Physician Practices and Beliefs about Ovarian Cancer Screening in High-Risk Patients

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Abstract

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Screening with transvaginal ultrasound and CA-125 is often recommended patients with pathogenic variants in the *BRCA1* or *BRCA2* genes despite evidence showing that screening does not result in mortality benefits. To better understand physician's attitudes and beliefs about ovarian cancer screening, including whether and why they recommend ovarian cancer screening to high-risk patients, we conducted semi-structured interviews with physicians knowledgeable about hereditary cancer prevention. The most important themes we identified in our conversations with physicians were that physicians have open conversations with patients about their desires related to surgery to make personalized recommendations that are best suited to each patient and their unique goals, there are many challenges to managing ovarian cancer risk, and it is reasonable to believe that a population wide approach to predictive genetic testing for ovarian cancer could save lives. Our results indicate there is more research needed to identify novel methods of ovarian cancer screening and to gain an understanding of the impacts of risk

reducing surgery. There is also a need to increase support for patients, helping them get access to genetic testing and the appropriate subsequent care.

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Introduction

Ovarian cancer is one of the deadliest gynecological cancers and the fourth most common cause of cancer deaths in women (Menon et al 2021, Jacobs and Menon 2000). While stage III and IV cancers have 34% and 15% five-year survival rates, respectively, the five-year survival rates for stage I and II cancers are 90% and 65% (Menon and Nash 2020). Having an effective method of screening for ovarian cancer would thus dramatically improve disease survival.

Menon and Nash define screening as "looking for early signs of a particular disease in apparently 'healthy' people who do not have 'any symptoms'" (Menon and Nash 2020). Screening reduces disease mortality by detecting "latent precancerous and/or early-stage invasive disease" (Menon and Nash 2020). Current ovarian cancer screening modalities include transvaginal ultrasound (TVUS) and CA-125 testing. TVUS includes direct visualization of the fallopian tubes and ovaries, where disease is detected directly through morphological changes (Menon and Nash 2020). CA-125 is a blood biomarker that is associated with the presence of high grade serous ovarian cancer (Menon and Nash 2020). Unfortunately, there is limited evidence that screening with TVUS and CA-125 leads to ovarian cancer diagnosis at an earlier stage or has a definitive mortality benefit (Buys et al 2011, Jacobs et al 2016, Nash and Menon 2020).

The United States Preventive Services Task Force (USPSTF) recommends against screening for ovarian cancer in asymptotic women (US Preventive Services Task Force 2018). Specifically, they state that the positive predictive value of TVUS and CA-125 are low, meaning

that most women with positive screening tests do not have ovarian cancer (false-positives), which can lead to unnecessary surgical intervention (US Preventive Services Task Force 2018). However, TVUS and CA-125 screening are often offered to patients at high risk of ovarian cancer due to hereditary risk factors, for example pathogenic variants (PVs) in the *BRCA1* and *BRCA2* genes. People with PVs in *BRCA1* or *BRCA2* have a lifetime risk of ovarian cancer of 36%-53% or 11%-25%, respectively, compared to a lifetime risk of 1-2% in the general population (Kotsopolous et al 2018, Petrucelli et al 1998). Until recently, the National Comprehensive Cancer Network Guidelines for genetic/familial cancers stated that in cases where people with PVs in *BRCA1* or *BRCA2* had not elected to undergo risk-reducing salpingo-oophorectomy (RRSO), ovarian cancer screening with TVUS and CA-125 could be utilized "at the clinician's discretion" despite the "uncertain benefit[s]" (National Comprehensive Cancer Network 2023).

Despite limited evidence of benefit, use of TVUS and CA-125 for ovarian cancer screening among individuals with PVs in *BRCA1* and *BRCA2* is common. For example, Baldwin et al found that "one in three physicians believed that ovarian cancer screening was effective, despite evidence to the contrary." To better understand how many women are exposed to the potential harms of ovarian cancer screening, Baldwin et al's study sought to explore physician non-adherence to ovarian cancer screening guidelines. There has been some research on beliefs and attitudes toward ovarian cancer screening in the general population. For example, Fallowfield Et al. (2010) asked participants in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOS) "about their awareness of [ovarian cancer] risk factors, and their views about putative benefits of screening, to identify possible misunderstandings or gaps in knowledge that might influence willingness to adhere to screening." They found "a need for

improved public understanding about [ovarian cancer] risks" (Fallowfield et al 2010). There has also been research done specifically in women at high risk of developing ovarian cancer that found anxiety about ovarian cancer rather than "objective risk, is the major factor which determines women's attitude to prophylactic oophorectomy" and that women would likely benefit from "interventions aimed at reducing breast/ovarian cancer anxiety" (Meiser et al 1999).

