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Gynecologic Cancers (RJ Morgan, Section Editor)

Management of Genetic Syndromes Predisposing to Gynecologic Cancers

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Opinion statement

Women with personal and family histories consistent with gynecologic cancer-associated hereditary cancer susceptibility disorders should be referred for genetic risk assessment and counseling. Genetic counseling facilitates informed medical decision making regarding genetic testing, screening, and treatment, including chemoprevention and risk-reducing surgery. Because of limitations of ovarian cancer screening, hereditary breast and ovarian cancer-affected women are offered risk-reducing bilateral salpingo-oophorectomy (BSO) between ages 35 and 40 years, or when childbearing is complete. Women with documented Lynch syndrome, associated with mutations in mismatch repair genes, should be screened at a young age and provided prevention options, including consideration of risk-reducing total abdominal hysterectomy and BSO, as well as intensive gastrointestinal screening. Clinicians caring for high-risk women must consider the potential adverse ethical, legal, and social issues associated with hereditary cancer risk assessment and testing. Additionally, at-risk family members should be alerted to their cancer risks, as well as the availability of risk assessment, counseling, and treatment services.

Introduction

In the decade since publication of the draft of the human genome sequence, research has led to recommendations about clinical management, screening, and prevention options for those at risk for

hereditary gynecologic cancers, particularly ovarian and uterine cancers. Up to 15 % of ovarian cancer is associated with high-penetrance hereditary cancer susceptibility disorders, particularly (i) hereditary breast and ovarian cancer (HBOC) associated with mutations in *BRCA1* and *BRCA2*, and (ii) Lynch syndrome (LS; also referred to as hereditary nonpolyposis colorectal cancer or HNPCC) linked to alterations in mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*. In addition to ovarian cancer susceptibility, LS-affected women are at risk for uterine and other cancers, including colorectal cancer (CRC). Specific characteristics of a personal and family medical history are suggestive of hereditary cancer susceptibility, including HBOC and LS (Table 1).

Other less common hereditary ovarian cancer-associated susceptibility disorders not covered in this review include: Peutz-Jeghers syndrome, nevoid basal cell carcinoma syndrome; with a small increased risk associated with Li-Fraumeni syndrome. Additionally, Cowden syndrome, a rare inherited condition associated with uterine and other cancer risk, is not discussed here.

Epidemiology

HBOC

Incidence

Estimates of *BRCA1/2* mutation frequency vary, ranging from 1/300 to 1/500 in the general population to much higher rates in populations with founder mutations such as those of Ashkenazi Jewish descent and populations from the Netherlands, Iceland, and Sweden [1], as well as in families with early-onset cancers or with multiple cases of breast and/or ovarian cancer [2]. An estimated 3-5 % of breast cancer and 10-15 % of ovarian cancer has been attributed to *BRCA1/2* mutations [1, 3].

Cancer risks associated with *BRCA1* and *BRCA2* mutations

Estimates of penetrance, the occurrence of cancer in individuals with *BRCA1/2* mutations vary widely, with greater risk predicted in those with strong family histories, in contrast to HBOC-affected individuals unselected for family history. Among a large pooled analysis of 22 studies of more than 8,000 breast and ovarian cancer patients, including 500 with documented *BRCA1/2* mutations, the mean breast cancer risk by age 70 years was 65 % (95 % confidence interval (CI) 44-78 %) for *BRCA1* and 45 % (95 % CI 31-56 %) for *BRCA2*. Mean ovarian cancer risks by age 70 years were 39 % (95 % CI 18-54 %) for *BRCA1* and 11 % (95 % CI 2.3-19 %) for *BRCA2* [4]. A more recent meta-analysis of ten studies revealed a cumulative breast cancer risk by age 70 years of 57 % (95 % CI 47-66 %) and 49 % (95 % CI 40-57 %), and an ovarian cancer risk of 40 % (95 % CI 35-46 %) and 18 % (95 % CI 13-23 %) for those heterozygous for *BRCA1* and *BRCA2* mutations, respectively [5]. Mean age at breast cancer diagnosis ranges from 39.9-44.1 years and 42.2-47.3 years for those with *BRCA1* and *BRCA2* mutations, respectively [6, 7], versus 61 years in the general population. The mean age of ovarian cancer onset also varies, ranging from 49–53 years and 55–58 years for women with *BRCA1* and *BRCA2* mutations, respectively, versus 63 years in the general population [8].

