ARTICLE TITLE: Missed Therapeutic and Prevention Opportunities in Women With BRCA-Mutated Epithelial Ovarian Cancer and Their Families Due to Low Referral Rates for Genetic Counseling and BRCA Testing: A Review of the Literature

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After reading the article “Missed Therapeutic and Prevention Opportunities in BRCA-Mutated Epithelial Ovarian Cancer Due to Low Referral Rates for Genetic Counseling and BRCA Testing: A Review of the Literature,” the learner should be able to:
1. Describe the therapeutic and prevention opportunities of genetic counseling and subsequent testing for BRCA breast cancer-susceptibility genes for women with epithelial ovarian cancer (EOC).
2. Highlight medical and surgical strategies, and their advantages and disadvantages, for preventing EOC among women with BRCA mutations.
3. Explain the relevance of BRCA mutations to the efficacy of poly ADP-ribose polymerase (PARP) inhibitors as treatment for EOC.

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Missed Therapeutic and Prevention Opportunities in Women With BRCA-Mutated Epithelial Ovarian Cancer and Their Families Due to Low Referral Rates for Genetic Counseling and BRCA Testing: A Review of the Literature

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Abstract: Fifteen percent of women with epithelial ovarian cancer have inherited mutations in the BRCA breast cancer susceptibility genes. Knowledge of her BRCA status has value both for the woman and for her family. A therapeutic benefit exists for the woman with cancer, because a new family of oral drugs, the poly ADP-ribose polymerase (PARP) inhibitors, has recently been approved, and these drugs have the greatest efficacy in women who carry the mutation. For her family, there is the potential to prevent ovarian cancer in those carrying the mutation by using risk-reducing surgery. Such surgery significantly reduces the chance of developing this, for the most part, incurable cancer. Despite these potential benefits, referral rates for genetic counseling and subsequent BRCA testing are low, ranging from 10% to 30%, indicating that these therapeutic and prevention opportunities are being missed. The authors have reviewed the relevant available literature. Topics discussed are BRCA and its relation to ovarian cancer, the rates of referral for genetic counseling/BRCA testing, reasons for these low rates, potential strategies to improve on those rates, lack of effectiveness of current screening strategies, the pros and cons of risk-reducing surgery, other prevention options, and the role and value of PARP inhibitors. CA Cancer J Clin 2017;67:493-506. © 2017 American Cancer Society.

Keywords: BRCA testing, poly ADP-ribose polymerase (PARP) inhibitors. prevention, therapy

Practical Implications for Continuing Education

> The failure to routinely test for the presence of a germline BRCA mutation in women with epithelial ovarian cancer results in a missed therapeutic opportunity because of the nonavailability of poly ADP-ribose polymerase (PARP) inhibitors under the current labelling indications.

> This same failure to test will cause family members to miss out on the all-important chance of prevention in a cancer that otherwise is ultimately fatal for most women and for which screening is ineffective.

> This failure to test is predominantly due to a lack of physician awareness about its value and problems with the genetic counselling/testing process. These problems will be relatively simple to fix with sufficient education and the will to change inefficient processes.

Introduction

Epithelial ovarian cancer (EOC) can result from inherited mutations in the genes involved in DNA repair, most commonly the BRCA1 and BRCA2 breast cancer susceptibility genes. Such germline BRCA mutations occur in up to 18% of women with high-grade EOC.1 Knowledge of the index patient’s BRCA status has 3 important downstream benefits: 1) therapeutic, because of the recent introduction of poly ADP-ribose polymerase (PARP) inhibitors; 2) prevention, because risk-reduction strategies...
can be offered previously unaffected family members who have the mutation; and 3) financial, because cost savings for the patient/family and the health care system from the prevention of EOC are more cost effective than treatment. Despite these potential benefits, less than 20% of women with EOC (on a population basis) in Ontario, Canada, are referred for counseling and BRCA1 mutation testing.

Novelty does not explain the low rates—the ability to test for mutated BRCA is about 20 years old. In state-funded systems like Canada, cost is not a major factor. BRCA testing is free and universally accessible, yet the rates are low, similar to those in user pay systems. Instead, the reasons for low rates fall into 4 major categories: 1) process issues (eg, availability of, access to, and timeliness of counseling/testing); 2) physician issues (eg, lack of knowledge, poor access to counseling/testing, and work load issues); 3) patient lack of knowledge/awareness; and 4) specific patient issues (eg, cost, fear of genetic discrimination, anxiety/psychosocial issues, impact on family dynamics, and patient lack of knowledge about the value of testing).

