXA may have been missed. We hypothesize that abnormality rates on DEXA are actually much higher than reported in our results.

We evaluated screening practices in eligible BRCA1/2 mutation carriers (breast and/or ovarian tissue still intact) in each year after receipt of positive BRCA1/2 results for five years. Currently, our study is the first that we are aware of that investigated screening adherence for this length of time. We found that overall
adherence to screening recommendations in this group was low for both breast and ovarian cancer screening. Approximately 43% of women got the recommended mammogram within the first year after positive genetic test results. Unexpectedly, we found that in year two, 27% of eligible women got a mammogram and this rate dropped to roughly 7% in year five. Previous studies have reported mammogram adherence rates of 56%-92% (Botkin et al., 2003; Campitelli et al., 2011; Schwartz et al., 2012; Tinley et al., 2004). However, few studies have evaluated adherence rates for longer than two years. About 35% of eligible women got a breast MRI in year one. These rates went down to 15% in year two and to about 3% in year five.

Comparatively, close to 47% of eligible women recommended to have CA-125 serum screening did so within the first year of receiving results. This rate dropped to 11% at year two. By year five, 2% complied with CA-125 screening. Rates were similar for transvaginal ultrasound; Close to 46% in year one, 11% in year two, and 2.3% by year five adhered to recommended screening. Previous studies in the US and Europe have reported ovarian cancer screening adherence rates between 2.8% and 75% for transvaginal ultrasound and up to 56% for CA-125 (Schwartz et al., 2012; Campitelli et al., 2011; Foster et al., 2009). McInerney-Leo et al., (2006) reported that only 7 out of 28 women who tested BRCA1/2 positive had a CA-125 test in the 6-9 months post-receipt of test results. The high rate of uptake of RRSO after the receipt of BRCA1/2 test results might have explained the low rate of screening uptake and subsequent adherence. However, we censored individuals from the screening group who elected RRSO at any point during follow-up. These results may say more about the women
who are choosing not to have RRSO within these first five years. It could be that these women are choosing not to go through with surgery or screening at any point.

Our findings suggest that implementation of effective follow-up strategies are necessary to increase breast and ovarian cancer surveillance. Perhaps alternative forms of outreach (social networking, mobile applications, etc.) would yield higher adherence. In addition, specialty clinics at which this population can receive genetic counseling, cancer screening, and post-RRSO follow-up all in one place may increase surveillance adherence and positive health outcomes.

More studies are needed to evaluate the long-term outcomes of RRSO and surgically-induced menopause in BRCA1/2 mutation carriers. Data from these studies will be needed to make recommendations for the care of these women following RRSO. We also support increased education of physicians to remind their patients about regular breast and ovarian cancer screening. This is important because previous studies have shown that screening adherence largely reflects physician recommendations. Our proposed recommendations are consistent with the limited number of previous studies have suggested guidelines for post-RRSO care (Chapman et al., 2011; Finch, Evans & Narod, 2012). They are summarized in Table 5.
**Table 5**

*Proposed Recommendations for Post-RRSO Health Maintenance*

<table>
<thead>
<tr>
<th>Gynecologic cancer risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Yearly pelvic examination</td>
</tr>
<tr>
<td>- Discussion of risks and benefits of CA-125 serum screening</td>
</tr>
<tr>
<td>- Counseling on the symptoms of primary peritoneal carcinoma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bone health</th>
</tr>
</thead>
<tbody>
<tr>
<td>- DEXA bone scan at the time of RRSO and 1-2 years after RRSO</td>
</tr>
<tr>
<td>- Vitamin D and calcium supplementation</td>
</tr>
<tr>
<td>- Weight bearing exercise</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiovascular health</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Lipid and glucose profiles at the time of RRSO and every year following</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Menopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Evaluation of menopausal symptoms including hot flashes, night sweats, sleep disturbances, psychological functioning, vaginal dryness, pain with sex, and changes in libido 3 months following RRSO</td>
</tr>
<tr>
<td>- Consideration of HRT for eligible patients</td>
</tr>
<tr>
<td>- Consideration of non-estrogen based HRT (SSRIs, testosterone, etc.)</td>
</tr>
</tbody>
</table>
CONCLUSION