In addition to cancers of the female breast and ovary, well-established HBOC-component tumors include primary peritoneal and fallopian tube

Table 1. Personal and family history characteristics suggestive of hereditary breast and ovarian cancer and Lynch syndrome risk

Cancer in two or more close relatives (on same side of family)
Closeness of biologic relationship of affected relatives
Early ages at cancer diagnoses
Synchronous or metachronous cancers
Presence of bilateral or multifocal disease
Rare cancers (i.e., cases of male breast cancer for HBOC)
Presence of syndrome-specific component tumors (i.e., uterine cancer and colorectal cancer in family suggestive of LS)
Presence of cancer in several generations (i.e., evidence of autosomal dominant transmission)
High ratio of affected to unaffected relatives
Personal cancer diagnosis and limited family history (i.e., adoption)

tumors, male breast cancer, cancers of the prostate, pancreas, as well as melanoma (skin and ocular), and possibly others [9]. Without additional intervention, i.e., BSO or tamoxifen, risk for contralateral breast cancer (CBC) is 27.1 % within 5 years, and 43.4 % at 10 years among those with *BRCA1* mutations, and 23.5 % and 34.6 % at 5 and 10 years, respectively, for those with *BRCA2* mutations. Factors associated with reduced risk for CBC include presence of a *BRCA2* mutation versus a *BRCA1* mutation (hazard ratio (HR) 0.73; 95 % CI 0.47-1.15), tamoxifen use (HR 0.59; 95 % CI 0.35-1.01), initial diagnosis at age 50 years or older (HR 0.63; 95 % CI 0.36-1.10), and BSO (HR 0.44; 95 % CI 0.21-0.91) [10]. A more recent population-based, nested case control study of CBC risk reported cumulative 5- and 10-year risks of 15.5 % (95 % CI 8.8-27.4) and 28.2 % (95 % CI 16–50) for those heterozygous for *BRCA1/2* mutations, diagnosed with initial primary invasive breast cancer before age 30 years, with 5-year and 10-year risks of 9.7 % (95 % CI 8.4-11.2) and 18.4 % (95 % CI 16.0-21.3) for all ages combined (range, 25–55 years) [11]. Long-term CBC risk among those with *BRCA1/2* mutations is reported as 47.4 % at 25 years [12].

LS

Incidence

General population risk of LS has been estimated at 1/370 in the United States, based on a 2.8 % incidence of this condition among those with newly diagnosed CRC [13]. Risk of LS increases substantially in families with multiple cases of colorectal, uterine, and other LS-associated cancers, as well as among those with early-onset, syndrome-associated cancers [14]. LS accounts for an estimated 2.3 % of all endometrial cancer cases, 10 % of those diagnosed before age 50 years [15].

Cancer risks associated with MMR gene mutations

Alterations in LS-associated DNA MMR genes *MLH1*, *MSH2*, *MSH6*, and *PMS2* are associated with different cancer risks; due to their low prevalence individually, aggregate risk data are usually shown. Studies of families attending high-risk clinics show higher cancer risks than affected

individuals ascertained from the general population, reflecting study biases. Cancer risks for those with this condition also appear to vary by gender [16].

Although CRC susceptibility is a major focus of care for women with LS, because those with MMR mutations face a 22-58 % risk of CRC by age 70 years [16], the syndrome's presence significantly impacts gynecologic care. LS-affected women face an estimated 30-60 % risk of endometrial adenocarcinoma by age 70 years, with risks greatest among those with *MSH6* mutations [16, 17]. The mean age at endometrial cancer diagnosis in varied study populations ranges from 48–62 years among those with *MLH1* and *MSH2* mutations. LS-associated ovarian cancer risk also varies, ranging from 4-12 %, with a mean age of onset of 42.5 years among those with *MLH1* and *MSH2* mutations [18].