This literature review describes BRCA1 testing rates in detail and why they are important with regard to the use of subsequent downstream actions. It is from an EOC perspective alone, except when prevention strategies overlap with those for breast cancer.

Background

An estimated 22,440 women will be diagnosed with EOC and 14,080 will die of it in the United States in 2017. Extraovarian spread is the norm at diagnosis, and a cure is unlikely in these women. Survival rates have improved modestly over the last 30 years, but these gains result from prolonged survival, not improved cure rates. Ten-year survival rates fall as stage increases and range from 75% to 84%, 50% to 60%, and 25% to < 10% for stages I through IV, respectively.

Approximately 24% of all women who develop EOC do so in the setting of an inherited syndrome. The most common mutations, which occur in 15% of all patients, are in the breast cancer susceptibility genes BRCA1 and BRCA2. The normal function of these genes is in the high-fidelity repair of double-stranded DNA breaks. If BRCA is mutated, then double-stranded DNA repair instead occurs using more error-prone pathways. The result is genomic instability, one consequence of which is cancer development. Women with BRCA mutations have an increased risk of EOC (the background population risk is 1.6%). The lifetime risk is from 35% to 60% for those with mutated BRCA1 and from 12% to 25% for those with mutated BRCA2. EOC is a conglomerate of biologically and genotypically different cancers, including high-grade serous (HGS) (70%), endometrioid (10%), clear cell (10%), mucinous (3%), and low-grade serous (5%). Mutated germline BRCA is most common in the high-grade cancers, rare in the low-grade mucinous or low-grade serous cancers, and has the highest prevalence (23%) in the HGS cancers. Mutation may truly occur only in HGS, because expert pathologic review coupled with immunohistochemistry often results in the reclassification of most high-grade cancers as HGS. Even the term EOC is somewhat of a misnomer, because evolving evidence indicates a fallopian tube origin for the majority of HGS cancers.

EOC in the setting of a BRCA mutation is often diagnosed at a younger age, is associated with a positive family or personal history of breast/ovarian cancer, and has a better prognosis. However, a family or personal history is often absent, and there is no definable older age limit. As a result, screening criteria based on age, personal/family history, and ethnicity (eg, Ashkenazi Jewish or French Canadian) will result in some affected kindreds being missed. More inclusive screening criteria, as reflected in current guidelines (ie, no histologic limitations [except mucinous] and irrespective of family history, personal cancer history or age), will lead to the highest pick-up rate.

The testing guidelines from the Society of Gynecologic Oncology include any woman with high-grade EOC. Guidelines from the National Comprehensive Cancer Network are slightly broader in scope and call for testing any woman with invasive EOC (in a footnote, they state that BRCA-related cancers are associated with the nonmucinous types, but they do not specifically exclude the mucinous types).

Genetics Referral/BRCA Testing Rates and Barriers

The current paradigm is that testing is only performed subsequent to genetics referral. The referral rates in the older reports were in the 10% to 32% range (Table 1). The more restrictive testing guidelines used, which limited testing to those at “high risk,” as defined by a personal history of breast cancer or family history of breast and/or ovarian cancer, contributed somewhat to the under testing. Such restrictions will lead to 40% of inherited mutations being missed. However, even in the current era of more inclusive testing criteria, the majority of women are still not referred for genetic counseling/testing. Additional reasons for the failure to get to the genetics team and thus not be tested include: 1) process issues with genetic counseling/testing; 2) physician lack of knowledge; 3) patient unawareness of testing; and 4) patient refusal. Patients for the most part are not the problem. Understanding who gets tested identifies some of the barriers. Population-based referral rates in Ontario were low despite a publically funded system and universal access. Rates were higher at academic centers compared with those in the community and in the presence of a family history (47%–55% vs 13%–16%) or a personal history (62% vs 16%) of breast cancer. This impact of a positive family history
was similar at the Princess Margaret Hospital, an academic oncology center. Rates fell with increasing patient age. 5,53 Rates increased slightly in the years 2009 to 2011 but were still low at 29% to 48% (despite the guidelines now being more inclusive) at academic centers. 5,52,53,55 These latter findings implicate physicians as part of the problem, with possible reasons including nonawareness of guidelines, nonadherence to them, or lack of belief in them. System access issues will also impact testing. Rates are lower in non-Caucasians, those with lower educational levels, and those living farther away from the genetic counseling center. 4,52,55 Up to 55% of patients seen at academic centers are unaware of testing, and the percentage is greater among African Americans and those who are less well educated. 53,62 When informed about the value of testing, greater than 85% reported they would be tested if it had a therapeutic implication for them or a benefit to their family.5,53,56 In a small Australian study of 22 women, all reported that they would be tested if there was a therapeutic implication and all believed the advantages outweighed the disadvantages they cited were 1) fear of a second cancer; 2) cancer fear in their daughters; 3) insurance discrimination for their children; and 4) additive stress at an already difficult time. 52

