

COUNSELING BRCA1/BRCA2 POSITIVE WOMEN OVER THE AGE OF 75
REGARDING RISK-REDUCING SALPINGO-OOPHORECTOMY (RRSO): THE
PERSPECTIVES OF GENETIC COUNSELORS

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ABSTRACT OF THE THESIS

Counseling BRCA1/BRCA2 Positive Women Over the Age of 75 Regarding Risk-Reducing Salpingo-Oophorectomy (RRSO): The Perspectives of Genetic Counselors

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Current literature suggests that, in general, RRSO is valuable for women who carry a BRCA1/BRCA2 mutation, but there is limited literature regarding the benefits and risks of RRSO for BRCA1/BRCA2 positive women over the age of 75. National Comprehensive Cancer Network (NCCN) guidelines recommend risk-reducing salpingo-oophorectomy (RRSO) for women with a BRCA1 mutation by the age of 35-40 and women with a BRCA2 mutation to have a RRSO by the age of 40-45 or after the completion of childbearing. NCCN does not provide upper age limit recommendations for RRSO and ovarian cancer management. Therefore, limitations to current studies and lack of professional guidelines for BRCA1/ BRCA2 positive women over the age of 75 pretenses the question if RRSO is an appropriate medical management option for this patient population. A survey was sent out through the National Society of Genetic Counselors (NSGC) to genetic counselors registered to the Cancer Special Interest Group (SIG) email listserv to investigate if cancer genetic counselors feel RRSO is an appropriate medical management option for women over the age of 75 who carry a BRCA1/BRCA2 mutation, and if they feel confident counseling this patient population.

In addition, it explored if differing patient factors influence cancer genetic counselors' feelings toward RRSO as an appropriate option and what resources are used when counseling this patient population. Overall, the majority of survey respondents (70%) reported that they felt RRSO was appropriate for a 77-year-old woman who carries a BRCA1 mutation. Answers differed significantly when the patient was 85-years-old or had comorbidities such as hypertension and type 2 diabetes. Overall, there is inconsistency in survey respondents' opinions regarding RRSO for this patient population, and our study results found this to be particularly true when counseling BRCA1/BRCA2 positive patients who are 85-years-old or have comorbid conditions. Additional research and development of professional guidelines are needed to help standardize care in regard to ovarian cancer risk reduction for this patient population.

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Introduction

Cancer is one of the leading causes of death in the United States and around the world. The World Health Organization estimates that there will be 15 million deaths due to cancer worldwide in 2020. In the United States, the top five cancers to affect women include lung, breast, colon, pancreatic, and ovarian. Cancer has many different etiologies, including aging, ethnicity or race, heredity, gender, chronic medical conditions, and chromosomal abnormalities (Schneider, 2012). The majority of cancers, 90-95%, occur sporadically due to a combination of environment, lifestyle risk factors, and chance. The other 5-10% of cancers are due to an inherited genetic variant, such as a pathogenic variant in BRCA1 or BRCA2. When a woman has a pathogenic variant in BRCA1 or BRCA2, she is considered to have Hereditary Breast and Ovarian Cancer syndrome (HBOC), and her risks for breast and ovarian cancer are significantly increased above the general population risks of 12% and 1%, respectively (Schneider, 2012).

Specifically, the cumulative breast cancer risk to age 80 was found to be 72% for BRCA1 carriers and 69% for BRCA2 carriers (Kuchenbaecker et al., 2017). The cumulative ovarian cancer risk to age 80 was found to be 44% for BRCA1 carriers and 17% for BRCA2 carriers (Kuchenbaecker et al., 2017). In addition to differing by gene, risk estimates for ovarian cancer also vary by the patient's age. The National Comprehensive Cancer Network (2019) provides screening and medical management guidelines for health care professionals regarding these patients. Version 3.2019 of NCCN guidelines recommend women with a BRCA1 pathogenic or likely pathogenic variant to have clinical breast exams every 6-12 months, starting at age 25, annual breast MRI with contrast for women ages 25-29, and an annual mammogram with consideration

of tomosynthesis and breast MRI with contrast for women ages 30-75. Per NCCN (2019), “Counseling includes a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, possible short-term hormone replacement therapy, and related medical issues.” Due to effective screening methods for breast cancer, women are able to decide whether frequent screening or surgical risk reduction is right for their lifestyle. Guidelines also state that BRCA1/BRCA2 positive women over the age of 75 should be managed on an individualized basis (National Comprehensive Cancer Network [NCCN], 2019).

With respect to ovarian cancer management, current NCCN guidelines recommend risk-reducing salpingo-oophorectomy (RRSO) for women with a BRCA1 pathogenic or likely pathogenic variant by the age of 35-40 and women with a BRCA2 pathogenic or likely pathogenic variant to have a RRSO by the age of 40-45 after the completion of childbearing (NCCN, 2019). Risk-reducing salpingo-oophorectomy is the preventive removal of a woman’s ovaries and fallopian tubes, and it has been shown to reduce the risk of ovarian cancer by 70-95% in women with a BRCA1/BRCA2 mutation (Schneider, 2012). RRSO is currently preferred to be done laparoscopically, with a 1.3% intraoperative complication risk and 3.1% postoperative complication risk (De Felice et al., 2017). For premenopausal women, surgical menopause is the largest side effect of RRSO due to the decreased estrogen and androgens (De Felice et al., 2017). NCCN (2019) states that counseling should include a discussion regarding reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, possible short-term hormone replacement therapy, and related medical guidelines. For patients who do not elect for RRSO, they may consider

transvaginal ultrasound combined with serum CA-125 for ovarian cancer screening starting at ages 30-35, but the benefit of these screening options is uncertain (NCCN, 2019). NCCN (2019) does not provide upper age limit recommendations for RRSO and ovarian cancer management as they do for breast cancer management.

Multiple prospective studies have found that RRSO reduces ovarian cancer risk and all-causes mortality in BRCA1/BRCA2 mutation carriers (Domchek et al., 2008; Finch et al., 2014; Kauff et al., 2008). Specifically, research by Finch et al. (2014) found RRSO reduced the risk of ovarian, fallopian tube, and peritoneal cancer by 80% and reduced all-cause mortality by 77%. Studies completed by Domchek et al. (2008) and Kauff et al. (2008) had similar findings, strengthening the value of RRSO for BRCA1/BRCA2 carriers. Currently, RRSO is the gold standard for women who are BRCA1/BRCA2 carriers because there is no effective screening for ovarian cancer (Lewis, Lu, Klimczak, & Mok, 2018).

Although RRSO is the recommended course of action for most women, there are limitations to these studies when applying the findings to women over the age of 75 who carry a BRCA1 or BRCA2 mutation. In two main retrospective studies studying the effectiveness of RRSO, ages of study participants were not reported (Domcheck 2008, Kauff 2008). Therefore, it is uncertain whether women over the age of 75 were included in these studies. In a retrospective study by Finch et al. (2014), the study population ranged from 30 to 88 years old, and out of 1,390 women in their study who chose preventive surgery, only 27 or 1.9% were over the age of 70. Due to the small sample of women over the age of 70, there were limitations to the data when applying the conclusions to this older patient population. Complicating the issue is that the actual

remaining risk of ovarian cancer in woman over 75 is estimated to be low. Research has shown that a BRCA1/BRCA2 positive woman is at highest risk for ovarian cancer between the ages of 55 and 59, with an annual risk of 1.8% (Kotsopoulos et al., 2018). Comparatively, they found that women ≥ 70 years old have an annual ovarian cancer risk of 0.61%. The annual risk for ovarian cancer in BRCA1/BRCA2 women over the age of 70 is approximately one third the risk of women ages 55-59 (Kotsopoulos et al., 2018). Therefore, limitations to current studies and decreased risk for ovarian cancer in BRCA1/BRCA2 carriers ≥ 70 years old pretenses the question if RRSO is an appropriate medical management option for BRCA1/ BRCA2 positive women over the age of 75.