In addition to uterine, ovarian, and CRC, classic LS-associated tumors include cancers of the stomach, urinary tract, hepatobiliary tract, brain (usually glioblastoma), small intestine, and skin (sebaceous cancers). Evidence suggests elevated pancreatic cancer risk as well [18].

Pathogenesis

HBOC

HBOC is an autosomal dominant disorder associated with mutations in *BRCA1* and *BRCA2*. Functioning as tumor suppressor genes and critical to DNA repair, *BRCA1* and *BRCA2* are localized on chromosome 17q21 and 13q12.3, respectively. Most mutations found in these genes result in protein inactivation, typically from protein truncation. In addition, missense mutations and large gene rearrangements are seen. Mutation type varies by ancestry, i.e., three distinct *BRCA1* and *BRCA2* mutations result in the majority of HBOC among those of Ashkenazi Jewish decent, including *BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT [19].

Carcinogenesis is the result of repeated DNA injury from stressors, including ionizing radiation, oxidative radicals, and certain cytotoxic agents. BRCA1 and BRCA2 serve a central role in the cell's response to these stressors by their involvement in repair of double-stranded DNA breaks via homologous recombination and other repair mechanisms [20]. BRCA1 plays a broader role in maintaining cellular integrity through its involvement in signaling DNA damage, homologous recombination, nucleotide-excision repair, and nonhomologous end-joining. BRCA2 plays a more specific role in DNA repair through control of RAD51, which is required for homologous recombination, thereby functioning to repair double-stranded DNA breaks and interstrand crosslinks [21]. BRCA deficiency leads to the accumulation of mutations, because it interferes with the cell's ability to repair DNA damage or undergo apoptosis, ultimately resulting in neoplastic transformation [22].

LS

LS is an autosomal dominant disorder associated with mutations in one of several genes encoding MMR gene complex proteins. Approximately 90 % of LS is associated with mutations in *MLH1* and *MSH2*, with 7-10 % attributed to *MSH6* and less than 5 % related to *PMS2*. Although not a mismatch repair gene, germline deletions in *EPCAM* silence *MSH2* expression in close to 1 % of individuals with LS [18]. MMR proteins function to identify and correct DNA

base mispairings occurring as a result of DNA polymerase slippage during the replication of repetitive genomic tracts, i.e., microsatellites. Failure of the MMR system to repair DNA mispairings results in microsatellite instability (MSI), where microsatellites undergo a somatic gain or loss in repeat length. The accumulation of such errors can inactivate genes critical to cellular function, including tumor suppressor genes, ultimately resulting in carcinogenesis. Close to 15 % of CRCs show MSI. Importantly, most MSI-positive tumors are caused by somatic (non-germline) hypermethylation of the *MLH1* CpG island promoter region; a smaller portion is caused by LS [23].

Presentation

HBOC

HBOC-risk is suspected based on clinical and family history features, including history of: (i) ovarian cancer; (ii) early-onset breast cancer ≤45 years or ≤50 years with limited family history; (iii) synchronous or metachronous breast and ovarian (fallopian tube, or peritoneal cancers); (iv) bilateral breast cancer with initial diagnosis ≤50 years; (v) male breast cancer; (vi) triple-negative breast cancer≤age 60 years; (vii) breast and ovarian cancer in a family; (viii) multiple cases of breast or pancreatic cancer in a family; (ix) population at risk, i.e., Ashkenazi Jewish; or (x) limited family history, i.e., adoption [24]. Probability models determine the pretest likelihood of an individual testing positive for a *BRCA1/2* mutation. Each of these models is unique due to the methods and populations used in developing them. The most widely applied models are BRCAPRO, Myriad II, and BOADICEA [25, 26•].