Current guidelines only recommend who should be referred and tested but do not describe how to make that happen. 50,51 Process improvements (eg, having referral forms embedded in the electronic chart, having counselors in the oncology clinics, getting the oncology team to order the testing ahead of genetics referral [mainstreaming], and routine electronic notification of the treating physician that testing is available) potentially can improve testing. Data from 2 newer approaches have been reported. A 100% rate was achieved at the Royal Marsden Hospital in the United Kingdom, with motivated staff using mainstreaming. 57,63 The ENGAGE study (Evaluating a Novel Onco-Geriatric BRCA Testing Counseling Model Among Patients With Ovarian Cancer), which has now finished accruing, is a prospective observational cohort study that replicates this mainstreaming model whereby oncologists or nurses inform the patients about BRCA testing and its values/drawbacks and obtain their consent before BRCA testing. The genetics team then only routinely sees in consult those with a mutation or a variant requiring evaluation. Another interesting and relatively effective way to improve upon BRCA testing rates has been tested in London, Ontario. 5 A diagnosis of EOC automatically triggers referral to genetics with a confirmed subsequent appointment. Patients then can choose to “opt out.” In a preliminary analysis, 77% went for the appointment.

The goal should be 100% rates of BRCA testing in women with EOC. Improving test rates using the current germline testing model can only come about by improved physician/patient awareness in conjunction with improved processes. In addition, patients need an affordable and geographically accessible process. This can be achieved, as discussed above, by highly motivated groups but, because of the human element, cost constraints, and geographic issues, this is unlikely to happen outside such well-resourced centers of excellence. One way to guarantee 100% test rates for all patients with EOC would be to eliminate physician/patient awareness and geographic/system barriers by instead using “reflex” (ie, guaranteed) tumor BRCA testing as part of the pathologic pathway, akin to estrogen receptor status reporting in breast cancer, with subsequent germline testing in those patients in whose tumors a BRCA mutation was found. An analogous process is used in testing for Lynch syndrome in colonic and uterine cancers whereby initial abnormal mismatch-repair immunohistochemistry triggers genetic testing.

The momentum for tumor testing has come because of the availability of the PARP inhibitors. 64-67 Tumor testing will identify germline BRCA mutations, somatic BRCA
mutations, and also homologous repair deficiency (HRD) (see the section below on PARP inhibitors), from either phenotypic DNA patterns or specific gene profiles, all of which predict for a greater PARP inhibitor effect. As an additional benefit, this tumor testing could be used as a preliminary step in identifying those women with EOC who potentially carry an inherited BRCA mutation. Only those women with mutations in the tumor, of which 75% are germline and 25% are somatic, would then need formal germline testing.

Tumor testing, as the initial step, could reduce the workload for the genetic counseling team. The current paradigm is for all women with EOC to be seen and fully consented before testing. Switching to tumor testing, provided that it accurately identifies those women with germline BRCA mutations (ie, with minimal false-negative results), will reduce the workload significantly, because only the 20% or so who have mutations in the tumor will need to be referred for full counseling and subsequent germline testing. It is a little more complicated now, in that multigene panels designed to detect other possible inherited mutations have become the norm despite our as yet limited knowledge as to what to do with these results in practice. If these can be accurately identified in the tumor, then this is not an issue; if not, then continued germline testing for all will still be needed (ie, it does not solve the workload issue). Germline testing is simpler from a technical standpoint, in that large amounts of high-quality DNA with no fixation artifacts are generated. In contrast, with formalin-fixed, paraffin-embedded specimens, the quality and quantity of DNA is variable. Next-generation sequencing is needed to be able to detect mutations in a rapid, accurate, effective, and cost-effective manner in this setting of low amounts of poor-quality DNA. The problem is that tumors contain a mixture of cancerous and normal cells, cellularity can be low, and necrosis may be present. Expert pathologic help (ie, access to pathologists) is needed to identify the best areas for sampling. In addition, the fixation process can lead to denaturing, and these degraded DNA products can lead to false-positive reporting as mutations in the absence of the correct sequencing technology. Validated testing panels are needed to minimize the chance of false-negative results, and updated bioinformatics are needed for variant calling.

