Review Article
Clinical Considerations of BRCA1- and BRCA2-Mutation Carriers: A Review

O. Bougie1 and J. I. Weberpals2,3

1 The Department of Obstetrics, Gynaecology, and Newborn Care, The Ottawa Hospital, Ottawa, ON, Canada K1H 8L6
2 Centre for Cancer Therapeutics, Ottawa Hospital Research Institute, The Ottawa Hospital, Ottawa, ON, Canada K1H 8L6
3 The Division of Gynaecologic Oncology, The Ottawa Hospital, Ottawa, ON, Canada K1H 8L6

Correspondence should be addressed to J. I. Weberpals, jweberpals@ottawahospital.on.ca

Received 2 April 2011; Accepted 16 June 2011

Academic Editor: Bernardo Garicochea

Copyright © 2011 O. Bougie and J. I. Weberpals. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Individuals who carry an inherited mutation in the breast cancer 1 (BRCA1) and BRCA2 genes have a significant risk of developing breast and ovarian cancer over the course of their lifetime. As a result, there are important considerations for the clinician in the counseling, followup and management of mutation carriers. This review outlines salient aspects in the approach to patients at high risk of developing breast and ovarian cancer, including criteria for genetic testing, screening guidelines, surgical prophylaxis, and chemoprevention.

1. Introduction

Research into the hereditary breast and ovarian cancer genes, breast cancer 1 (BRCA1) and BRCA2, is an area of ongoing discovery in the molecular biology of cancer. For clinicians, it can be an overwhelming challenge to keep a breast with the latest studies and incorporate the most up-to-date evidence into their practice. There are many unique considerations that should be addressed when approaching patients with a predisposition to hereditary breast and ovarian cancer, including counseling, followup and management of mutation carriers. It is also important to understand which high-risk patients should be referred for genetic counseling for consideration of BRCA1/2 gene testing, an approach which is often underutilized in physicians’ practices [1]. In this review, the most relevant and current studies in hereditary breast and ovarian cancer epidemiology, screening, and prevention are outlined to guide the clinician in the management of high-risk individuals. Also highlighted is the role of BRCA in sporadic breast and ovarian cancer and the emergence of novel targeted therapies such as poly(ADP-ribose) polymerase inhibitors (PARPi) in BRCA1-deficient patients.

2. Cancer Risk in BRCA1- and BRCA2-Mutation Carriers

In the general population, a woman’s lifetime risk of breast cancer is 1 in 8 [2], and the risk of ovarian cancer is 1 in 70 [3]. It is estimated that a BRCA1/2 mutation is found in 2–6% of breast cancer patients [4–6] and 10–15% of epithelial ovarian cancer patients [7–9]. In all women, the prevalence of a BRCA1 mutation is 1 in 800 to 1 in 1400 and the prevalence of BRCA2 mutation is slightly lower at 1 in 450 to 1 in 800 [6, 10, 11]. The lifetime risk of breast cancer in BRCA1- and BRCA2-mutation carriers is 45–80% [12, 13]. The lifetime risk of ovarian cancer is 45–60% for BRCA1-mutation carriers and 11–35% for BRCA2-mutation carriers [12–14]. A number of studies examining the incidence of breast cancer have reported a lower likelihood amongst BRCA2-mutation carriers compared to BRCA1-mutation carriers [13, 15]. Among the Ashkenazi Jewish population, the prevalence of a BRCA1/2 mutation is as high as 2.5% [16]. In breast cancer patients of Jewish origin, the BRCA1 mutation rate is increased at 10% compared to the general breast cancer population [16]. Even more significant, among Jewish woman with ovarian cancer, there is an estimated 29% risk of carrying a BRCA1 or BRCA2 mutation [17].
Cancer risk has been shown to increase substantially with each decade of life for BRCA1- and BRCA2-mutation carriers [12]. A woman with a BRCA mutation has a 20% chance of developing breast cancer by the time she is 40 years old. However, the risk increases to 37% by the age of 50, 55% by the age of 60, and is over 70% by the age of 70. For BRCA1-mutation carriers, the risk of ovarian cancer rises sharply in the 4th decade of life and then increases progressively by approximately 10% with each subsequent decade of life.