LS

LS-risk assessment is based on established personal and family history criteria, i.e., the Amsterdam II Criteria or the Revised Bethesda Guidelines [27, 28]. These criteria include: (i) young age at CRC onset (before age 50 years); (ii) presence of synchronous or metachronous CRCs or other LS-associated component tumors; (iii) multiple family members of successive generations with LS-associated tumors; and (iv) suggestive CRC pathologic findings, i.e., microsatellite instability or absence of mismatch repair protein expression. Several models, including PREMM1,2,6, MMRpredict, and MMRpro, have been developed to provide a quantitative estimate of an individual testing positive for an MMR gene mutation. These models have been validated in a number of CRC populations [29, 30]. Although they showed a strong ability to distinguish mutation carriers from noncarriers with a high sensitivity and specificity among CRC cases, the discriminative ability of these models is much lower among endometrial cancer cases [30].

Diagnosis

HBOC

In addition to personal and family history, incorporating examination of breast and ovarian cancer pathologic features can assist in identifying HBOC [31–33]. Specifically, compared with sporadic breast cancer, *BRCA1*-associated tumors

often are triple-negative (estrogen receptor [ER], progesterone receptor [PR], and HER-2 negative). Additionally, *BRCA1*-associated tumors tend to be high grade, exhibit p53 mutations, and stain positive for high-molecular weight epithelial cytokeratins (CKs), CK5/6 and CK14, known as "basal" cytokeratins. In contrast, breast cancers diagnosed in women with *BRCA2* mutations, similar to sporadic comparators, often are hormone receptor-positive [3, 34]. Likewise, there appear to be characteristic pathologic features associated with HBOC-associated ovarian cancer. A recent population-based study showed that in comparison with a 14.1 % rate of *BRCA* mutations among the overall study population of 1001 women with nonmucinous ovarian cancer, 16.6 % of those with serous histology tested positive, whereas 22.6 % of those with high-grade serous tumors tested positive [35••].

LS

Preliminary screening of paraffin-embedded CRC tissue for evidence of defective MMR function can be used to determine an individual's candidacy for genetic testing. There are two CRC tumor-based screening tests available. First, tumors can be assayed through microsatellite instability (MSI) testing. A high amount of MSI (MSI-high; MSI-H) is found in nearly all LS-associated colorectal tumors. Importantly, MSI-H is also found in about 15 % of all colorectal tumors due to another mechanism, age-related somatic (non-germline) methylation of the *MLH1* gene promoter. Therefore, those with tumors lacking the MSI-H phenotype are unlikely to have LS, but MSI-H is not diagnostic of LS.

Immunohistochemistry (IHC) is the second means of screening tumors for evidence of MMR gene alterations. LS-IHC testing determines the expression of mismatch repair enzymes MLH1, MSH2, MSH6, and PMS2 in CRC specimens. Additional tumor tissue testing is warranted (*BRAF* mutation testing and/or *MLH1* hypermethylation analysis) if there is loss of expression of MLH1, because this finding occurs in nearly 75 % of these cases due to somatic *MLH1* promoter hypermethylation [36••]. Abnormal IHC for one or more DNA MMR enzyme(s) directs germline mutation testing of the corresponding gene(s). The clinical sensitivity of MSI and IHC testing is estimated at 85 % and 83 %, respectively among those with *MLH1* and *MSH2* mutations. Estimates of clinical specificity of these two tests among CRC patients are 90.2 % and 88.8 %, respectively [36••]. High amounts of MSI or lack of expression of one or more MMR protein(s), including abnormal expression of the MLH1 protein, not explained by a somatic inactivation of the gene, is highly suggestive of LS.

In 2009, an independent evidence-based review by the Evaluation of Genomic Applications in Practice and Prevention Working Group issued recommendations regarding universal CRC tissue screening (IHC and/or MSI) for evidence of LS [16]. Despite the potential benefits of universal CRC-based LS screening, there is a recognition of: (i) the significant challenges and barriers of this strategy; (ii) the need for education of clinicians, patients, and other stakeholders; and (iii) the need for additional pilot studies to demonstrate evidence of screening efficacy, feasibility, and utility on a broader population-based level [37•].