BRCA mutation testing is more complex per se, whether it is germline or somatic, because the gene is very large, and there are thousands of different potential mutations spread throughout the coding regions (ie, no mutation hotspots). The mutations vary from single nucleotide mutations, to insertions/deletions, to copy number variations. The sequencing approach adopted is all important, because false-negatives need to be kept at an absolute minimum. Copy number variations are a major issue in this regard. Weren et al used a combined technique of single molecular inversion probe-based next-generation sequencing combined with multiplex ligation-dependent probe amplification. Those authors achieved a 99.998% accuracy rate, with a false-negative reading of nucleotides of only 1 in 1 million. Finally, a stringent validation process is needed for laboratory accreditation, ie, use of next-generation sequencing, use of proven gene testing panels, and the availability and ability to use the bioinformatics needed for variant calling.

Currently, tumor testing is still not ready for routine, day-to-day use, but the technology is available as is the underlying laboratory expertise to allow its introduction in the near future. Until then, maximizing germline testing is paramount.

The Differential Effectiveness of Screening and Prevention

Advanced-stage, high-grade EOC is rarely cured by the combination of chemotherapy and surgery. Other approaches (eg, screening and prevention) are needed to reduce mortality. Unfortunately, early detection via screening has not yet been shown to be effective. Prevention is currently the only viable, efficacious strategy.

Screening

Successful screening detects cancer earlier, when it is more likely curable, reducing mortality. Studies evaluating the currently available tools for early detection have not shown benefit. The original pilot trial of 22,000 women used initial cancer antigen 125 (CA 125) levels followed by pelvic ultrasound if elevated. Median ovarian cancer-specific survival was improved, but this could reflect lead-time bias from earlier detection and not a real effect. There were slightly less EOC-related deaths: 9 in the screened cohort and 18 in the controls (not statistically significant; P = .83). Of note, more of the cancers were low grade in the screened cohort (69% vs 25%). Subsequently, 3 large, randomized studies have been reported. The Japanese study reported more stage I cancers (63% vs 38%) in the screened group, which was a prerequisite for screening effectiveness; however, this on its own was not proof of benefit, which would have required a reduction in mortality. However, only 62 cancers occurred in the 82,487 participants, and greater than one-half were low grade, with a greater incidence in the screened cohort. No mortality data have been reported. The Prostate, Lung, Colorectal, and Ovarian study (n = 78,216) reported neither down staging (only 15% were stage I) nor a mortality reduction. In contrast, the UK study, which excluded women thought to be at a higher risk of EOC based on a personal or familial cancer history, using a more nuanced analysis of CA 125 (including an increase within the normal
range over time as abnormal) demonstrated 11% and 15% mortality reductions in the 2 annual “screening” arms: ultrasound alone or combined CA 125 measurement and ultrasound, respectively. There were 649 deaths from EOC, in 0.34% and 0.29% of the nonscreened and screened populations, respectively. In total, 345,570 screens were carried out in 50,640 women, potentially saving 20 lives: a huge time commitment for the women and at great cost to the system, about £17 million, for little real benefit. Unfortunately, these “positive” mortality results may have been due to flaws that were unforeseeable during the design phase and to interpretation issues. Screening will detect them when smaller, but this does not increase curability. Benefit was only seen after an individual woman had been screened for 10 years or longer, raising the possibility that only biologically indolent cancers were those detected by screening. The second confounder is the removal of ovaries and fallopian tubes secondary to false-positive screening. Like “opportunistic salpingectomy,” this unintended consequence of screening, and not screening itself, prevents cancer and lowers mortality.