Individuals who have a known BRCA mutation are also at risk for other malignancies. Approximately 30% of women with fallopian tube cancer have a mutation in BRCA1 or BRCA2 [18]. In addition, the inheritance of a BRCA1 mutation has been linked with an increased risk of endometrial, pancreatic, and prostate cancer [19, 20]. Specifically, the increased risk of prostate cancer is associated with the BRCA1 4153delA and the C61G mutations [21]. A BRCA1 mutation has been shown to be associated with an increased risk of early onset colon cancer in a defined population but does not seem to increase the overall risk of colon cancer [22]. Patients with a BRCA2 mutation have an increased risk of prostate and pancreatic cancer [23–25]. An earlier study by the Breast Linkage Consortium reported an increased incidence of gallbladder, bile duct, stomach cancer, and malignant melanoma in BRCA2-mutation carriers, yet recent evidence has not substantiated this association [26]. Only the study by Debniak et al. [27] demonstrated that one common variant of the BRCA2 gene, the N991D variant, is linked with an increased malignant melanoma risk.

3. Clinicopathologic Features of Hereditary Breast and Ovarian Cancer

There are several distinguishing clinical and pathologic features of breast and ovarian cancer related to BRCA mutation status. The features of hereditary breast and ovarian cancers are summarized in Table 1. Compared to nonhereditary breast cancer patients, BRCA1-mutation carriers are diagnosed with breast cancer at a younger age [18, 28], and up to 80% of cancers occur prior to menopause [18, 29]. At initial presentation, hereditary breast cancer patients have a higher incidence of bilateral breast cancer, poorly differentiated tumours, and lymph node positivity [18]. BRCA1-associated tumours are more often estrogen receptor (ER) [18], progesterone receptor (PR) [30], and human epidermal growth factor 2 (HER2) negative compared to their sporadic counterparts [31]. BRCA2 tumours, in turn, demonstrate more ER positivity [18], while the rate of PR and HER2 receptor positivity is similar to that of sporadic tumours [30]. BRCA1 tumours are more likely to be p53 positive, while BRCA2 tumours are usually p53 negative [32]. Lee et al. [33] conducted a recent systemic review to assess the survival pattern of breast cancer patients with BRCA1 and BRCA2 mutations and found that the BRCA1-mutation carriers had a significantly decreased progression-free as well as overall survival compared to non-BRCA1-associated breast cancer patients, while BRCA2 mutations carriers had survival patterns comparable to the general breast cancer patients.

<table>
<thead>
<tr>
<th>Pathological features</th>
<th>Breast cancer</th>
<th>Ovarian cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ differentiation</td>
<td>BRCA1 ↓</td>
<td>BRCA1 ↓</td>
</tr>
<tr>
<td>↑ bilateral tumours</td>
<td>BRCA2 ↔</td>
<td>BRCA2 ↔</td>
</tr>
<tr>
<td>↑ # lymph nodes</td>
<td>BRCA1: ↑</td>
<td>BRCA2: similar to sporadic tumours</td>
</tr>
<tr>
<td>Receptor status</td>
<td>ER−/PR−/HER2−</td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>↓ progression</td>
<td>↑ progression-free</td>
</tr>
<tr>
<td></td>
<td>free-survival</td>
<td>survival</td>
</tr>
<tr>
<td></td>
<td>↓ overall survival</td>
<td>↑ overall survival</td>
</tr>
</tbody>
</table>

Table 1: Clinicopathologic characteristics of hereditary versus sporadic breast and ovarian cancer.

There is emerging evidence to suggest that BRCA1-linked breast cancer patients treated with chemotherapy regimens containing platinum or doxorubicin and cyclophosphamide have a high likelihood of achieving pathologic complete remission [34].

BRCA1-mutation carriers are diagnosed with ovarian cancer at a younger age (average age 52) compared to BRCA2-mutation carriers (age 62) and sporadic cases (age 63) [35]. In contrast to breast cancer, BRCA-associated and sporadic ovarian tumours have been reported to have similar clinicopathological features (histology, grade, and stage at diagnosis) [35]. While Boyd et al. [35] found comparable ovarian tumour histology between BRCA-associated and sporadic ovarian tumours, Piek et al. [36] found a higher incidence of papillary serous histology among BRCA-associated ovarian tumours. Patients with BRCA1- or BRCA2-linked ovarian cancers were shown to have a longer disease-free interval following chemotherapy and improved survival compared to patients with sporadic ovarian cancer ovarian cancer [35, 37, 38].