There has been incomplete study of the clinical utility and validity of tumor-based LS screening among gynecologic cancer patients. Recent data suggest that

IHC-based uterine cancer screening for absence of MMR enzyme expression is a feasible and cost-effective way to identify LS-risk, particularly among those with suggestive clinical (i.e., early-onset disease, low BMI), pathological (tumor infiltrating lymphocytes and peritumoral lymphocytes), or family history characteristics. MSI has a lower predictive value in *MSH6*-associated LS. Because of the higher rate of *MSH6* mutations in LS-associated uterine cancer, IHC alone is considered the primary LS screening tool among women with this disease [15].

Genetic counseling

Among those meeting characteristic personal medical, pathological, or family history criteria for risk for HBOC and LS, guidelines recommend referral for genetic counseling by suitably trained health care providers [2, 38•]. Genetic counseling facilitates informed decisions about genetic testing and medical management options, improves knowledge of cancer risk, provides information on available support resources (Table 2), and often reduces anxiety. Elements of genetic counseling include: (i) pedigree analysis; (ii) risk assessment; (iii) recommendations for genetic testing; (iv) genetic test results interpretation; (v) medical management decision making; and (vi) impact of risk for others in the family [2]. In response to growing demands for cancer genetic risk assessment, counseling, and testing, cancer genetic counseling services have recently increased nationally [39]. The National Society of Genetic Counselors provides an up-to-date link to available genetic counseling services across the country (http://www.nsgc.org).

Prognosis

HBOC

Although prognosis is similar between breast cancer-affected women with *BRCA* mutations and those with presumed noninherited breast cancer [7], women with *BRCA*-associated ovarian cancer appear to have improved overall survival compared with those with presumed noninherited disease [35••, 40–44]. Consistent with survival data, studies reveal improved response to first-line therapy among ovarian cancer patients with *BRCA* mutations compared with those with

Table 2. Patient and family support resources: hereditary breast and ovarian cancer and Lynch syndrome

Hereditary breast and ovarian cancer
Facing Our Risk of Cancer Empowered (FORCE) - http://www.facingourrisk.org/
Bright Pink - http://www.brightpink.org/
American Society of Clinical Oncology oncologist-approved cancer information - http://www.cancer.net/
Lynch syndrome
Lynch Syndrome International - http://www.lynchcancers.com/
American Society of Clinical Oncology oncologist-approved cancer information - http://www.cancer.net/
General genetics resources
National Society of Genetic Counselors – http://www.nsgc.org
Genetics Home Reference – http://ghr.nlm.nih.gov/
National Organization for Rare Disorders (NORD) - http://www.rarediseases.org/
National Human Genome Research Institute - http://www.genome.gov/19516567

sporadic disease. Furthermore, a recent study comparing HBOC-affected ovarian cancer patients with those with presumed noninherited disease suggests improved response to both non-platin and platin-containing regimens in the treatment of disease-relapse, including those women with early relapses. This study also suggests that somatic (non-germline) *BRCA* mutations predict treatment responses [35••].

LS

There are limited data regarding the impact of MMR gene mutations on prognosis among women with gynecologic cancers. However, a meta-analysis of 7642 CRC patients from 32 studies, including 1277 MSI-H patients, revealed an improved overall survival among those with MSI-H tumors versus those with microsatellite stable (MSS) tumors (HR 0.65; 95 % CI 0.59-0.71) [45]. Patients with MSI-H CRCs are less prone to have lymph node involvement and systemic metastases [46].

Management

HBOC

Management interventions available to women with or at risk for HBOC include high-risk screening, chemoprevention, and risk-reducing surgery.