There are no high-level data on screening in a BRCA-mutated population. The available data do not indicate that screening is useful. The National Ovarian Cancer Early Detection program evaluated gynecologic examination every 6 months plus ultrasound in 4526 high-risk women (with a personal history of breast cancer, a family history of breast or ovarian cancer, or the presence of a BRCA mutation). In those women, 12,709 scans identified 98 adnexal masses, leading to 49 operations. Twelve cancers were present, and all were stage III, ie, they did not result in the prerequisite for screening success, which was down staging to stage I. In the UK Familial Ovarian Cancer Screening Study of women with a predicted risk of EOC of 10% or greater (essentially a family history or predisposing mutations), CA 125 was measured every 4 months and, if levels were normal, then ultrasound was carried out yearly, whereas, if levels were abnormal, then ultrasound occurred within 2 months. Thirteen screen-detected cancers were identified in 4348 women. The one diagnosed at the initial screen was stage III, and only 2 of the 12 discovered within a year of the prior screen were stage I.

In contrast, prevention in BRCA carriers is effective. Prophylactic/risk-reducing surgery is highly effective, more so than chemoprevention. Knowledge of risk factors for EOC and the likely sites of origin of the different histologies provide an underlying biologic rationale for prevention.

Surgical Prevention/Risk-Reducing Surgery
EOC rates increased with increasing age, early menarche, late menopause, infertility, and nulliparity and decreased with oral contraceptive use and multiparity. Endometriosis increased the risk of clear cell and endometrioid cancers but not HGS cancers. “Incessant ovulation” was the original unifying hypothesis used to explain these associations. Ovulation traumatizes the ovarian epithelium. More ovulations mean more damage and a greater risk of resulting malignant transformation. This hypothesis has since been revised, because the fallopian tube, not the ovary, is thought to be the usual site of origin for most HGS EOCs. Previously, fallopian tube cancer had been regarded as rare and, when diagnosed, its histology was HGS, often with adjacent precursor lesions (suggesting that it was the true primary site), and the fimbria was the usual location. Evolving evidence for a fallopian tube origin for most HGS is as follows: 1) The risk reduction with tubal ligation is from 40% to 60% for clear cell and endometrioid histologies but only 20% for HGS. Techniques that instead involve fimbrial excision hint at a greater risk reduction for HGS. The best data on absolute risk reduction come from the population-based Danish study. With tubal ligation, the risk reduction was 13% versus 42% with salpingectomy. The explanation is that clear cell and endometrioid cancers are ovarian in origin, arising from foci of endometriosis exfoliated from the endometrium that then transit the fallopian tube to reach the ovary. Tubal ligation prevents this. In contrast, ligation does not remove the fimbrial end of the fallopian tube, where HGS develops with subsequent seeding to the ovary. 2) Further evidence came from risk-reducing bilateral salpingo-oophorectomy (BSO) in BRCA mutation carriers. There was a 2.7% rate of cancer in the 3030 prophylactic surgeries, of which 70% were tubal in origin. Premalignant changes in the tubal epithelium were identified in another 3%. Removing only the ovaries and leaving the fallopian tubes behind resulted in an increased risk of subsequent cancers (11% vs 5%).

In view of these discoveries, pathologic techniques have changed to include extensive fimbrial sectioning. Serous tubal intraepithelial neoplasia is now recognized in up to 40% of women who would otherwise be regarded as having ovarian or primary peritoneal cancers. These serous tubal intraepithelial neoplasia is fimbrial in location with the same p53 mutations as the invasive cancers. The current explanatory hypothesis that links an increased number of menstrual cycles to a fallopian tube origin for HGS is that both ovulation and retrograde menstruation lead to an inflammatory environment in the distal fallopian tube that is cancer-promoting.