4. Pathophysiology of BRCA-Mutations

BRCA1 and BRCA2 are tumour suppressor genes located on chromosome 17q21 [39] and 13q12-13 [40], respectively. Hundreds of different mutations can occur within a gene leading to protein inactivation, with the genetic defect resulting most commonly in a truncated protein product. However, a number of missense mutations and large gene rearrangements can also cause a mutant phenotype [41]. Mutation types tend to correspond with various populations and ethnicities. For instance, in African Americans, 25% of BRCA1 mutations were frameshift, 38% missense, 13% nonsense, and 25% splice mutations, while in non-Hispanic white patients, 36% of BRCA1 mutations are frameshift, 14% are missense, 29% nonsense, and 21% are splice mutations [5]. In the Ashkenazi Jewish population, there are three distinct mutations in BRCA1 and BRCA2 genes that are responsible for the majority of the BRCA mutations seen...
in this population; namely, these are the \(BRCA1\) 185delAG, \(BRCA1\) 5382insC, and \(BRCA2\) 6174delT mutations [42].

The process of carcinogenesis is often initiated by repeated episodes of DNA damage, which can occur secondary to a number of stressors, such as reactive oxygen species, cytotoxic chemotherapy, and ionizing radiation. DNA double-strand breaks (DSB) are particularly harmful, as both complementary strands of DNA are damaged leading to replication arrest. \(BRCA1\) and \(BRCA2\) play an integral role in the response to cellular stress, the localization to sites of damaged DNA, and the activation of DNA repair processes. In particular, \(BRCA1\) and \(BRCA2\) usually repair DSB through the conservative mechanism of homologous recombination [43–45]. Central to the process of homologous recombination, the \(BRCA\) proteins bind an essential recombinant, RAD51, and mutations affecting the binding ability of \(BRCA1/2\) to RAD51, which lead to genomic instability [45–47]. While \(BRCA2\) is primarily involved in homologous recombination repair, \(BRCA1\) is involved in alternate DNA repair processes such as nonhomologous end joining, which is error prone [48]. \(BRCA\) deficiency ultimately leads to the accumulation of genetic alterations as a result of the failure of cells to arrest and repair DNA damage or to self-destruct, resulting in neoplastic progression.

### 5. Genetic Testing

Identifying patients that should be considered for genetic testing is an important aspect of practice that is often overlooked [1]. Pedigree analysis can be used in conjunction with available risk assessment models to determine whether a family is suspected of having hereditary, familial, or sporadic cancer [49]. \(BRCA1\) or \(BRCA2\) gene mutations are inherited in an autosomal dominant fashion. The Manchester scoring system is a risk assessment model which may be applied to evaluate an individual’s risk of having a \(BRCA1\) or \(BRCA2\) mutation [50]. The scoring system considers the age of cancer diagnosis as well as a family history of female breast, male breast, ovarian, prostate, and pancreatic cancer in the risk stratification model. Recently, breast cancer pathology has been included in this model to increase predictive accuracy. It is considered the most sensitive method in predicting mutations in both \(BRCA\) genes [49, 50]. The disadvantage of the model is that it has been shown to lead to over-referral for genetic testing.

Specific criteria for referral for genetic testing vary amongst institutions but are all based on clinical characteristics that increase one’s chance of developing a hereditary breast and/or ovarian cancer. Clinical features that should prompt one to consider a genetic counseling referral are outlined in Table 2 [49]. It is important to include genetic counseling in the cancer risk assessment process [51]. A number of reports propose criteria for referral for genetic counseling regarding hereditary risk of breast and/or ovarian cancer, including the National Comprehensive Cancer Network (NCCN) [52], the U.S. Preventive Services Task Force (USPSTF) [53], American Congress of Obstetricians and Gynecologists (ACOG) [54], the National Institute for Health and Clinical Excellence (NICE) [55], and the European Society for Medical Oncology (ESMO) [56]. Guidelines in most countries use a 10–20% threshold of detecting a mutation in \(BRCA1/2\) within a given family before mutational analysis is considered. A recent study analyzed the cost effectiveness of screening for cancer susceptibility genes and reported that when one’s risk of having a mutation is at only 10%, genetic screening is not cost effective [57].