Screening

The goal of a screening intervention is to detect disease at an early stage in asymptomatic individuals, when treatment will affect the disease's natural history. In making breast cancer screening recommendations for women with documented *BRCA1/2* mutations, clinicians must consider two unique disease features. First, HBOC-associated breast cancer usually occurs at an earlier age than sporadic breast cancer, when routine mammography is less sensitive due to increased breast density. Second, women with *BRCA1/2* mutations have an increased rate of interval cancers (cancers detected between screening exams) [47, 48]. Furthermore, data are limited regarding the safety of early mammograms among those with *BRCA* mutations. A recent retrospective cohort study of 1993 women with *BRCA1/2* mutations showed that compared with no diagnostic radiation, any exposure before age 30 years was associated with increased breast cancer risk (HR 1.9; 95 % CI 1.2-3), with a dose–response seen. This association was not evident among those exposed between ages 30–39 years [49••].

Several large observational studies have evaluated the effectiveness of routine mammography in women with *BRCA1/2* mutations. Although studies demonstrated significant variations, the sensitivity of mammography is lower and the percentage of advanced stage cancers is higher among these women compared with the general risk population [50]. Documented limitations of mammograms in HBOC-affected women prompted study of alternative imaging modalities, including MRI. Data indicate that MRI is almost twice as sensitive as mammography in detecting invasive breast cancer in high-risk women (77 % vs. 39 %) [50, 51].

Although the overall sensitivity of MRI for detecting invasive cancers is better than that of mammography, the specificity and corresponding positive predic-

tive value (PPV) of MRI is lower (PPV 63 % for MRI: 95 % CI 43-79 %) versus 77 % for mammography (95 % CI 50-92 %) [52] creating potential for unnecessary follow-up procedures, including biopsies. Other limitations of MRI are high cost, lack of universal availability, and the need for intravenous contrast. However, because of the improved sensitivity of MRI for detecting HBOC-associated breast cancer, national guidelines recommend incorporating it into a surveillance program that also includes ongoing mammograms and close clinical surveillance [24]. The sensitivity of the combined screening approach among high-risk women is 80-100 % [51]. Cost analysis data reveal that MRI screening, when added to mammography, is more cost effective for *BRCA1* mutation carriers than for those with *BRCA2* mutations, and that the cost-effectiveness of this procedure varies by age [53].

The natural history of preclinical ovarian cancer is incompletely understood. The majority of women with ovarian cancer present with advanced stage disease resulting in high mortality rates. Although a number of studies demonstrate that most women with ovarian cancer experience prediagnosis symptoms [54, 55], these studies fail to identify a consistent symptom pattern that differentiates ovarian cancer from other medical conditions, or early from late-stage disease. To date, ovarian cancer screening among *BRCA1/2* mutation carriers has largely focused on serum CA-125 levels and transvaginal ultrasound imaging. Studies examining the impact of each of these methods on stage at diagnosis and mortality have shown them to be largely ineffective [56–59].

Chemoprevention

Chemoprevention for women with known *BRCA1/2* mutations includes consideration of agents aimed at breast cancer prevention (i.e., tamoxifen) as well as ovarian cancer prevention. Because this review is focused on gynecologic cancers, we have limited the following discussion to ovarian cancer chemoprevention.

Oral contraceptive (OC) use has been associated with more than a 40 % reduction in ovarian cancer risk and often is recommended for disease prevention for those at known risk. The benefits of OCs have extended to studies of women with *BRCA1/2* mutations [60••, 61]. Increased risk of breast cancer has been attributed to OC use in some studies, particularly among women who used them before age 20–30 years and those with *BRCA1* mutations [62, 63], whereas other studies fail to show an elevated risk [64, 65].

A randomized clinical trial to assess the impact of OCs on ovarian and/or breast cancer risk is unlikely. The potential reduction in ovarian cancer risk must be weighed against a potential increase in breast cancer risk among women with *BRCA1/2* alterations who are considering the use of OCs [8].