Targeting BRCA mutation-carrying members of ovarian cancer kindreds for surgical prevention is not a new concept and is guideline recommended. The lifetime risk of developing EOC for those with BRCA1 and BRCA2 mutations is 35% to 60% and 12% to 25%, respectively.
Risk-reducing surgery potentially could prevent 90% of these EOCs, although the actual reported rates, from short follow-up, are from 72% to 80%. Three more pieces of information help in understanding the current recommendation for surgical prevention, which is BSO: 1) the low-grade histotypes, likely not \( \text{BRCA1} \) related (ie, endometrioid, clear cell, and mucinous), are ovarian in origin; 2) \( \text{BRCA} \) mutations increase the risk of breast cancer, and oophorectomy diminishes the risk of breast cancer; and 3) the adverse effects of premature menopause. Relying on the fallopian tube theory of origin of HGSs, some have suggested that salpingectomy alone would be sufficient. This would avoid oophorectomy-induced premature menopause with, all of its negative consequences, but would lose the positive benefit of breast cancer prevention. Current guidelines recommend BSO, the reasons for this are: 1) not all HGS cancers originate in the fallopian tube; 2) salpingectomy will not prevent those histologies that are ovarian in origin (ie, clear cell, endometrioid, and mucinous); 3) salpingectomy has no impact on breast cancer prevention; and 4) lack of estrogen can be treated with topical or systemic estrogen replacement. There is a concern that such replacement therapy could increase breast cancer risk, similar to oral contraceptives, which conferred a 20% increased risk in a meta-analysis, with a similar effect size in a \( \text{BRCA} \) mutation carrier population. However, no study has demonstrated an increased breast cancer risk with “replacement” therapy in \( \text{BRCA} \) carriers after BSO. Risk-reducing BSO in those carrying \( \text{BRCA} \) mutations is recommended after child bearing by age 35 to 40 years, because breast cancer and EOC can occur in the late 30s. Some reports have shown that oophorectomy has an additive advantage by reducing the risk of breast cancer by 40% and 60% in women with \( \text{BRCA1} \) and \( \text{BRCA2} \) mutations. However, bilateral mastectomy provides greater risk reduction, up to 90%. An alternative to up front salpingo-oophorectomy for EOC prevention would be initial salpingectomy followed by delayed oophorectomy at age 50 years. Because \( \text{BRCA2} \)-related EOC occurs later, it may also be reasonable to delay risk-reducing surgery until ages 45 to 50 years in this group.

Chemoprevention

Chemoprevention with oral contraceptives, metformin, or aspirin is being investigated. Phase 3 data are unavailable. The combined contraceptive pill decreased the risk of EOC, in contrast to the increased risk for breast cancer, in the general population. The average risk reduction was 5% to 8% per year, with 10 years of use reducing the risk by 50%. Progestin-only products were not protective. A multistudy analysis of histology-specific outcomes reported protection against serous, clear, and endometrioid tumors, but not against mucinous tumors. In those with \( \text{BRCA} \) mutations, there was a 50% reduction in the rate of subsequent EOC with any prior use of the combined contraceptive pill, and the reduction increased to 60% if used for 6 or more years. In a recent meta-analysis, the risk reduction with use for at least one year was from 33% to 80% for \( \text{BRCA1} \) and from 58% to 63% for \( \text{BRCA2} \). Data on metformin are scant. Metformin use has been shown to decrease the risk of EOC by 43% to 50%. In a meta-analysis of 12 case-control studies, aspirin reduced the risk of EOC by 10%, which increased to 20% in daily users. Three of those studies looked at daily, low-dose usage, and the risk reduction was 34%. Risk reduction was seen for serous, endometrioid, and mucinous subtypes. No data specific to \( \text{BRCA} \) carriers are available.

Cost of Surgical Prevention Compared With Treating Ovarian Cancer

Preventing EOC, as opposed to treating it with surgery and chemotherapy, likely represents better “value for money.” This “value” can be reported in 2 ways: 1) budget impact (ie, the actual cost); or 2) cost effectiveness (ie, putting a dollar figure to each life-year saved, which allows for a comparison with other therapies [eg, renal dialysis]). There are 2 published cost-effectiveness analyses. The UK study assumed that all women with EOC would have germline \( \text{BRCA} \) testing and that 88% and 30% of affected carriers would undergo risk-reducing salpingo-oophorectomy and mastectomy, respectively. All costs were included, ie, testing, risk-reducing or therapeutic surgeries, chemotherapy, and palliative care. The incremental cost-effectiveness ratio (ICER) was £4339 per quality-adjusted life-year gained, which was well below the UK willingness-to-pay threshold of £20,000. The results were predominantly driven by reductions in the number of cases of ovarian and breast cancers and the resulting reduced mortality. In the other report, US costs were used. The cost of 3 different \( \text{BRCA} \) testing strategies, based on different criteria for testing the index case, followed by testing of family members with risk-reducing mastectomy/salpingo-oophorectomy in carriers, was compared with treating the cancers surgically (no chemotherapy) once they developed. ICER values ranged from US $32,000 to $149,000 per year of life gained. The most cost-effective strategy was if \( \text{BRCA} \) screening was limited to those of Ashkenazi Jewish ancestry or if there was a personal or family history of breast cancer/EOC. The highest ICER was for testing any invasive, non-mucinous EOC. There is no generally accepted ICER that represents value for money, but $100,000 is commonly used in North America. The estimates were potentially “worst-case,” because 1) they assumed low rates of \( \text{BRCA} \) testing and poor compliance with risk-reducing surgery, and 2) the

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cost of subsequent chemotherapy and palliative care was not included.