### 6. Surveillance

#### 6.1. Breast Cancer

The NCCN recommends that breast cancer screening for \(BRCA1\)- and \(BRCA2\)-mutation carriers should include annual mammography and clinical breast examination every 6–12 months, starting at age 25 or individualized based on one’s family history [52]. In Europe, ESMO also recommends screening with annual mammography and MRI starting at age 25–30 [56]. Ultrasound is generally not recommended as part of a screening algorithm but is utilized when mammography or MRI reveals abnormalities. The addition of ultrasound to screening mammography will yield an additional 1.1 to 7.2 cancers per 1000 high-risk women but will also substantially increase the number of false positive tests [58].

Several studies have confirmed that MRI has a higher sensitivity for the detection of invasive breast cancer compared to conventional screening [59, 60], and this has been reported to be most applicable to \(BRCA1/2\)-mutation carriers [59]. Rijnsburger et al. [60] found that 45.8% of breast cancers in \(BRCA\)-mutation carriers and 30.8% of breast cancers in \(BRCA2\)-mutation carriers were detected only by MRI. However, MRI specificity for cancer detection is lower than that of conventional screening, thereby resulting in more unnecessary biopsies [61]. Thus, it may be prudent to use MRI in conjunction with conventional imaging in screening women with a high genetic risk of breast cancer. In the study by Trecate et al. [61], it was advised to consider ultrasound evaluation when MRI yielded the only positive diagnostic result.

Lord et al. [62] conducted a systematic review to assess the effectiveness of adding MRI to mammography with or without ultrasound and clinical examination in screening young women at high risk for breast cancer. Consistent evidence in a number of studies suggests that adding MRI provides a highly sensitive screening strategy (sensitivity
range: 93–100%) compared to mammography alone (25–59%), or mammography and ultrasound with or without clinical examination (49–67%). In considering the use of MRI, there are no studies which have assessed whether MRI surveillance reduces the rates of advanced breast cancer or mortality. Thus, the effectiveness of MRI on improved survival stems from the assumption that earlier detection improves survival.

6.2. Ovarian Cancer. To date, no effective screening strategy has been found for either sporadic or hereditary ovarian cancer. At this time, the NCCN [52] and ACOG [54] guidelines suggest that for patients with BRCA1 or BRCA2 mutations, pelvic ultrasound and CA125 every 6 months may be considered for the detection of early ovarian cancer. It is recommended that screening be initiated at age 35 or 5–10 years prior to the age of the earliest ovarian cancer diagnosis in an individual’s family.

Studies which have examined ovarian cancer screening specifically in BRCA1/2-mutation carriers did not find that pelvic ultrasound and CA125 were effective as a screening method [63–66]. In a retrospective audit of 341 asymptomatic, high-risk women enrolled for ovarian cancer screening, 31 women underwent exploratory surgery because of abnormal findings at surveillance. At surgery, 3 cancers were diagnosed (2 ovarian, 1 endometrial) and 28 women were cancer free, suggesting that the diagnostic yield in screening women with a hereditary predisposition is very low [65].

The largest of the ovarian cancer screening studies for BRCA1-mutation carrier studies included 981 women with BRCA1/2 mutations who underwent screening with annual pelvic ultrasound and CA125 [63]. The study concluded that there was no improvement in survival in the cohort of patients that underwent screening when compared to an unscreened population.

Importantly, women should be made aware of symptomatology associated with ovarian cancer which should prompt medical evaluation. Symptoms associated with ovarian cancer include abdominal bloating, urinary urgency and/or frequency, increased abdominal girth, and early satiety [67]. Goff et al. attempted to develop a symptom index for the diagnosis of ovarian cancer by using the symptoms previously described with a time frame of symptoms occurring more than 12 days per month and less than 1 year in duration. The symptom index shows promise for advanced stage ovarian cancer diagnosis, with a sensitivity of 79.5% and specificity nearing 90%. However, for the detection of early stage disease, the sensitivity value was only 56.7%.