Although RRSO is currently recommended to reduce ovarian cancer risk, long-term studies of post-RRSO surveillance and optimal health management strategies have not been established. This study attempted to provide a baseline of current health maintenance practices of KPNC BRCA1/2 positive women who elected RRSO both pre- and post-menopausally and to help establish guidelines for ongoing care. We observed a high rate of uptake of RRSO soon after receipt of positive BRCA1/2 results. The majority undergo RRSO after age 40 years. Women are having at least one DEXA, lipid profile, and blood glucose level after RRSO. We also aimed to determine if there is sufficient evidence to recommend the addition of ovarian cancer screening to the BCTS. Unexpectedly, we observed low adherence and subsequent drop off of both breast and ovarian cancer screening over five years. These findings warrant further investigation and additional evaluation of the barriers to screening. We propose that women with deleterious mutations in BRCA1/2 should ideally be referred to clinics specializing in hereditary cancer syndromes. We support the education of physicians who are not familiar with hereditary cancer and the NCCN guidelines. We recommend that patients with identified deleterious mutations in BRCA1/2 be provided counseling and follow up by providers with extensive knowledge and experience in caring for patients with hereditary risk.
Study Limitations

The limitations of the study include those inherent to this retrospective study design. The data were limited by the availability and accuracy of information reported in medical records. There may be some degree of selection bias since eligible cases were identified through the Kaiser Permanente databases BCTS and IRGS; any cases not followed by either would theoretically be missed. Additionally, there may be confounding factors outside of those directly investigated that may have contributed to a woman’s post RRSO morbidity. Being a retrospective study that utilized chart review and data extraction, there was no direct patient contact, thus, valuable patient perspective was excluded. Although our proportion of non-white participants is higher than that of similar studies (Schwartz et al., 2012; Greene et al., 2008), it was not large enough to run separate statistical associations and draw conclusions based on race. However, we do feel that this larger proportion more closely reflects the diversity of northern California and strengthens the generalizability of our findings. Lastly, all participants are currently or formerly KPNC patients whose care may be different from those patients who do not have Kaiser Permanente insurance. However, KPNC serves an ethnically and socioeconomically diverse patient population, thus the study participants are more likely to reflect the broader spectrum of the general population.

Future Directions

We are coming close to the twenty year mark since beginning of clinical BRCA1/2 testing; we are just now seeing the long term effects of surgeries, screening,
HRT use in surgically induced menopause, and other management measures.

Guidelines for management of women with BRCA1/2 germline mutations have evolved since 1996. It would be interesting to compare participants diagnosed between 1996–2004 and 2005–present because guidelines have changed over time. Would there be differences in management observed in more recently diagnosed women? Could this explain the low adherence to screening we observed? Some studies have suggested that physician recommendations may explain the low adherence to ovarian cancer screening. If we stratified different KPNC hospitals, would we find differences in surgical uptake versus screening uptake among institutions, for example among Kaiser San Francisco, San Jose, Sacramento and Oakland? Would we find differences in screening adherence among centers that offer specialty clinics and those that do not? Anecdotally, surveillance fatigue has been cited as a reason for low adherence to ovarian cancer screening in premenopausal BRCA1/2 mutation carriers. It would be important to explore this topic further through surveys and interviews; patient perspective may help answer the following questions: are there differences in attitudes among those women who choose neither RRSO nor screening? What are the other barriers to screening adherence? What are physicians advising these patients? These and other questions may help identify more effective strategies and modes of communication to increase follow-up.
REFERENCES
REFERENCES


Gronwald, J., Tung, N., Foulkes, W. D., Offit, K., Gershoni, R., Daly, M., ... Narod, S. A. (2005). Tamoxifen and contralateral breast cancer in BRCA1 and BRCA2 carriers:


Metcalfe, K. A., Lubinski, J., Ghadirian, P., Lynch, H., Kim-Sing, C., Friedman, E., ...


APPENDIX
APPENDIX

STUDY POPULATION FLOW CHART

Eligible participants identified in BCTS/IRGS  
N = 563

Participants included in chart review  
N = 460

EXCLUDE: Left Kaiser within 1 year of testing  
N = 34
EXCLUDE: Died within 1 year of testing  
N = 2
EXCLUDE: Diagnosed with ovarian cancer prior to testing  
N = 67

Final study population  
N = 305

EXCLUDE: VUS result  
N = 92
EXCLUDE: Insufficient information in chart  
N = 63