To better understand physician's attitudes and beliefs about ovarian cancer screening, including whether and why they recommend ovarian cancer screening to high-risk patients, we conducted semi-structured interviews with physicians knowledgeable about hereditary cancer prevention. We asked them how they make decisions to offer patients' TVUS and CA-125 and to describe challenges that arise when caring for individuals at substantially increased risk for ovarian cancer. We also asked about how the existing options for preventing ovarian cancer (screening/surgery) influenced their opinions about predictive genetic testing for ovarian cancer risk, including population screening for PVs in *BRCA1* and *BRCA2*.

Methods

Participants and Recruitment

We conducted interviews with physicians with a specialty in treating those at high risk for ovarian cancer because they were thought to have the most insight into our research questions, as they are most often the physicians who are having conversations with patients about ovarian cancer screening and risk-reducing surgery. Interviewees were all known by the study team and invited to participate in the study via email.

Data Collection

The interview guide was developed collaboratively among all three researchers and with the goal of answering our research questions. We broke down the questions into three main sections, including questions about managing care for high-risk patients, questions about patient needs related to ovarian cancer prevention, and finally questions about how these issues relate to population genomic screening. These questions were informed by current recommendations and guidelines that exist for the management ovarian cancer risk for those with pathogenic variants such as *BRCA 1* or *2.*

One researcher (MR) completed all interviews between December 2022 and March 2023 via Zoom video conferencing software. Interviews were both recorded and transcribed by Zoom. Transcripts were verified and edited (by MR) to have identifying information omitted.

Data Analysis

A thematic approach was used to analyze the interview data (Bond et al 2023). A preliminary codebook was developed using five interview transcripts. The codebook was then applied to one transcript at a time by the primary coder (MR). Codes and excerpts of text were iteratively examined and refined by the full research team. The primary coder (MR) developed a list of preliminary themes based on coded data. The research team then discussed all preliminary themes and came to a consensus on the final themes.

Results

All physicians that were invited participated in the study (n=10). The majority (n=6) practiced in Washington State, primarily in Seattle. Almost all were gynecologic oncologists (n = 8), with one family medicine doctor and one medical geneticist, although this specialist was trained in gynecologic oncology in a different country before coming to practice in the United

States. In talking with physicians, we identified three main themes related to our research questions. Themes could be further broken down into five subthemes that are described in detail below.

How and Why Physicians Make Ovarian Cancer Screening Recommendations

Physicians told us conversations about managing patients' risk of ovarian cancer are highly nuanced. They saw learning patients' individualized needs as essential for making recommendations about ovarian cancer screening. They described making risk management recommendations on a case-by-case basis and highlighted the importance of having honest conversations. For example, one physician said:

> *I think it really is a shared decision-making situation, where people need all the information about risks and upsides, downsides, pros, cons, of the different [risk management] strategies and then ultimately when I say shared decision-making, I mean that providers are supporting patients and giving recommendations when desired.*

Thus, physicians did not see decisions about offering ovarian cancer screening as a clear-cut laying out of clinical guidelines, but a process of education and values clarification that they engaged in with their patients.

All of the physicians we interviewed described how their screening recommendations were inextricably linked to patients' decisions about RRSO, which NCCN guidelines recommend people with PVs in *BRCA1* and *BRCA2* have around age 35 or 40 for *BRCA1*, and 40 – 45 for *BRCA2* (National Comprehensive Cancer Network 2023). As one physician told us, "…if you want to do something preventative for your lifetime risk […] the intervention is surgery." Thus, patient age and fertility desires were primary factors driving recommendations

related to ovarian cancer screening. Fertility desires were often front of mind as, in the words of one physician, "… oftentimes women are finding out about these mutations right in sort of the prime years in which they're considering their future fertility." Screening was seen as a stop-gap for patients who were waiting to have RRSO, whether they had not yet reached the recommended age or were delaying surgery to complete childbearing. For example, one physician told us they "do offer ovarian cancer screening, but it's meant to be a bridge until they're ready to get surgery, and I try to convey that it's not effective." While some physicians described screening as a way to keep patients connected to care while they wait for surgery, one physician brought up that screening, "…can result in false reassurance that there isn't anything wrong and somebody might be more inclined to delay the evidence-based intervention, which is risk reducing surgery."