Although the efficacy of RRSO has been proven, there are surgical risks associated with RRSO that may influence a patient's decision to proceed with the surgery. Surgical risks for all women associated with oophorectomy include bleeding, infection, and damage to nearby organs, and these risks are increased when a woman has certain medical conditions or poor health (Mayo Clinic, 2017). Kenkhuis (2010) reported a 1.3% intraoperative complication risk and a 3.1% postoperative complication risk. The participants in this study ranged from 30.3-68.7 years old, so risk estimates may not be accurate for individuals over the age of 69 and research has shown that the rate of morbidity and mortality increases significantly for elderly patients undergoing surgery (Turrentine, Wang, Simpson, & Jones, 2006). Additionally, for premenopausal women, loss of estrogen and androgens due to removal of the ovaries results in surgical menopause (Finch et al., 2011). Side effects of surgical menopause include vasomotor symptoms, including hot flashes, night sweats, and additional sweating. Premenopausal women also experience sexual dysfunction due to decreased androgen levels, reporting

increased discomfort and decreased pleasure (Finch et al., 2011). Contrastingly, postmenopausal women did not experience a significant increase in vasomotor symptoms, but they did report a significant increase in sexual dysfunction (Finch et al., 2011). Overall, women over the age of 75 may experience an increase in sexual dysfunction, but additional research is needed to explore if women over the age of 75 who are carriers of BRCA1/BRCA2 are at an increased risk for surgical risks such as bleeding, infection, or other surgical complications.

While research suggests that, in general, RRSO is valuable for women who carry a BRCA1/BRCA2 mutation, there is limited literature regarding the benefits and risks of RRSO for BRCA1/BRCA2 positive women over the age of 75. With the increase in online, direct-to-consumer, and lower cost genomic technologies through genetic testing companies such as Color and 23andMe, the number of individuals utilizing cancer genetic testing is increasing (Caswell-Jin et al., 2019). Thus, more women over the age of 75 are likely to find out they are a carrier for a BRCA1/BRCA2 mutation through participating in cascade testing or direct-to-consumer genetic testing. Genetic counselors and physicians who are working with women who are over 75 and BRCA1/BRCA2 positive, will counsel surrounding management in light of these positive test findings. In contrast to younger populations, as NCCN guidelines do not provide recommendations for this age group, it is unknown how these women are counseled regarding their options for ovarian cancer risk management.

This study will explore if cancer genetic counselors feel RRSO is an appropriate medical management option for women over the age of 75 who carry a BRCA1/BRCA2 mutation, and if they feel confident counseling this patient population. In addition, it will

explore if differing patient factors, such as the patient's family history, mutation status, personal cancer history, and current health status, influence cancer genetic counselors' feelings toward RRSO as an appropriate option. The study will also investigate what resources are used by cancer genetic counselors when counseling women over the age of 75 who test positive for BRCA1/BRCA2 about RRSO risks and benefits.

Materials and Methods

Survey participants and procedures

The survey was sent out through the National Society of Genetic Counselors (NSGC) to genetic counselors registered to the Cancer Special Interest Group (SIG) email listserv. Participation in the survey was anonymous and voluntary, and no incentives were provided for participating in the survey. The survey was open for responses from November 19, 2018 to December 20, 2018. Genetic counselors were excluded if they were currently not seeing patients for hereditary cancer indications. There were 60 survey respondents who met inclusion criteria and were included in data analysis.

Survey development

A survey was designed to explore the counseling trends of cancer genetic counselors and to investigate pertinent resources and patient factors used by genetic counselors when counseling BRCA1/BRCA2 positive women over the age of 75 regarding the medical management option of RRSO. These questions were developed after a careful literature search for current BRCA1/BRCA2 screening guidelines and RRSO-focused research and input from genetic counselors with extensive experience in hereditary cancer genetics and research. The research instrument utilized in this study was uploaded in an online software program, Qualtrics.

The survey was piloted by a group of genetic counselors currently practicing and counseling patients for hereditary cancer indications. Feedback was requested regarding question comprehensibility, survey relevance, and ease of completion. This feedback was incorporated into the final version of the study survey.

The research instrument consisted of two parts and a total of 26 questions. The first part addressed survey respondent demographics and their corresponding clinical setting demographics. The second part assessed how survey respondents felt, on a scale of 0 (absolutely not) to 10 (absolutely), regarding RRSO as an appropriate medical management option for six different scenarios. These scenarios are listed in *Figure 1*.

For each scenario, genetic counselors were asked to rank eight different provided factors in order of most to least influential to their decision about RRSO as an appropriate medical management option for the patient. These factors included patient's age, patient's mutation status, patient's ancestry, patient's personal cancer history, patient's family history, patient's current health status, available literature, and available guidelines.

After completing questions for each scenario, participants were asked to rate their confidence level, on a scale of 0-10, with respect to counseling this patient population. Respondents also ranked their most utilized resources when counseling this patient population. They were provided with ten resource options, including NCCN guidelines, SGO guidelines, ASHG guidelines, NSGC email listserv, PubMed search, Google search, OBGYN, Surgical gynecologist, Gynecological oncologist, and Other physician.

| | |
|------------|--|
| Scenario 1 | A 77-year-old woman of Eastern European ancestry comes in for a follow-up appointment because she recently tested positive for a pathogenic variant in the BRCA1 gene. She was tested because her daughter has breast cancer and previously tested positive for the same pathogenic variant in the BRCA1 gene. The patient has no personal history of cancer, and her ovaries are intact. Her medical history is unremarkable. |
| Scenario 2 | A 77-year-old woman of Eastern European ancestry comes in for a follow-up appointment because she recently tested positive for a pathogenic variant in the BRCA2 gene. She was tested because her daughter has breast cancer and previously tested positive for the same pathogenic variant in the BRCA2 gene. The patient has no personal |

| | |
|------------|--|
| | history of cancer, and her ovaries are intact. Her medical history is unremarkable. |
| Scenario 3 | A 77-year-old woman of Eastern European ancestry comes in for a follow-up appointment because she recently tested positive for a pathogenic variant in the BRCA1 gene. She was tested because her daughter has breast cancer and previously tested positive for the same pathogenic variant in the BRCA1 gene. The patient has a personal history of breast cancer diagnosed at 45 , and her ovaries are intact. Her medical history is unremarkable. |
| Scenario 4 | An 85 -year-old woman of Eastern European ancestry comes in for a follow-up appointment because she recently tested positive for a pathogenic variant in the BRCA1 gene. She was tested because her daughter has breast cancer and previously tested positive for the same pathogenic variant in the BRCA1 gene. The patient has no personal history of cancer, and her ovaries are intact. Her medical history is unremarkable. |
| Scenario 5 | A 77-year-old woman of Eastern European ancestry comes in for a follow-up appointment because she recently tested positive for a pathogenic variant in the BRCA1 gene. She was tested because her daughter has breast cancer and previously tested positive for the same pathogenic variant in the BRCA1 gene. The patient has no personal history of cancer, and her ovaries are intact. Her medical history is notable for high blood pressure and type 2 diabetes . |
| Scenario 6 | A 77-year-old woman of Eastern European ancestry comes in for a follow-up appointment because she recently tested positive for a pathogenic variant in the BRCA1 gene. She was tested because her daughter has breast cancer and previously tested positive for the same pathogenic variant in the BRCA1 gene. The patient's sister was diagnosed with ovarian cancer at 52 years old . The patient has no personal history of cancer, and her ovaries are intact. Her medical history is unremarkable. |

Figure 1: Survey respondents answered, “On a scale of 0 (absolutely not) to 10 (absolutely), do you feel RRSO is an appropriate management option for this patient?” in response to these six scenarios. Bolded text represents the variable changed in each scenario

Data analysis

After the survey closed, responses were exported from Qualtrics into Microsoft Excel.

Data analysis included the utilization of descriptive statistics due to small sample size.

Demographic information was collected and presented in respect to number (n) and

percent (%). Questions that required the survey participants to rank their answers on a

scale of 0-10 in response to the scenarios were separated into three categories: 0-3 (No),

4-6 (Unsure), and 7-10 (Yes) to allow for statistical analysis. These categories were presented in respect to percent (%) in *Figure 2*. With Scenario 1 set as the baseline, Scenarios 2-6 were compared using Fisher's exact test p-value calculator to calculate a p-value and assess for significance. Most influential factors were reported by percent (%) and displayed in pie charts for each scenario in *Figures 3-9*. The first, second, and third most utilized resources by survey respondents when counseling this patient population were reported in the text.