Budget impact, ie, what it actually costs, is more relevant to the payer. Costs will only increase as the population both increases and ages and therapy gets more expensive. US estimates of the direct costs for all cancers are for a 27% increase to $158 billion in 2020. Factoring in increased drug costs resulted in a 39% increase. Such costs are not sustainable in any healthcare system. Cost estimates also ignore the indirect costs, similar to the direct costs, to the patient/family and society because of lost productivity. There are only a few published reports of the costs of treating EOC. US population-based data indicate that these costs are from $82,000 to $99,000 in the first year (surgery and chemotherapy driving the cost), $8000 per subsequent year, and from $100,000 to $150,000 in the last year of life. In a similar analysis, Canadian costs were about 50% less. Patient-specific data from Australia in 2008 estimated that the total treatment cost over 2.5 years in 85 women would be 4 million Australian dollars. Canadian data from 40 women treated between 1989 and 1992 had median costs from commencing second-line or third-line treatment to death or last follow up of C$37,000 (range, C$5000–C$163,000). The US costs of prevention for both EOC and breast cancer are more precise. Prophylactic mastectomy with reconstruction, BSO, and hospitalization costs $28,000, with ancillary costs, including BRCA testing, of $2000, for a total of $30,000 per individual. Our own very preliminary calculation of the cost savings arising from preventing EOC in Canada, using US prices, is for a potential cost saving of $11 million per year (unpublished observations). Figure 1 is a flow diagram of the numbers of women involved. It assumes 100% testing of women with EOC for BRCA and 2 female first-degree relatives (each of whom has a 50:50 risk of inheriting the gene), then 100% testing rates in their first-degree relatives, followed by 100% rates of risk-reducing salpingo-oophorectomy in all carriers. This optimistic goal would prevent 124 new cases of EOC per year. A total of 306 risk-reducing operations would be carried out to try to prevent 138 cancers at a cost per person of $30,000, for a total of $9 million. These 306 operations would prevent 90% of EOCs from occurring. In contrast, treating these 124 cancers (90% of 138) would cost conservatively $150,000 each, for a total of $20 million, for a potential cost saving of $11 million.

Therapeutic Benefit Resulting From BRCA Testing in Women With EOC

In this review, it is not possible to discuss in detail all aspects relating to the use of PARP inhibitors. Instead, the important components are summarized below. For the reader who wishes more detailed information, reviews discussing their mechanism of action, the concept of “synthetic lethality,” resistance mechanisms, activity, and toxicity are referenced. High-grade EOC is often associated with deficient double-stranded DNA repair, and multiple defective genes have been identified. The most common is mutated BRCA. Both copies of the BRCA gene need to be mutated for loss of function. In the inherited (ie, germline scenario), one mutation is inherited, and the other is acquired. Approximately 20% of high-grade EOCs are BRCA-related, 15% are germline, and 5% are somatic (both mutations acquired). Another 30% of those with high-grade EOC have other causes of DNA repair deficiency, so-called BRCAness or HRD. This will likely provide an additional therapeutic target. Single-stranded DNA breaks (SSBs) are estimated to occur up to 20,000 times per day in any individual. PARP is a nuclear protein that binds to SSBs and acts as a positive signal to initiate base and nucleotide excision repair. PARP inhibitors interfere with this process. These SSBs as a result cannot then be repaired and are converted during replication to double-strand breaks (DSBs). Such DSBs are lethal unless accurately repaired via homologous repair. If there is defective homologous repair, far less accurate mechanisms predominate, with a greater chance of apoptotic cell death. BRCA/BRCAness-driven, high-grade
EOC has normal SSB repair but deficient homologous repair. On its own, deficient homologous repair matters less, because it is a "back up" pathway for the SSB repair process. However if PARP is also inhibited, then homologous repair becomes all important. This is an example of "synthetic lethality," wherein an abnormality in one pathway alone is nonlethal, but when a second, interlinked pathway (eg, PARP) is targeted, it results in cancer cell death. Normal cells are unaffected, because they only have one mutated copy of the gene.