There was considerably less support for recommending ovarian cancer screening as a long-term risk management strategy. However, one physician told us their "enthusiasm for offering [screening] or discussing it with the patient goes up the older the patient is because they're entering a higher risk category where the risk of a false positive is less harmful." Another physician argued that with screening, "you're doing something with a low downside that is not dangerous, and so I think, for a patient who wants to…as long as they're aware it's not evidence based, I think it's acceptable." Thus, though the physicians agreed that TVUS and CA-125 were not effective long-term risk management strategies, there was some variability in opinions about their potential harms and how to weigh those harms against patient's desires to "do something" to address their ovarian cancer risk.

Challenges to Managing Ovarian Cancer Risk

During interviews, we heard from physicians that there are several challenges to making ovarian cancer risk management recommendations (for providers) and acting on ovarian cancer risk management recommendations (for patients). First, providers told us that both patients and less specialized physicians such as primary care doctors or OBGYN's lack knowledge about ovarian cancer screening and prevention. For example, one physician stated that "a very large proportion of OBGYN's probably think that CA-125 and pelvic ultrasound is a reasonable way to screen for ovarian cancer." This leads to patients having false expectations when they go on to discuss managing their risk of ovarian cancer with a more knowledgeable specialist. Physicians we interviewed identified two key knowledge gaps related to ovarian cancer prevention that need to be addressed. First, patients need to understand that "there really is no screening for ovarian cancer [and] we don't have a good early detection method for ovarian cancer." Second, there needs to be more awareness around the symptoms of ovarian cancer. As one physician said, there is "a pervasive [belief] that people with ovarian cancer don't have symptoms, and then it just pops up out of nowhere, when actually the evidence tells us that people...usually do have symptoms." Overall, misunderstanding, misinformation, and lack of knowledge make delivering high quality risk management to high-risk patients is difficult. We heard from physicians that "we need more education for patients...more resources that can educate patients" to ultimately help them make more informed decisions about the care they receive while managing their ovarian cancer risk.

Physicians identified the burden of self-management placed on high-risk patients in our health care system as a second challenge to ovarian cancer risk management. As one physician told us "this is on you [the patient] because we don't have someone to help you with this … the patients are supposed to remember and schedule that [screenings]." We heard from physicians

that there is a need for more resources to help reduce the number of obstacles patients face to get access to care, and "make the things that they're going to go through easier." One suggestion physicians had to do so is "mandatory [coverage of certain services] for everyone with a hereditary cancer gene mutation" so insurance and costs of services are less of a barrier to receiving care. Another suggestion was patient support groups, as "the support group systems really help people navigate through" the decision-making process revolving around screening and surgery.

Finally, physicians told us that managing emotionality around ovarian cancer risk and the lack of high-quality screening is a challenging part of caring for high-risk individuals. We heard from physicians that patient's most common reaction when they learn about screening options are disappointment, frustration, and sometimes confusion. For example, one physician stated that:

> *[Patients] feel frustrated by it because you know, they're also typically in the same appointment being told how important it is that they get their breast MRI or mammogram or other modalities for screening that are actually effective … but unfortunately that's not the case for ovarian cancer screening.*

Increasing education about the limitations of available screening modalities may be helpful to reduce patients' feelings of disappointment and frustration when they learn about ovarian cancer screening in the context of learning about their increased lifetime risk.

Views About Predictive Genetic Testing for Ovarian Cancer

When asked about population screening for PVs in *BRCA1* and *BRCA2*, we heard that most physicians were in favor of genetic testing, generally. As one physician argued, "I think

that if someone is at significantly elevated risk for ovarian cancer that's a very meaningful thing to know because we have interventions that are effective and lifesaving." Another considered that screening healthy adults for *BRCA1* and *BRCA2* could be justified because:

> *We don't have an alternative [method of screening for ovarian cancer], and we know that risk-reducing surgery decreases risk substantially. And, even in cases where [during surgery] we're finding small cancers that are early stage, the prognosis for those cancers is so markedly better*.

While implementing a large-scale screening program in the near future may not be feasible, we heard from physicians that continuing current risk-based genetic testing is valuable because it allows people to receive risk reducing surgeries that save lives.