Answers to each scenario were then separated by years of cancer genetic counseling experience, clinical setting, and number of BRCA1/BRCA2 positive women counseled over the age of 75 in the past 5 years to allow for further analysis (*Figures 5, 6, 7*). First, years of cancer genetic counseling experience were separated by survey respondents with ≥ 4 years of cancer experience and ≤ 3 years of cancer experience. Clinical setting options of laboratory, private practice, and other were excluded from analysis due to small sample size. Survey answers by respondents who work at academic institutions and community hospitals were compared. Number of BRCA1/BRCA2 positive women counseled over the age of 75 in the past 5 years were sorted into the categories of less than 5 patients, 5-10 patients, and more than 10 patients. These 3 categories were compared. Each demographic characteristic was compared by number (n) and assessed for significance using Fisher's exact p-value calculator. Confidence level of survey respondents with respect to their decisions for this patient population were presented in respect to percent (%) and displayed in a pie chart (*Figure 4*). Answers to this question were also separated by years of experience, clinical setting, and number of BRCA1/BRCA2 positive women counseled over the age of 75 in the past 5 years in the

same method as already described. Results were reported in terms of percent (%) and Fisher's exact p-value calculator was used to assess for significance.

Results

Participant characteristics

A total of 61 survey responses were completed through Qualtrics Survey Software, and one survey respondent was excluded because they were currently not seeing patients for hereditary cancer indications. Of the survey responses, 100% were by female genetic counselors (n=60), and 75% of survey respondents dedicated more than 75% of their clinical time to counseling patients in a cancer setting (n=45). The majority of respondents work at an academic institution or community hospital (35%, 43.33%). Approximately 43% of survey respondents had ≤ 3 years of experience as a genetic counselor and half of survey respondents had ≤ 3 years of experience as a cancer genetic counselor (n=30, 50%). Specific genetic counselor demographic information can be found in *Table 1*.

| <i>Genetic Counselor Demographic Information</i> | | |
|---|-------------------|--------------------|
| <u>Characteristic</u> | <u>Number (n)</u> | <u>Percent (%)</u> |
| Gender | | |
| Male | 0 | 0 |
| Female | 60 | 100 |
| Other | 0 | 0 |
| Prefer not to say | 0 | 0 |
| See patients for hereditary cancer indications | | |
| Yes | 60 | 98.3 |
| No | 1 | 1.7 |
| Percent time counseling cancer patients | | |
| Less than 25% | 3 | 5 |
| 25%-50% | 4 | 6.7 |
| 51-75% | 8 | 13.3 |
| More than 75% | 45 | 75 |
| Clinical setting | | |
| Academic institution | 21 | 35 |

| | | |
|-----------------------------------|----|------|
| Private practice | 7 | 11.7 |
| Community hospital | 26 | 43.3 |
| Laboratory | 3 | 5 |
| Other | 3 | 5 |
| Years practicing | | |
| Less than 1 year | 5 | 8.3 |
| 1-3 years | 21 | 35 |
| 4-7 years | 15 | 25 |
| 8-10 years | 6 | 10 |
| More than 10 years | 13 | 21.7 |
| Years practicing in cancer | | |
| Less than 1 year | 5 | 8.3 |
| 1-3 years | 25 | 41.7 |
| 4-7 years | 15 | 25 |
| 8-10 years | 6 | 10 |
| More than 10 years | 9 | 15 |

Genetic counselors were surveyed regarding more specific information about patient indications and clinical setting demographic information. The majority of genetic counselors see more than 75 patients per year for hereditary breast and ovarian cancer (n=56, 93.3%). Survey answers to the number of patients counseled who were BRCA1/2 positive and over the age of 75 in the last 5 years were split between answer choices without an overwhelming majority, with the highest number of survey respondents having seen more than 15 patients in the last 5 years (n=17, 28.3%). Specific information can be found in *Table 2*.

| Table 2 | | |
|---|-------------------|--------------------|
| <i>Clinical Setting Demographic Information</i> | | |
| <u>Characteristic</u> | <u>Number (n)</u> | <u>Percent (%)</u> |
| Number patients seen for HBOC per year | | |
| Less than 25 patients | 3 | 5 |
| 25-50 patients | 0 | 0 |
| 51-75 patients | 1 | 1.7 |

| | | |
|---|----|------|
| More than 75 patients | 56 | 93.3 |
| Number of patients seen over age 75 and BRCA1/2+ in past 5 years | | |
| None | 6 | 10 |
| Less than 5 patients | 14 | 23.3 |
| 5-10 patients | 16 | 26.7 |
| 11-15 patients | 7 | 11.6 |
| More than 15 patients | 17 | 28.3 |
| Provides medical management recommendations to BRCA+ women | | |
| Genetic counselor | 17 | 28.3 |
| Physician | 2 | 3.3 |
| Both | 38 | 63.3 |
| Other | 3 | 5 |
| Discuss medical management options with BRCA+ patients | | |
| Yes, without a physician present | 57 | 95 |
| Yes, with a physician present | 2 | 3.3 |
| No | 0 | 0 |
| Missing | 1 | 1.7 |
| Provide medical management recommendations for BRCA+ patients | | |
| Yes, without a physician present | 56 | 93.3 |
| Yes, with a physician present | 2 | 3.3 |
| No | 2 | 3.3 |

Scenario 1 results

When presented with Scenario 1, the majority of survey respondents felt RRSO was an appropriate medical management option for the patient as seen in *Figure 2* (n=42, 70%).

On a scale of 0 (absolutely not) to 10 (absolutely), the highest percentage of survey respondents chose 8 (n=22, 36.7%) regarding if they felt RRSO was in an appropriate medical management option for the patient in Scenario 1. The first, second, and third most influential factors reported by survey respondents overall were the patient's mutation status, patient's current health status, and patient's age. Survey respondents who

said No or Unsure reported patient's mutation status (50%), patient's age (43.8%), and patient's current health status (11.1%) as the most influential factor (*Figure 3*). Survey respondents who said Yes reported patient's mutation status (64.3%), patient's current health status (31%), and available guidelines (4.8%) (*Figure 3*).

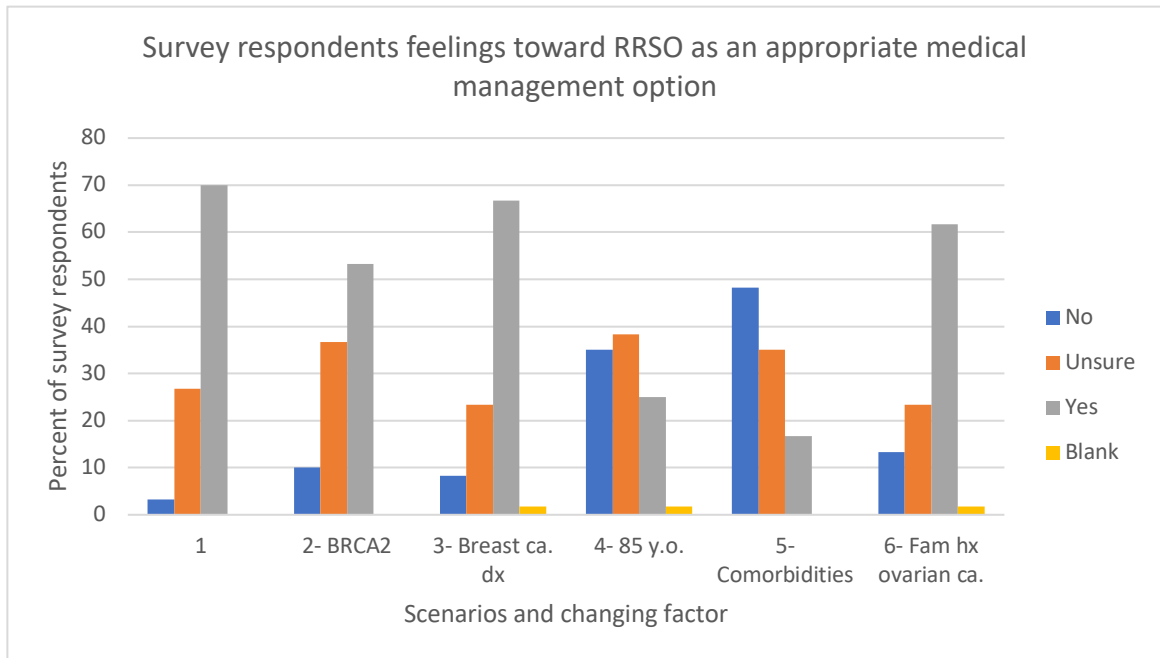


Figure 2. Survey respondents' feelings toward RRSO as an appropriate medical management option. Sample size = 60 survey respondents