The single-agent activity of PARP inhibitors ranges from 26% to 67% in BRCA1-mutated individuals and up to 76% if CA 125 responses are included. Combining the results from these studies, the response rate was 36%, and it decreased as lines of prior therapy increased and as the patient’s sensitivity to platinum decreased. The side effects of these oral drugs are generally mild and easily managed by dose delays or reductions. Common side effects include nausea, diarrhea, anemia, and thrombocytopenia. Myelodysplasia is a rare but usually fatal complication and occurred in 1.4% and 1.1% of patients receiving niraparib or placebo, respectively, in the NOVA study (niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer). Olaparib and rucaparib have US regulatory approval in those with known BRCA mutations as monotherapy in third or greater relapse (ie, knowledge of BRCA mutation status is required to ensure access to these drugs). Ongoing studies are seeking evidence that the larger “BRCAness” group can also benefit.

Approval on a worldwide basis is more common as maintenance therapy after successful retreatment with platinum-based therapy in those with sensitive disease (defined as EOC relapsing ≥ 6 months after completing prior treatment). Three randomized studies of maintenance PARP inhibitor therapy have been published, and a fourth has just been presented at a conference. Study 19 was a randomized phase 2 study comparing maintenance olaparib versus placebo after successful second-line chemotherapy for platinum-sensitive, HGS EOC. It was not powered for overall survival (OS), and there was a 20% rate of crossover to olaparib, which will confound OS analysis. BRCA1 mutation status did not need to be known for entry into the study. The median progression-free survival (PFS) was superior with olaparib at 8.4 versus 4.8 months (hazard ratio [HR], 0.55) in all patients and 11.2 versus 4.3 months (HR, 0.18) in the BRCA1-mutated subset. OS was 29.8 versus 27.8 months (HR, 0.72) in all patients and 34.9 versus 30.2 months (HR, 0.62) in the BRCA1-mutated subset. Study 41 confirmed these results in a similar population, but the comparison was between chemotherapy with olaparib followed by maintenance olaparib versus chemotherapy alone. PFS was 12.2 versus 9.6 months (HR, 0.51) in all patients and was not reached versus 9.7 months (HR, 0.21) in the BRCA1-mutated subset. The OS curves were overlapping. These data led to regulatory approval in those with a BRCA1 mutation. SOLO2, an appropriately powered, phase 3 study, reiterated the Study 19 design but are now using a tablet formulation at a dose of 300 mg twice daily instead of capsules at 400 mg twice daily. PFS increased from 5.5 to 19.1 months (HR, 0.3; P < .0001). The NOVA study compared niraparib versus placebo in a platinum-sensitive, relapsed population. The presence of a BRCA1 mutation was not required for study entry. PFS results were similar to Study 19 results in those with a germline BRCA1 mutation (PFS, 21 vs 5.5 months; HR, 0.27). Benefit was also seen in patients with an HRD profile (PFS, 13 vs 4 months; HR, 0.38) and in those without HRD (PFS, 7 vs 4 months; HR, 0.56). The current data are too immature for an OS analysis. US Food and Drug Administration approval was granted in March 2017 and did not require a BRCA1 mutation to be present. However, because these drugs are still very expensive, it is likely that many jurisdictions will limit their use to those with a BRCA1 mutation, because this is where the absolute benefit is the greatest. Knowledge of the patient’s BRCA1 status will still be needed. PARP inhibitors improve short-term and median-term outcomes but are not a cure. Almost inevitably, resistance develops.

Knowledge of BRCA1 status may also impact routine chemotherapy decisions. A retrospective analysis using immunohistochemistry as a surrogate for BRCA1 mutation demonstrated that it predicted for a markedly greater OS benefit with intraperitoneal-containing therapy. Because intraperitoneal chemotherapy is used as first-line treatment, knowledge of BRCA1 status is needed as early as possible, preferably in the tumor so that both germline and somatic mutation status is known.

Conclusions

Referral rates for genetic counseling and subsequent BRCA1 mutation testing are low. Failure to test for BRCA1 mutation leads to: 1) missed therapeutic opportunities for women with EOC to receive PARP inhibitors, which can be used as either maintenance therapy earlier in the disease course after successful retreatment with chemotherapy or as stand-alone treatment later on; and 2) missed prevention opportunities for their families. Lack of knowledge on the part of physicians and patients and process issues represent the major barriers. In institutions with motivated individuals, these barriers have been fixed with simple process modifications. To ensure testing for the wider population (ie, the geographically dispersed or those not attending centers of expertise), a switch to “reflex” tumor BRCA1 testing of the initial pathologic specimen, akin to estrogen receptor or Lynch syndrome testing, would be a possible solution to ensure that all women are tested without exception and in a timely fashion.
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