7. Surgical Prophylaxis

Women with a known BRCA1 or BRCA2 mutation should be offered prophylactic mastectomy and bilateral salpingo-oophorectomy (BSO) in order to decrease the risk of breast and ovarian cancer. Bilateral mastectomy decreases breast cancer risk by 90% [68, 69], and BSO decreases the relative risk of ovarian and fallopian tube cancer by 80% [70, 71]. However, BSO does not affect the risk of primary peritoneal cancer [71]. BSO also leads to a reduction of estrogen stimulation on breast tissue, leading to a 50% relative risk reduction in the development of breast cancer [71]. The NCCN recommendation is that mutation carriers are offered BSO by age 40 or after they have completed childbearing [52]. Similarly, ESMO recommends prophylactic BSO after age 35 and when childbearing decisions are complete [56]. Overall, counseling on risk-reducing surgery should take into account the cumulative risk of developing breast and ovarian cancer with each decade of life as well as a woman’s reproductive plans.

To quantify the protective effect of risk-reducing surgery, Domchek et al. [72] completed a large prospective, multicenter cohort study which included 2482 women with BRCA1 or BRCA2 mutations ascertained between 1974 and 2008. There were no breast cancers diagnosed in the 247 women with prophylactic mastectomy compared with 98 breast cancers diagnosed in 1372 women who did not undergo a mastectomy. Compared with women who did not undergo risk-reducing BSO, undergoing BSO was associated with lower all-cause mortality (10% versus 3%; HR, 0.40 [95% CI, 0.26–0.61]). In high risk women who are diagnosed with breast cancer, a contralateral prophylactic mastectomy in addition to the therapeutic mastectomy is associated with a significant survival advantage [73]. It has been reported that only approximately 20–25% of eligible patients choose to proceed with a prophylactic mastectomy and 50–55% undergo prophylactic BSO [74, 75].

To compare the effectiveness of prophylactic surgery versus breast screening on the reduction of cancer mortality, Kurian et al. [76] developed a unique computational model. Using this model, a 25-year-old BRCA1/2-mutation carrier was analyzed to compare enrolment in a breast screening program with annual mammography and MRI from age 25 to 69, with prophylactic mastectomy at various ages +/- BSO at age 40 or 50. With no intervention, survival probability by age 70 was estimated at 53% for BRCA1 and 71% for BRCA2 mutation carriers. The most effective single intervention for BRCA1-mutation carriers was a BSO at age 40, yielding a 15% absolute survival gain. For BRCA2-mutation carriers, the most effective single intervention was a prophylactic mastectomy, yielding a 7% survival gain if performed at age 40. The combination of prophylactic mastectomy and BSO at the age of 40 improved survival more than any single intervention, yielding a 24% and 11% survival gain for BRCA1- and BRCA2-mutation carriers, respectively.

When choosing a surveillance option, patients must be cautioned that premalignant and malignant changes can occur in spite of normal radiological investigations. When prophylactic mastectomy samples were compared between BRCA1-mutation carriers and healthy controls, there was an increased incidence of pre-malignant and malignant lesions detected in BRCA1 prophylactic mastectomy samples (42.3 versus 5.8%; P < 0.001) [77]. Similarly, approximately 6%
of BRCA1 carriers and 2% of BRCA2 carriers who undergo prophylactic BSO will have occult carcinomas [78]. Hirst et al. [79] examined the tumours of 45 BRCA-mutation carriers who underwent a prophylactic BSO and discovered 5 occult malignancies. Recently, insight into the pathogenesis of hereditary of ovarian cancer has revealed that some cancers believed to be of primary ovarian origin, in fact, arise from the fallopian tube [80]. As such, Greene et al. [81] have suggested that a bilateral salpingectomy with ovarian retention might serve as a temporary measure while definitive risk-reducing surgery is being contemplated in women who have completed childbearing.