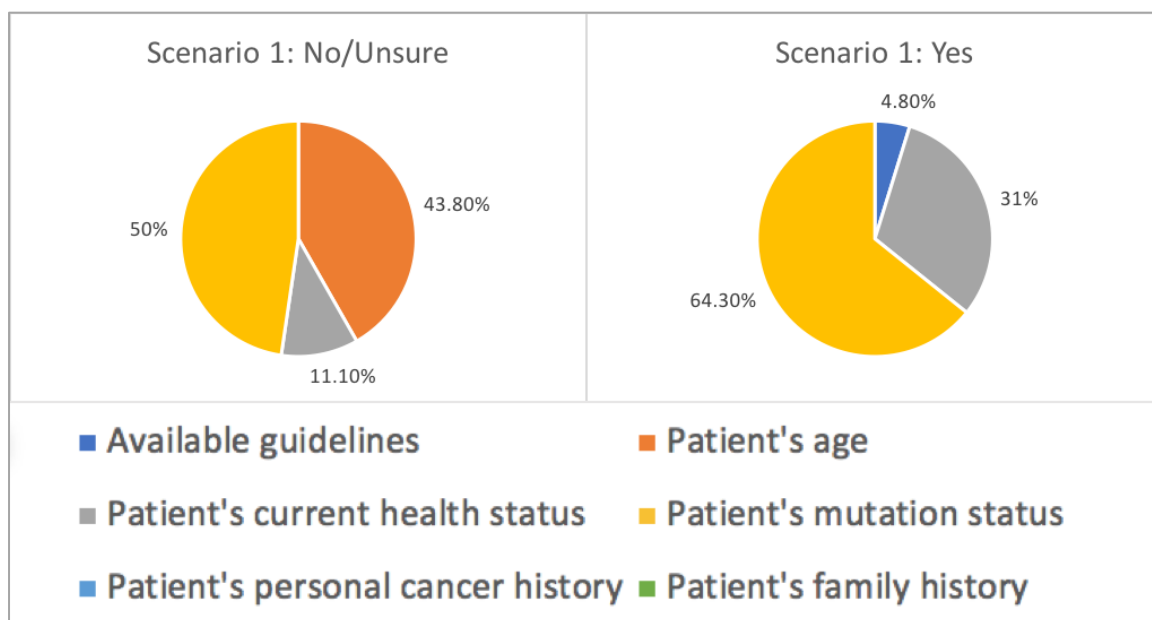


Figure 3: Most influential factor for survey respondents who answered No/Unsure or Yes for Scenario 1

Scenario 2 results

In Scenario 2, the patient had a BRCA2 as opposed to BRCA1 pathogenic variant. When presented with Scenario 2, approximately half of genetic counselors felt RRSO was an appropriate management option for the patient as seen in *Figure 2* (n=32, 53%). On a scale of 0 (absolutely not) to 10 (absolutely), the highest percentage of survey respondents chose 8 (n=15, 25%) regarding if they felt RRSO was in an appropriate medical management option for the patient in Scenario 2. While there was more uncertainty regarding RRSO as an appropriate medical management option for a woman with BRCA2 mutation compared to a BRCA1 mutation (*Figure 2*, 37% v. 27%), the differences in survey answers between and Scenario 1 and 2 were not significant (p=0.12). Consistent with Scenario 1, the first, second, and third most influential factors reported by survey respondents were the patient's mutation status, patient's current health status, and patient's age. Survey respondents who said No or Unsure reported patient's mutation status (57.1%), patient's age (25%), and patient's current health status (17.9%)

as the most influential factor (*Figure 4*). Survey respondents who said Yes reported patient's mutation status (65.6%), patient's current health status (28.1%), and available guidelines (6.3%) (*Figure 4*).

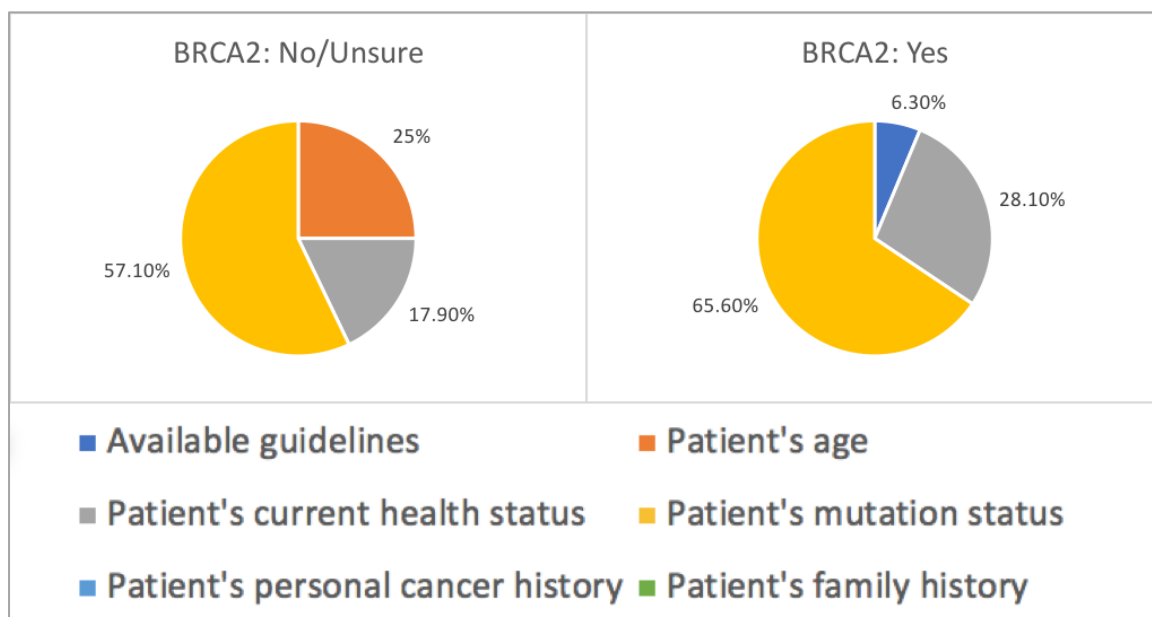


Figure 4: Most influential factor for survey respondents who answered No/Unsure or Yes for Scenario 2

Scenario 3 results

In Scenario 3, the patient had a breast cancer diagnosis at the age of 45 as opposed to no cancer history in Scenario 1. When presented with Scenario 3, the majority of survey respondents felt RRSO was an appropriate medical management option for the patient as seen in *Figure 2* (67%). The differences in survey answers between Scenario 1 and 3 were not significant ($p=0.55$). On a scale of 0 (absolutely not) to 10 (absolutely), the highest percentage of survey respondents chose 8 ($n=18$, 30.5%) regarding if they felt RRSO was in an appropriate medical management option for the patient in Scenario 3. Consistent with Scenarios 1 and 2, the first, second, and third most influential factors reported by survey respondents were the patient's mutation status, patient's current health status, and patient's age. Survey respondents who said No or Unsure reported patient's

mutation status (52.6%), patient's age (31.6%), patient's current health status (10.5%), and patient's personal cancer history (5.3%) as the most influential factor (*Figure 5*).

Survey respondents who said Yes reported patient's mutation status (57.5%), patient's current health status (27.5%), patient's personal cancer history (7.5%), available guidelines (5%), and patient's age (2.5%) (*Figure 5*).

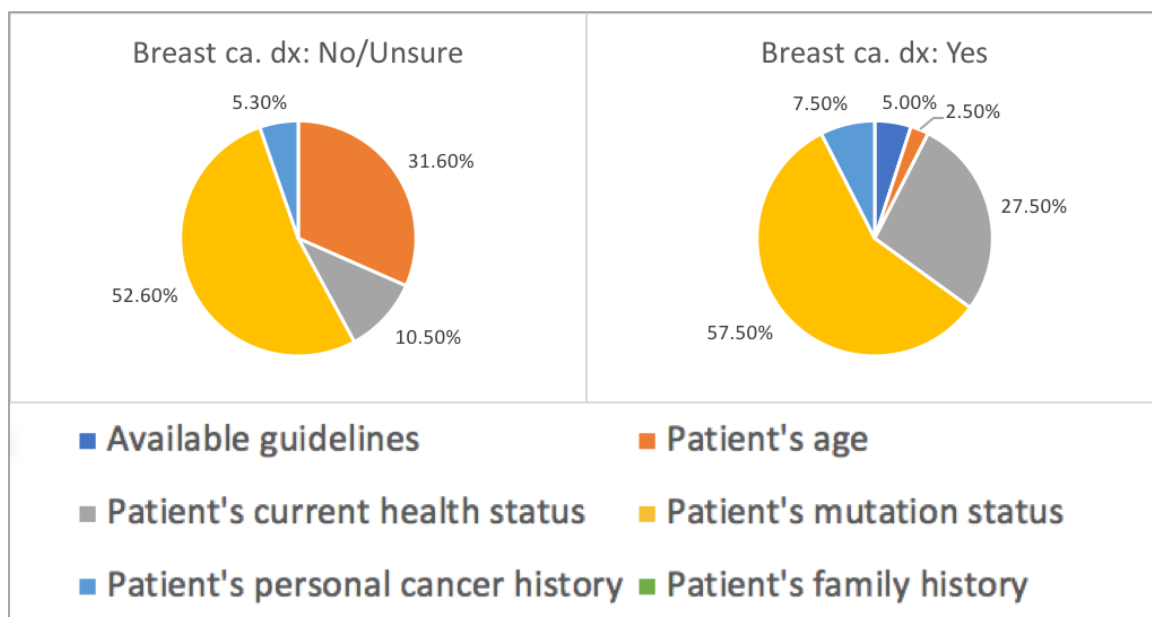


Figure 5: Most influential factor for survey respondents who answered No/Unsure or Yes for Scenario 3