Discussion

This study is unique in its focus on physicians' perspectives on ovarian cancer screening and insight into real-world practices around caring for patients at high risk of ovarian cancer. During these interviews, we learned that physicians make personalized risk management recommendations on an individual basis by having open and honest conversations with patients about their desires related to surgery. We also heard that the healthcare system needs to invest in educational resources and support groups for patients that help them navigate the difficult process of making decisions about screening and risk-reducing surgery. Lastly, physicians told us that they are in support of predictive genetic testing because it allows high-risk individuals to receive risk-reducing surgery, which is currently the only intervention proven to reduce the mortality of ovarian cancer.

The lack of evidence-based methods for ovarian cancer screening and early detection of disease is an important scientific knowledge gap. Our study highlighted that both physicians and patients are disappointed and frustrated by the ineffectiveness of currently available screening options. While ovarian cancer may not be a common disease, it is one of the deadliest cancers for women. Thus, more time and money should be spent researching other screening modalities to enable the detection of early disease that would improve many patients' prognoses and ultimately save lives. As of 2017, there is some research being done to try and identify other biomarkers "besides CA-125, which could serve as either early detection markers or as markers of cancer recurrence" (Chien and Poole 2017). There has also been some research on RNA as it relates to ovarian cancer, one of which found that long non-coding RNA's "are involved in the regulation of the occurrence, development, prognosis, and treatment of" (Qui et al. 2023) ovarian cancer. It is believed that the research on long non-coding RNA's or other biomarkers may help identify novel prognostic markers for ovarian cancer (Qui et al 2023).

While research to identify an effective means of screening for ovarian cancer is an important area of focus, our study identified several ways in which current risk management delivery could be improved. Several physicians told us that there is a lack of knowledge on the symptoms of ovarian cancer, with many people believing that ovarian cancer has no real symptoms. In one study, it was found that "95% of women with ovarian cancer developed symptoms an average of 3 to 6 months before seeing a physician" (Goff 2012). While "gynecological symptoms were the least common" abdominal, gastrointestinal, pain, and constitutional symptoms were reported in at least 50% of patients (Goff 2012). They also found that 89% of women with early-stage disease complained of symptoms before their diagnosis (Goff 2012). Given these statistics and the fact that early-stage ovarian cancer has a significantly

better prognosis, with cure rates of 70% to 90% (Goff 2012), it seems critical that more physicians and patients are aware of the symptoms of ovarian cancer. It is important that women are educated on these symptoms so they can recognize what may be the signs of early ovarian cancer and seek care, as well as advocate for themselves so they receive the appropriate care to address these symptoms. As one physician told us, it is also critical that physicians are able to recognize these symptoms that may be indicative of ovarian cancer, and that they respond appropriately.

In this study, most physicians told us they support some form of a genetic screening program to identify more individuals at high risk of ovarian cancer. Currently, most individuals who receive genetic testing for PV's associated with ovarian cancer are those who have a relevant family history of cancer. Studies have shown "40% of [ovarian cancer] patients with a BRCA pathogenic variant do not have a relevant family history of cancer" (Amin and George 2020). Given this statistic, it seems that screening a larger proportion of the population, not just those with relevant family history (e.g. population screening), would lead to greater identification of those with PVs and thus allow more women access to risk reducing surgery. Physicians in this study noted the various difficulties with implementing a screening program of this type, in which all healthy individuals would undergo genetic testing for *BRCA1* and *BRCA2* PVs. While physicians told us that everyone who wants to have access to genetic testing should be able to get tested, there are some huge infrastructure issues to overcome if we want to achieve that. One of the biggest problems is that genetic counselors are typically the most common providers who order cancer genetic testing, and they are a very limited resource. This problem could be mitigated by increasing the number of genetic counselors and/or training more physicians to be better equipped to perform similar tasks as genetic counselors. Another strategy

that is used includes online education in some format prior to genetic testing and reserves genetic counseling for those who receive a positive test result, reducing the number of patients who need to interact directly with genetic counselors.

The main limitation of this study is its small sample size and homogeneous group of respondents. This limits the number of perspectives represented in the results and reduces generalizability. The focus on a subset of physicians who have very specific practices may have also reduced generalizability, although that was done with the goal of ensuring we were obtaining opinions from physicians who actively treat patients at high risk for ovarian cancer. In future work it will be critical to interview more physicians, and include genetic counselors, who also may discuss screening and surgery with patients after they receive their genetic testing results.

Conclusion

Findings from this study suggest that there is more research needed to identify novel methods of ovarian cancer screening and to gain an understanding of the impacts of risk reducing surgery. There is also a need to increase support for patients, helping them get access to genetic testing and the appropriate subsequent care. These findings should inform future research on ovarian cancer and the development of resources for patients with *BRCA* variants.

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