8. Chemoprophylaxis

8.1. Tamoxifen. Tamoxifen is a selective estrogen receptor modulator that has an inhibitory effect on estrogen receptors in breast tissue and a proliferative effect in the endometrium. BRCA-mutation carriers may be offered tamoxifen for primary prevention of breast cancer [52]. However, since BRCA1-mutation carriers are more likely to develop ER-breast tumours, there may be little rationale to support tamoxifen for the prevention of breast cancer in this population. The effect of chemoprophylaxis with tamoxifen in patients with a hereditary predisposition has been extrapolated from studies examining the risk of developing contralateral breast cancer in BRCA1/2-mutation carriers who were treated with tamoxifen after their primary breast cancer diagnosis, as well as tamoxifen use in the general population.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) initiated the breast cancer prevention trial (P-1) which enrolled 13,388 high risk patients to determine the efficacy of tamoxifen in reducing breast cancer risk [82]. This study substantiated that 20 mg per day of tamoxifen for 5 years reduced the risk of primary invasive breast cancer by 49%. Genomic analysis of BRCA1 and BRCA2 for 288 women who developed breast cancer was completed after entry into the trial [83]. There were 19 patients with BRCA1 or BRCA2 mutations. 83% of BRCA1 breast tumours were ER−, whereas 76% of BRCA2 breast tumours were ER+. It was concluded that tamoxifen reduced breast cancer incidence among BRCA2 carriers by 62%, similar to the reduction of ER+ breast cancer among all women in the breast cancer prevention trial. In contrast, tamoxifen use did not reduce breast cancer incidence among women with inherited BRCA1 mutations. However, the results of the study were limited by the small number of patients in the cohort.

Gronwald et al. [84] completed a case control study looking at BRCA1- and BRCA2-mutation carriers who developed bilateral breast cancer (n = 285) versus those who had unilateral breast cancer (n = 781). The multivariate odds ratio for contralateral breast cancer associated with tamoxifen use was 0.50 for carriers of BRCA1 mutations (95% CI, 0.30–0.85) and 0.42 for carriers of BRCA2 mutations (95% CI, 0.17–1.02). However, the protective effect of tamoxifen was not seen among women who had undergone a BSO (OR = 0.83; 95% CI, 0.24–2.89), although there was only a small number of patients in this subgroup. In contrast, a strong protective effect of tamoxifen was apparent among women who were premenopausal or who had undergone natural menopause (OR = 0.44; 95% CI, 0.27–0.65). This study suggests that using tamoxifen in BRCA1/2-mutation carriers who have not undergone a BSO may result in a decreased risk of breast cancer. It has been estimated that tamoxifen reduces breast cancer risk in BRCA1-mutation carriers by 13% and in BRCA2-mutation carriers by 27% [85]. Similar results were found with respect to the reduction of contralateral breast cancer risk in patients with a BRCA1/2 mutation treated with tamoxifen after first diagnosis of breast cancer [86, 87].

It has been reported that only 5.5% of women with a BRCA1 or BRCA2 mutation have used tamoxifen to reduce their breast cancer risk [88]. Approximately half of the population at risk relied solely on screening for the early detection of breast cancer. Patients should be counseled about the increased risk of endometrial cancer following tamoxifen treatment (RR = 11.6, P = 0.0004) compared to BRCA1/2-mutation carriers without a history of tamoxifen use [89]. Hence, the risks and benefits of prophylactic hysterectomy should be discussed with those patients. It has been reported that in BRCA1-associated patients with a history of breast cancer, subsequent treatment with tamoxifen does not increase ovarian cancer risk [90]. Thus, it is anticipated that primary prophylactic tamoxifen treatment would not increase ovarian cancer risk.

8.2. Raloxifene. The study of tamoxifen and raloxifene (STAR) examined the efficacy of tamoxifen and raloxifene to decrease breast cancer risk [91, 92]. Raloxifene is a selective estrogen receptor modulator, which is used primarily for the prevention of osteoporosis. The advantages of raloxifene are that it is as effective as tamoxifen in reducing the risk of invasive breast cancer while having a lower risk of thromboembolic events and a trend towards a lower risk of uterine cancer. However, there was a nonstatistically significant higher risk of noninvasive breast cancer observed with raloxifene. BRCA status was not ascertained in this study, and, thus, raloxifene efficacy has not specifically been evaluated in this patient population.

8.3. Oral Contraceptive Pill (OCP). OCP use has been found to have different effects on the lifetime risk of ovarian and breast cancer. It has generally been accepted that OCP use decreases one’s risk of ovarian cancer. However, much debate has ensued on whether the OCP increases one’s risk of developing breast cancer. Recently, Iodice et al. [93], have performed a meta-analysis updated to March 2010 on the association between OCP use and breast or ovarian cancer in BRCA1/2-mutation carriers. Based on 18 studies, a total of 2855 breast cancer cases and 1503 ovarian cancer cases were reviewed. As previously noted, OCP use at any point during one’s life was associated with a 50% relative risk reduction in developing ovarian cancer for BRCA1/2-mutation carriers. Looking specifically at duration of OCP use, each 10-year period of OCP use resulted in a 36% relative risk reduction.
for the development of ovarian cancer. In the meta-analysis, there was no evidence of a significant association between OCP use and breast cancer risk (summary relative risk (SRR): 1.13; 95% CI, 0.88–1.45). Specifically, OCP formulations used before 1975 correlated with an increased risk of breast cancer (SRR: 1.47; 95% CI: 1.06, 2.04), but there was no correlation with the use of more recent formulations (SRR: 1.17; 95% 0.74,1.86). There are studies which have correlated past users of the OCP to an increased risk of breast cancer [26, 94].