Scenario 4 results

In Scenario 4, the patient was 85-years-old as opposed to 77-years-old in Scenario 1.

When presented with Scenario 4, survey respondents were split between feeling RRSO was appropriate (25%), inappropriate (35%), or being unsure (38.3%) (*Figure 2*). There

was a significant difference in answers between Scenarios 1 and 4 ($p=1.0 \times 10^{-7}$). On a

scale of 0 (absolutely not) to 10 (absolutely), the highest percentage of survey

respondents chose 3 (n=11, 19%), 4 (n=10, 17%), and 5 (n=10, 17%) regarding if they

felt RRSO was in an appropriate medical management option for the patient in Scenario

4. The first, second, and third most influential factors reported by survey respondents

were the patient's age, patient's current health status, and patient's mutation status. Survey respondents who said No or Unsure reported patient's age (50%), patient's mutation status (25%), patient's current health status (20.5%), and available guidelines (2.3%) as the most influential factor (*Figure 6*). Survey respondents who said Yes reported patient's mutation status (46.7%), patient's age (40%), and patient's current health status (13.3%) (*Figure 6*).

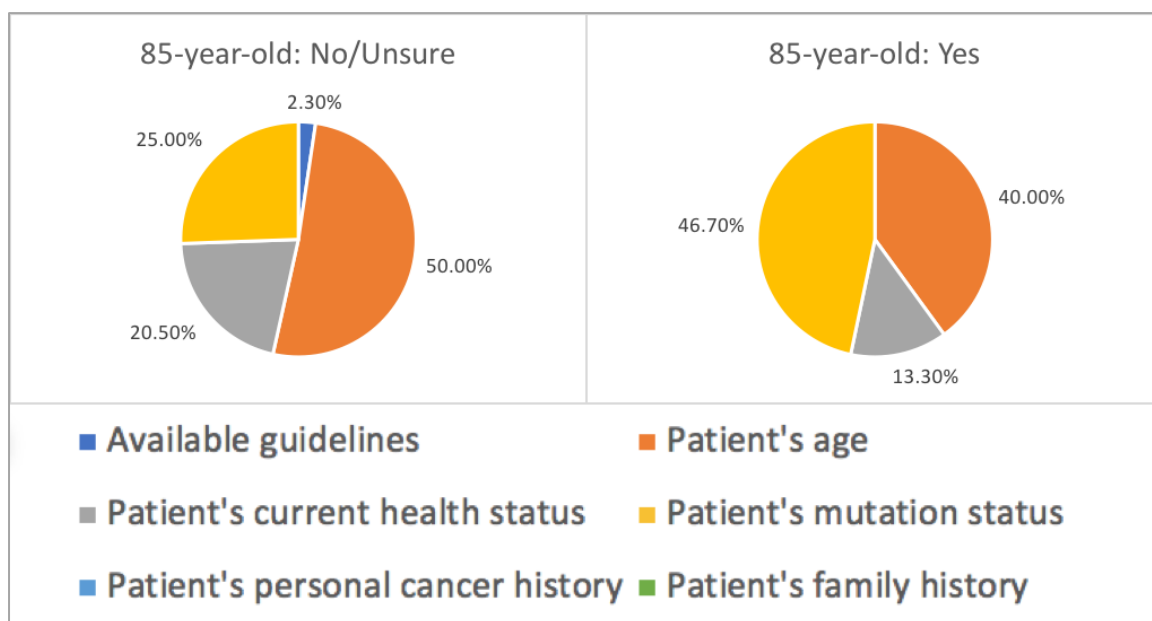


Figure 6: Most influential factor for survey respondents who answered No/Unsure or Yes for Scenario 4

Scenario 5 results

In Scenario 5, the patient had hypertension and type 2 diabetes compared to an unremarkable medical history in Scenario 1. When presented with Scenario 5, 48% of genetic counselors did not feel that RRSO was an appropriate medical management option for the patient, while 35% were unsure, and 17% felt RRSO was an appropriate option (*Figure 2*). There was a significant difference in answers between Scenarios 1 and 5 ($p=2.3 \times 10^{-11}$) as more respondents felt RRSO was inappropriate in the context of comorbidities. On a scale of 0 (absolutely not) to 10 (absolutely), the highest percentage

of survey respondents chose 5 (n=11, 18%) and 2 (n=10, 17%) regarding if they felt RRSO was in an appropriate medical management option for the patient in Scenario 5. The first, second, and third most influential factors reported by survey respondents were the patient's current health status, patient's age, and patient's mutation status. Survey respondents who said No or Unsure reported patient's current health status (50%), patient's mutation status (32%), and patient's age (14%) as the most influential factor (Figure 7). Survey respondents who said Yes reported patient's mutation status (80%), patient's current health status (10%), and patient's age (10%) (Figure 7).

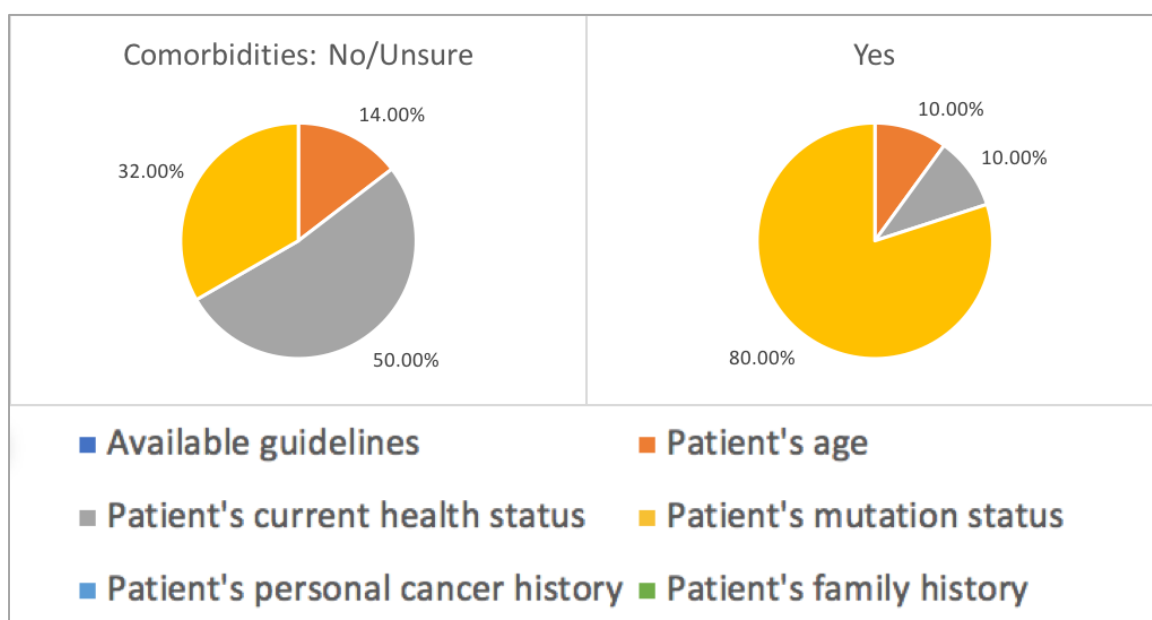


Figure 7: Most influential factor for survey respondents who answered No/Unsure or Yes for Scenario 5

Scenario 6 results

In Scenario 6, the patient's family history was notable for a sister with a history of ovarian cancer diagnosed at 52 years old. When presented with Scenario 6, the majority of respondents felt RRSO was an appropriate medical management option for the patient as seen in Figure 2 (62%). On a scale of 0 (absolutely not) to 10 (absolutely), the highest percentage of survey respondents chose 8 (n=13, 22%) regarding if they felt RRSO was

in an appropriate medical management option for the patient in Scenario 6. The differences in survey answers between Scenario 1 and 6 were not significant ($p=0.15$). Consistent with Scenarios 1, 2, and 3, the first, second, and third most influential factors reported by survey respondents were the patient's mutation status, patient's current health status, and patient's age. Survey respondents who said No or Unsure reported patient's family history (36.4%), patient's age (27.3%), and patient's mutation status (27.3%) as the most influential factor (*Figure 8*). Survey respondents who said Yes reported patient's mutation status (64.9%), patient's current health status (18.9%), patient's family history (13.5%), and patient's personal cancer history (2.7%) (*Figure 8*).

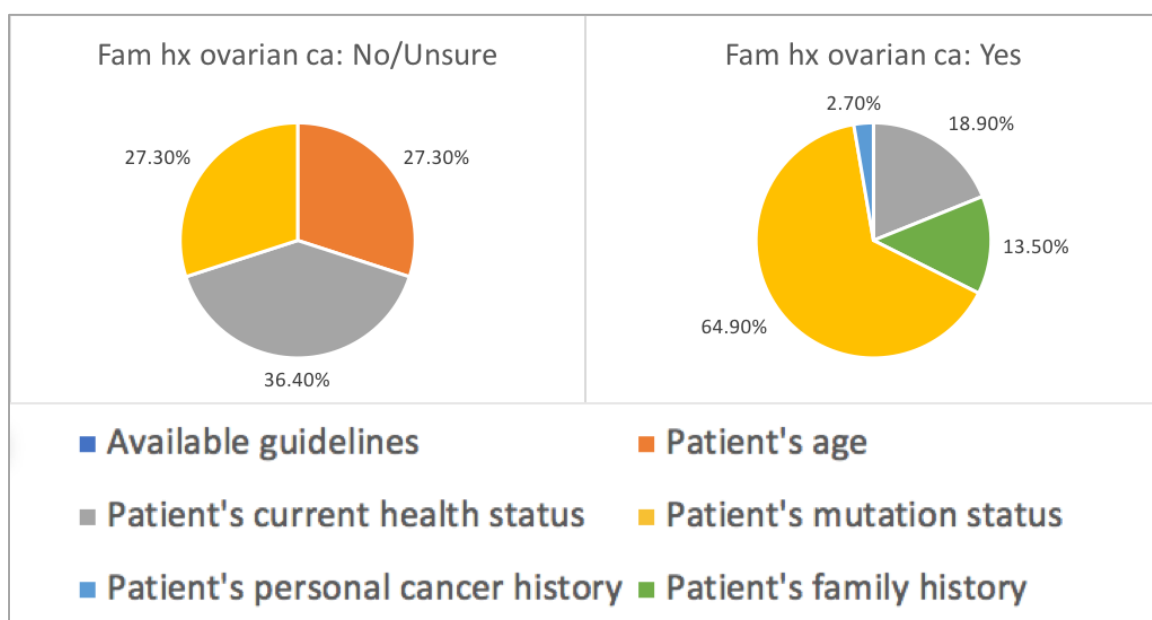


Figure 8: Most influential factor for survey respondents who answered No/Unsure or Yes for Scenario 6

Confidence level and resources results

In addition to responding to each scenario, cancer genetic counselors were surveyed regarding their confidence level when counseling BRCA1/2 positive women over the age of 75. On a scale of 0 (not confident) to 10 (extremely confident), the most common

answer was 7 (27%). Of survey respondents, 56.7% reported high confidence (7-10), 25.0% were unsure (4-6), 16.7% reported low confidence (1-3), and 1.7% did not answer. Additional breakdown of answers to this question can be found in *Figure 9*. Genetic counselors with ≥ 4 years of cancer experience were more likely to feel confident compared to genetic counselors with ≤ 3 years of cancer experience (70% v. 43.3%). This difference was significant ($p=0.01$). Findings for confidence level when compared by clinical setting ($p=1.0$) or number of BRCA1/BRCA2 positive women counseled over the age of 75 ($p=0.08$) were not significant. Genetic counselors were also surveyed regarding which resources they use most often when counseling this patient population. The most utilized source for genetic counselors when counseling this patient population is NCCN guidelines, with 74.1% of survey respondents ranking this source as number one. Other resources ranked as a top resource included gynecological oncologist (20.7%), surgical gynecologist (3.5%), and PubMed search (1.7%).

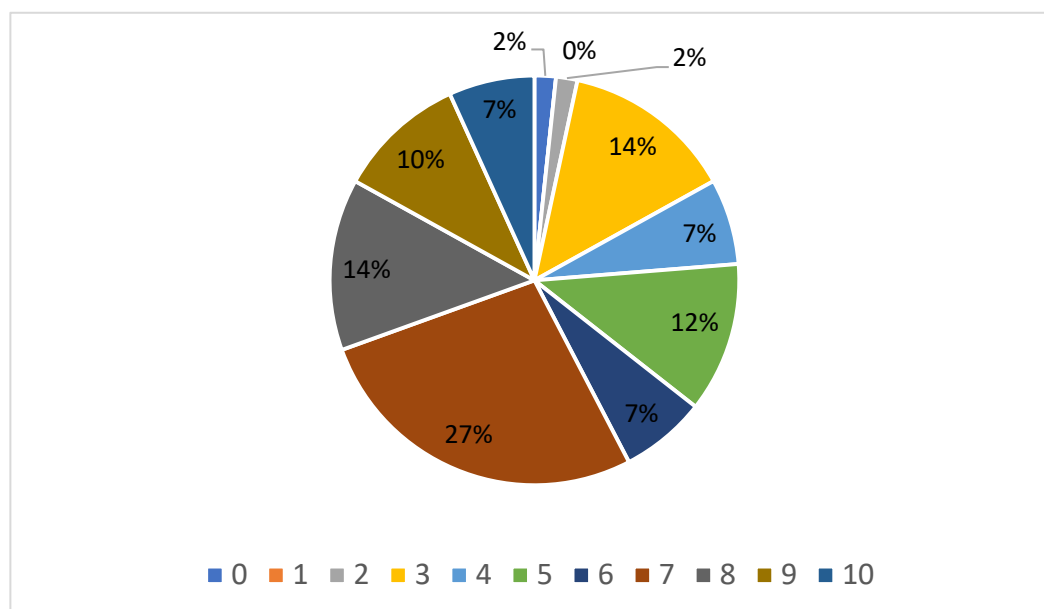


Figure 9: Breakdown of answers when survey respondents answered, “On a scale of 0 (not at all) to 10 (extremely confident), how confident are you that you have the knowledge to present recommendations for RRSO to a woman over 75 with a BRCA mutation and ovaries intact?”

Survey answers by demographic characteristics

Survey answers to each scenario were also analyzed by demographic characteristics including years of cancer genetic counseling experience (*Figure 10*), clinical setting (*Figure 11*), and number of BRCA1/BRCA2 positive women counseled over the age of 75 in the past 5 years (*Figure 12*). There was no significant difference in answers when analyzed by demographic factors; however, several trends were observed when survey answers were compared by years of cancer genetic counseling experience. Survey respondents with ≥ 4 years of cancer experience were more likely to feel RRSO is an appropriate management option for scenarios when the women were 77-years-old and did not have any comorbidities (Scenario 1, 2, 3, 6). Survey respondents with ≤ 3 years of cancer experience were more likely to be unsure in these scenarios (*Figure 10*). No trends were found when survey answers were analyzed by clinical setting or number of BRCA1/BRCA2 positive women counseled over the age of 75 in the past 5 years.