Figueiredo et al. [95] examined the effect of oral contraceptives and hormone replacement therapy (HRT) on the development of contralateral breast cancer in BRCA1/2-mutation carriers with a history of breast cancer. OCP use was not associated with increased contralateral breast cancer risk in BRCA2-mutation carriers (RR = 0.82; 95% CI = 0.21–3.13), and BRCA1-mutation carriers who used the OCP trended towards a greater risk of contralateral breast cancer compared to nonusers, but this risk was not significant (RR = 2.38; 95% CI = 0.72–7.83). Few women had ever used HRT and there were no significant associations found between lifetime use and contralateral breast cancer risk among BRCA1/2-mutation carriers and noncarriers.

9. Hereditary Breast and Ovarian Cancer and HRT

Known BRCA1/2 carriers often choose to undergo a risk-reducing BSO, thereby, entering a surgical menopause at an earlier age. As such, many would benefit from HRT to help alleviate menopausal symptoms. Rebbeck et al. [96] completed a prospective cohort study looking at 462 women with BRCA1/2 mutations to evaluate breast cancer risk after BSO with and without HRT use. They found that BSO was significantly associated with breast cancer risk reduction overall (hazard ratio [HR] = 0.40; 95% CI, 0.18 to 0.92). HRT of any type after BSO did not significantly alter the reduction in breast cancer risk (HR = 0.37; 95% CI, 0.14 to 0.96) when compared to women who have not had a BSO or used HRT. In a matched case-control study of 472 postmenopausal women with a BRCA1 mutation, the adjusted odds ratio for breast cancer in HRT users versus nonusers was 0.58 (95% CI = 0.35 to 0.96; P = 0.03) [97]. Overall, it appears that short-term HRT use does not negate the protective effect of BSO on subsequent breast cancer risk in BRCA1/2-mutation carriers.

Recently, the MARIE-GENICA Consortium on Genetic Susceptibility for Menopausal Hormone Therapy Related Breast Cancer Risk [98] has investigated HRT use and breast cancer risk in 3,149 postmenopausal breast cancer patients and 5,489 controls from the two German case-control studies. The study was initiated to determine the modification of breast cancer risk associated with hormone use by a subset of genes involved in hormone metabolism and cell cycle regulation, of which BRCA1 is included. A minor allele of BRCA1, which carries an amino acid substitution due to a single nucleotide polymorphism, was found to affect the interaction with both RAD51 as well as the androgen receptor [98]. Preliminary evidence trended towards an increased risk in postmenopausal breast cancer in BRCA1 minor allele carriers on estrogen hormone therapy compared to those with the major BRCA1 allele genotype.

10. BRCAness and Sporadic Cancer

The concept of “BRCAness” has evolved to reflect the traits that some sporadic cancers share with BRCA1/2-mutation carriers [99]. The inactivation of BRCA1 is a relatively frequent event in sporadic ovarian cancer and has been shown to occur through a number of epigenetic mechanisms such as promoter hypermethylation and loss of heterozygosity [100]. Decreased BRCA1 expression has been found in approximately 30–40% of sporadic breast cancers [101] and 15–80% of ovarian cancers [102]. BRCA1 has recently been evaluated as a tumour biomarker in a number of malignancies including ovarian [103, 104], breast [105, 106] and nonsmall cell lung cancer [107].