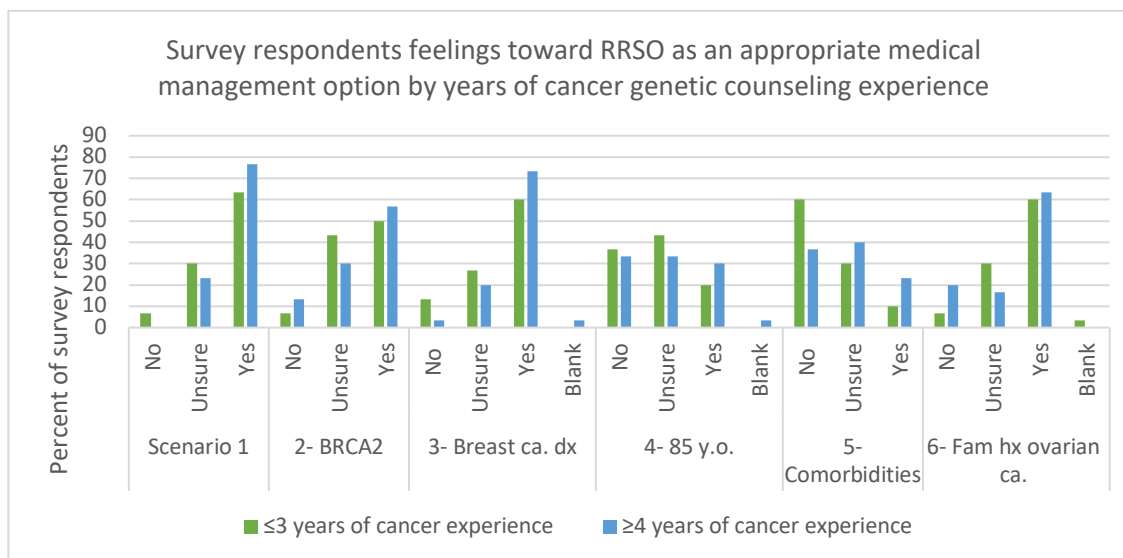


Figure 10. Genetic counselors' feelings toward RRSO as an appropriate medical management option by years of experience. Sample size ≤ 3 years of cancer experience= 30 respondents. Sample size ≥ 4 years of cancer experience= 30 respondents

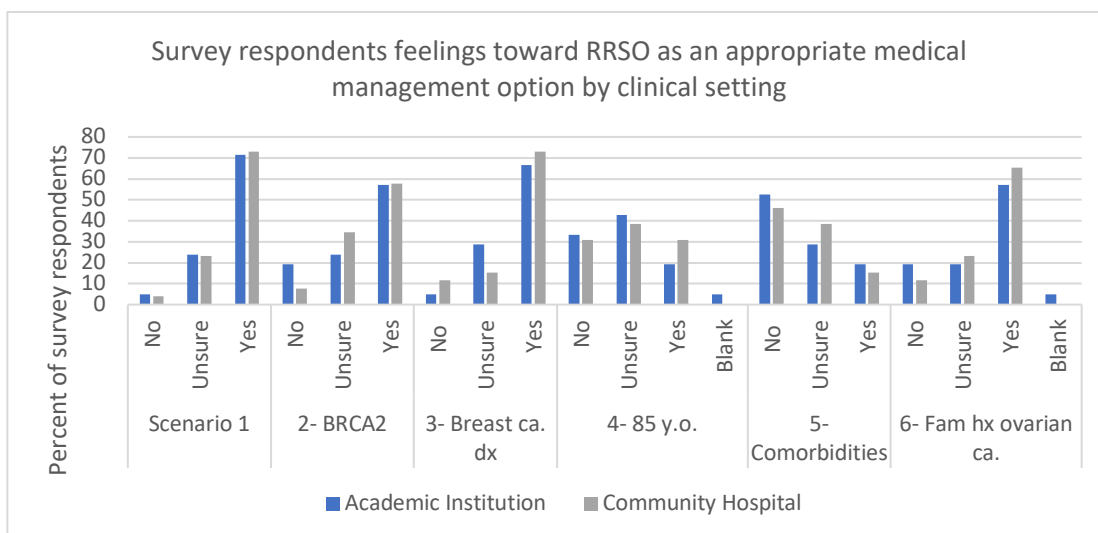


Figure 11. Genetic counselors’ feelings toward RRSO as an appropriate medical management option by clinical setting. Sample size academic institution= 21 respondents. Sample size community hospital= 26 respondents

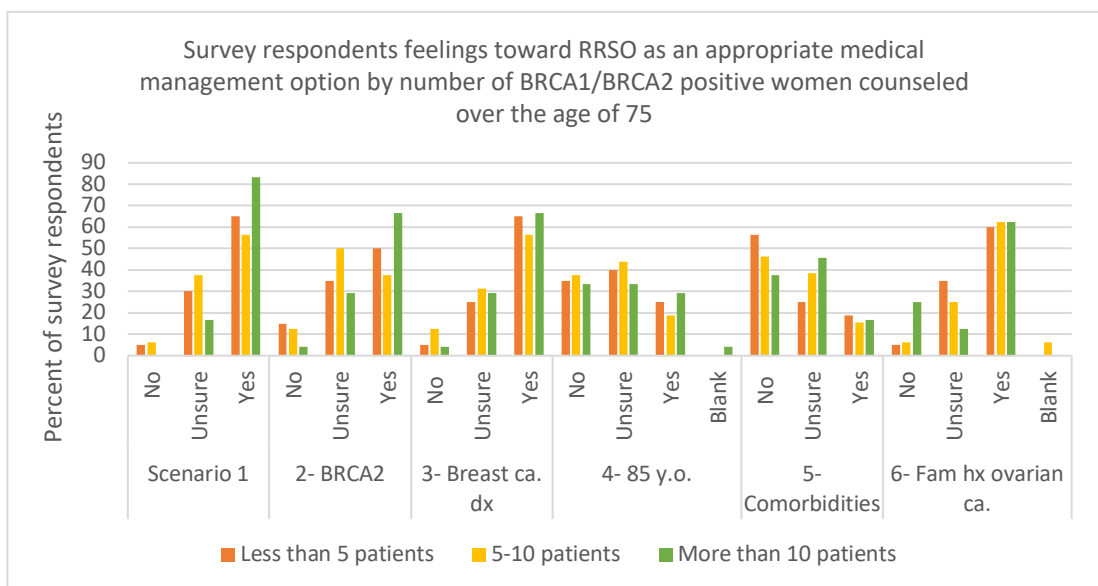


Figure 12. Genetic counselors’ feelings toward RRSO as an appropriate medical management option by the number of BRCA1/BRCA2 positive women counseled over the age of 75 in the past 5 years. Sample size less than 5 patients= 20 respondents. Sample size 5-10 patients= 16 respondents. Sample size more than 10 patients= 24 respondents

Discussion

Goals and objectives of the study

This study explored if cancer genetic counselors feel RRSO is an appropriate medical management option for women over the age of 75 who carry a BRCA1/BRCA2 mutation, and if they feel confident counseling this patient population. In addition, it explored which factors, such as the patient's family history, mutation status, personal cancer history, and current health status, may influence cancer genetic counselors' feelings toward RRSO as an appropriate option. The study also investigated what resources are used by cancer genetic counselors when counseling women over the age of 75 who test positive for BRCA1/BRCA2 about RRSO risks and benefits. Without guidelines for medical management for this patient population, it is unknown how these women are currently being counseled. Our study investigated this question by surveying cancer genetic counseling who are members of the Cancer SIG through NSGC.

Main findings

Overall, the majority of survey respondents (70%) reported that they felt RRSO was appropriate for a 77-year-old woman who carries a BRCA1 mutation, while the other 30% of survey respondents were either unsure or felt RRSO was not appropriate. Survey responses did not differ significantly if the patient had a BRCA2 mutation, personal breast cancer history, or family history of ovarian cancer. This overall response is interesting because it is different than what we would expect for a 40-year-old woman with a BRCA mutation. For 40-year-old BRCA1/BRCA2 carriers, we would expect that all women would be recommended to have a RRSO (NCCN, 2019). Therefore, there are differing opinions in the cancer genetic counseling community about RRSO as an

appropriate medical management option for BRCA1/BRCA2 positive women over the age of 75. This is likely due to the lack of professional guidelines for this patient population.

While there is a lack of guidelines, 74% of survey respondents ranked NCCN guidelines as their number one resource when counseling this patient population. Interestingly, NCCN does not provide ovarian cancer recommendations for women over the age of 45. Based on responses to our survey, it is possible that cancer genetic counselors are making recommendations that the woman over 75 in our scenario have RRSO because she is over the age of 45 and is a BRCA carrier. In addition, when a 77-year-old patient had a BRCA1 or BRCA2 mutation, none of survey respondents who felt RRSO was appropriate selected the patient's age as their most influential factor. In contrast, patient's age was the second most selected influential factor for respondents who did not feel RRSO was appropriate. Therefore, survey respondents who felt RRSO was appropriate weighed the patient's positive mutation status, current health, and available guidelines to guide their decision instead of the patient's age.