Emerging evidence suggests that tumours may be characterized by a relative level of BRCA1 deficiency at both the mRNA and protein level, resulting in BRCA1 having a potentially broader clinical relevance as a prognostic and predictive marker for patients with sporadic disease. A study in sporadic breast cancer by Margeli’s group [108] found that patients with lower BRCA1 mRNA expression who were treated with neoadjuvant chemotherapy (fluorouracil, epirubicin, and cyclophosphamide) had a lower relapse rate and longer survival when compared to patients with higher BRCA1 expression. An analysis of 70 tumours from patients with sporadic ovarian cancer for BRCA1 mRNA expression correlated low BRCA1 mRNA expression with improved survival following platinum-based chemotherapy [109]. This finding was supported by our group which associated low BRCA1 mRNA expression with improved overall survival in 51 patients with sporadic ovarian cancer [104]. Thrall et al. [103] examined BRCA1 protein expression in 230 sporadic ovarian cancers and demonstrated that compared to high BRCA1 expression, low BRCA1 expression was predictive of longer overall survival (aHR = 0.51 (95% CI 0.32–0.83). Recently, our group has showed that in optimally debulked advanced ovarian cancer patients treated with platinum-based chemotherapy, low BRCA1 protein expression was significantly associated with a better progression-free survival (PFS) (median PFS was 24.7 and 16.6 months in patients with low and high BRCA1, resp.; HR = 0.56) [110]. Such findings extend the clinical importance of BRCA in women with breast and ovarian cancer patients, and further study is needed to explore BRCA as a predictive marker to targeted therapies.

11. Targeted Therapies for BRCA-Deficient Tumours

While DNA defects are often a step in the process of tumorigenesis, once a cell becomes cancerous, such defects may be exploitable to enhance susceptibility to chemotherapeutic agents. It is well accepted that BRCA1 deficiency leads to the dysregulation of DNA repair pathways, which in turn renders
tumour cells more vulnerable to DNA damaging agents such as platinum-based chemotherapy. Poly (ADP-ribose) polymerase inhibitors (PARPi) are a novel therapeutic option for the treatment of ovarian and breast cancers which preferentially target BRCA1-defective cells and spare those with normal function [111]. The PARP family of enzymes serves a vital role in the repair of single-stranded DNA breaks (SSBs). Normally, unrepaired SSBs lead to double-strand breaks (DSBs), which are subsequently repaired in cells with normal BRCA function. However, in cells where BRCA is nonfunctioning or deficient, DSB are left unrepaired, leading to genomic instability and cell death [111]. The use of the PARPi and PARP2 inhibitor, olaparib, has been studied in a phase I clinical trial for the treatment of advanced breast and ovarian cancer patients with BRCA1/2 germline mutation as well as in a phase II trial in advanced breast cancer patients with BRCA1/2 mutations, with both studies showing promising results [112, 113]. A number of clinical trials are currently ongoing with the use of various PARP inhibitors, both as single agents and in combination with chemotherapy, for both hereditary and sporadic breast and ovarian cancer.

12. Conclusion

Hereditary breast and ovarian cancer patients are unique in terms of age of diagnosis, pathological features, and prognosis. Clinicians working in the area of surgical oncology should be familiar with the criteria for referral of high-risk individuals for genetic testing. BRCA1/2- mutation carriers should be offered risk reduction strategies, in the form of prophylactic bilateral mastectomy and/or bilateral salpingo-oophorectomy at an early age. If a patient declines surgery, appropriate screening should ensue with an understanding of the limitations that exist. Chemoprevention with tamoxifen or raloxifene is used to decrease ones risk of breast cancer, and OCPs may be used effectively to reduce the risk of ovarian cancer. New evidence suggests that BRCA has a broader role as a potential biomarker in sporadic breast/ovarian cancer for the management of this patient population. Targeted therapy with PARPi is an exciting novel treatment option being tested in clinical trials, particularly for ovarian cancer patients where chemotherapy is limited.

Conflict of Interests

The authors have declared that there are no conflicts of interests.

Abbreviations

BRCA1: Breast cancer protein 1
ER: Estrogen receptor
BSO: Bilateral salpingo-oophorectomy
OCP: Oral contraceptive pill
HRT: Hormone replacement therapy
PARPi: Poly(ADP-ribose) polymerase inhibitors
RR: Relative risk.

Acknowledgments

This work was supported by the Ottawa Regional Cancer Foundation (J.I.W.), the Department of Obstetrics and Gynecology, (J.I.W.) and the Division of Gynecologic Oncology, Ottawa.

References


Submit your manuscripts at http://www.hindawi.com