Age and significant findings

When asked about RRSO for an 85-year-old woman, answers differed significantly than if the woman was 77-years-old ($p=1.0 \times 10^{-7}$). The number one factor reported as influencing survey respondents' decisions was the patient's age, whereas the patient's mutation status was the number one influencer for Scenarios 1, 2, 3, and 6. In addition, for survey respondents who answered No or Unsure, patient's age was the largest influencer. In contrast, for survey respondents who answered Yes, the patient's mutation status was the largest influencer. We can hypothesize that the difference is due to the

patient's life expectancy and increased risk of complications from RRSO surgery. However, these factors were not included as potential influential factors that survey respondents ranked and is a limitation of our survey. Several survey respondents commented that they base their medical management recommendations for this patient population on life expectancy, and one respondent provided a life expectancy tool that can be found at <https://www.ssa.gov/oact/population/longevity.html>. Using this tool, a 77-year-old woman has 12.1 years and an 85-year-old has 7.3 years of additional life expectancy. Therefore, it is interesting that a life expectancy difference of approximately five years significantly changed survey respondents' feelings toward RRSO.

Comorbidities and significant findings

When a BRCA1 positive 77-year-old woman presented with type 2 diabetes and hypertension, the largest number of survey respondents (48%) felt that RRSO was not an appropriate management option for this patient. The number one factor reported as influencing survey respondents' decisions was the patient's current health status as opposed to the patient's mutation status in Scenarios 1, 2, 3, and 6. We hypothesize that it was the perceived notion of life expectancy for a 77-year-old patient with comorbidities by the survey respondents that influenced these findings. For survey respondents who answered No or Unsure, the patient's current health status was the most influential factor, deterring them from feeling RRSO was appropriate for this patient. Contrastingly, for respondents who selected Yes, the overwhelming majority selected the patient's mutation as the most influential factor to their decision. Therefore, some survey respondents still felt the patient's mutation status outweighed other patient factors, such as the patient's

current health status and age, that could influence medical decision making and patient risk.

It was noteworthy that the introduction of comorbidities significantly changed survey respondents' answers even though genetic counselors are not trained about the risk of complications in surgery due to comorbidities. Answers to this scenario did not change significantly based on demographic information, but trends were seen when answers were analyzed by years of cancer genetic counseling experience. Surprisingly, genetic counselors with ≥ 4 years of cancer experience were more likely to be unsure compared to survey respondents with ≤ 3 years of cancer experience (40% v. 30%). While interesting, the overall survey result was consistent with what was expected due to the increased surgical risks of RRSO in patients with poor health, specifically type 2 diabetes and hypertension. Type 2 diabetes and hypertension are associated with an increased risk of surgical-site infections, making them risk factors for elderly patients undergoing surgery (Harris et al., 2017; Turrentine et al., 2006). Therefore, results from this scenario indicate that pertinent risk factors such as comorbidities are being considered by some survey respondents when counseling women over 75, making them less likely to feel RRSO is an appropriate medical management option this patient population.

Patients with a family history of ovarian cancer

When the 77-year-old patient was presented with a sister with a history of ovarian cancer at the age of 52, the majority of survey respondents felt that RRSO was an appropriate medical management option (61.7%). While not a significant difference when compared to Scenario 1, this percentage was less than if the patient did not have a sister with a history of ovarian cancer (61.7% v. 70%). The patient's mutation status was the most

influential factor while the patient's family history was the 4th most influential factor behind the patient's current health status and age. In addition, only 13.5% of survey respondents who felt RRSO was an appropriate medical management option selected family history as their most influential factor. This survey result disagrees with what we expected and is discordant with current literature. Teixeira et al. (2018) concluded that a family history of ovarian cancer in BRCA1/BRCA2 carriers tends to be associated with a higher risk of ovarian cancer. Further investigation of this result would be needed to explore why fewer survey respondents felt RRSO was appropriate for this patient and why family history was not given more weight as an influential factor.

Confidence level without guidelines

Furthermore, it was surprising that over half of survey respondents felt confident counseling this patient population about RRSO despite a lack of professional guidelines (56.7%). Survey respondents with ≥ 4 years of cancer experience were significantly more likely to feel confident counseling this patient population than survey respondents with ≤ 3 years of cancer experience. While more years of experience translates to higher confidence, 43% of survey respondents with ≤ 3 years of cancer experience still reported that they feel confident counseling this patient population. It would be interesting to further explore why these cancer genetic counselors feel confident and if resources they use outside of professional guidelines, such as published literature or advice from physicians, adds to their confidence. While most respondents reported high confidence, 41.7% of survey respondents reported being unsure or having low confidence. Therefore, there is room for improvement in confidence level for survey respondents when counseling this patient population. We hypothesize that an increase in published literature

and development of professional guidelines regarding RRSO for this patient population would result in higher confidence of cancer genetic counselors when counseling BRCA/BRCA2 women over the age of 75.

Lack of significant findings when comparing demographic characteristics

When investigating why survey answers differed between cancer genetic counselors, results were analyzed by different demographic information. Surprisingly, no significant differences were found when results were analyzed by years of cancer genetic counseling experience, clinical setting, or number of BRCA1/BRCA2 positive women counseled over the age of 75 in the past 5 years. We hypothesize that feelings toward RRSO as an appropriate management option differed due to lack of professional guidelines and differing opinions of physicians, such as gynecological oncologists or surgical gynecologists, that cancer genetic counselors use as a resource.

Future directions and research

There is a lack of professional guidelines for cancer genetic counselors when counseling this patient population, and additional guidelines are needed for medical management of ovarian cancer risk for BRCA positive women over the age of 75. NCCN guidelines contributors perform a literature search annually to determine new research evidence that needs to be incorporated into guidelines. Therefore, there is a need for further published research to assess the risks and benefits of RRSO for this patient population. Specifically, a survey investigating what recommendations gynecological oncologists are making for this patient population would help demonstrate current practices in light of a lack of professional guidelines. In addition, a study looking at health outcomes for BRCA1/BRCA2 positive women over the age of 75 who elect or do not elect to have

RRSO would help assess the risks and benefits. Our study suggests inconsistency in survey respondents' opinions regarding RRSO for this patient population, and our study results found this to be particularly true when counseling BRCA positive patients who are 85-years-old or have comorbid conditions. It would be interesting to further explore why survey respondents felt differently about RRSO for a 77-year-old woman compared to an 85-year-old woman and why over half of cancer genetic counselors feel confident counseling this patient population without guidelines. BRCA1/BRCA2 positive women over the age of 75 may receive different recommendations regarding RRSO simply based on what cancer genetic counselor they are scheduled to see. Without guidelines regarding RRSO for this patient population, medical management recommendations by genetic counselors are influenced by their own attitudes, ideas, and experiences. Additional research and development of professional guidelines would help standardize care in regard to ovarian cancer risk reduction for this patient population.

Limitations

Limitations of our study include that the survey was only sent out to genetic counselors who are members to the NSGC Cancer Special Interest Group. Therefore, the survey may not be representative of the opinions of all cancer genetic counselors. In addition, not all members of the Cancer Special Interest Group participated in the survey and results may be skewed due to ascertainment bias. For example, genetic counselors that decided to participate in the survey may have strong opinions or relevant experience on the specific topic. Limitations also include that not all possible scenarios were presented in the survey, and there were limited answer selections for questions that concerned most influential factors or most utilized resources. There may be other scenarios or answer

choices that genetic counselors view as important that were not represented by the survey and survey results. In addition, we cannot be certain that questions were interpreted the same by all survey respondents. Questions misinterpreted due to wording have the potential to skew survey results.

Conclusion

After surveying cancer genetic counselors, our study showed that there is inconsistency among survey respondents in feeling whether RRSO is an appropriate medical management option or not for BRCA1/BRCA2 positive women over the age of 75. In addition, it showed that not all survey respondents are confident counseling this patient population about RRSO. We hypothesize that this is due to limitations in current literature and lack of professional guidelines for RRSO for this patient population. An increase in published literature and development of professional guidelines regarding RRSO for this patient population would likely result in higher confidence of cancer genetic counselors and standardize care in regard to ovarian cancer risk reduction for BRCA1/BRCA2 positive women over the age of 75.

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