Risk-reducing surgery

Given the high cancer risk and known limitations of screening in HBOC-affected women, risk-reducing mastectomy is considered an alternative way to reduce breast cancer risk for mutation carriers. Risk-reducing BSO is recommended between ages 35–40 years, when childbearing is complete, or based on ages at ovarian cancer diagnosis in the family [24]. Studies examining the impact of risk-reducing mastectomy among those with known

BRCA mutations are largely limited to observational study design, thereby limiting the generalizability of this work to the care of HBOC-affected women. Despite these limitations, data consistently show an 85-100 % reduction in breast cancer risk among those undergoing risk reducing mastectomy [2]. A meta-analysis of ten studies revealed a HR of 0.21 (95 % CI 0.12-0.39) for ovarian/fallopian tube tumors and a HR of 0.49 (95 % CI 0.37-0.65) for breast cancer among women with *BRCA1/2* mutations electing BSO [66]. Although the reduction in risk is remarkably consistent across studies, the benefits of risk-reducing surgery, both mastectomy and BSO, must be weighed against its impact on the woman's physical, emotional, reproductive, and sexual health. Those electing risk-reducing bilateral mastectomy should be educated regarding reconstruction options and risks.

Emerging therapies

Poly(ADP-ribose) polymerase (PARP) is a novel target for the management of those with HBOC-associated cancers, including ovarian cancer. This enzyme plays a critical role in the repair of single-stranded DNA breaks through the base excision repair pathway. Deficient PARP function results in double-stranded DNA breaks when single-stranded DNA breaks are encountered at the replication fork. Normally, the cell repairs double-stranded DNA breaks through homologous recombination. However, in BRCA deficient cells, homologous recombination repair is defective, resulting in the accumulation of lethal levels of DNA damage. Among those with documented *BRCA* mutations, PARP-inhibition is unique in its ability to target tumor cells—a process called "synthetic lethality". Specifically, in HBOC-affected individuals, noncancer cells maintain one functional *BRCA* allele, supporting ongoing homologous recombination repair. However, PARP inhibition becomes selectively lethal in tumor cells that have lost the normal *BRCA* allele. As part of the treatment of HBOC-associated tumors, this mechanism of action may improve disease control with limited toxicity [67].

The initial phase I study of an oral PARP inhibitor, olaparib, reported a response rate of 47 %, with manageable adverse toxicities among those with documented *BRCA* mutations and classic HBOC-associated cancers, including eight patients with ovarian cancer [68••]. A single-stage expansion of this trial examined response to olaparib among 50 previously treated ovarian cancer patients with known or likely BRCA mutations, categorized based on platinum sensitivity. This showed an overall response rate of 46 %, with 6 % of participants experiencing stable disease for 4 months or more. Toxicities were largely low-grade; the most common were nausea (48 %) and fatigue (44 %) [69••]. The overall clinical benefit of olaparib was significantly higher in the platinum-sensitive group (69.2 %) versus the platinum-resistant (45.8 %) and platinum-refractory (23.1 %) groups (p=0.03) [69••]. Laboratory studies suggest that platinum-insensitive tumors may reacquire BRCA function, thus regaining DNA repair mechanisms facilitating resistance to PARP-inhibition [70].

PARP inhibitors are being investigated in combination with cytotoxic agents for management of HBOC-associated ovarian cancer. Although results of these combined modality studies show promise for improved response,

caution has been raised regarding the added toxicity of these combinations. Further study of the role of these agents for the management of HBOC-associated ovarian cancer (as well as other HBOC-associated cancers) is ongoing [67]. Not only are these therapies promising among ovarian cancer-affected women with documented germline *BRCA* mutations, but somatic *BRCA* mutations occur in a substantial percentage of sporadic ovarian cancers, particularly high-grade serous ovarian cancers. Furthermore, genetic and epigenetic events can silence other components of the homologous recombination pathway. This suggests a much wider applicability of PARP-inhibition for the management of ovarian cancer with molecular evidence of "*BRCA*ness" [67].

LS

In addition to CRC screening and prevention being important components of care among those with or at risk for LS, women with this condition face significant risk for other cancers, including uterine and ovarian cancers. Management issues reviewed here are limited to the gynecologic care of LS-affected women.

Screening and chemoprevention

There are incomplete data on the efficacy of endometrial cancer screening in women with LS. The clinical utility of transvaginal ultrasound to assess the thickness of the endometrial stripe has been questioned, given that many seeking high-risk care are premenopausal. Previous studies confirmed the limited efficacy of screening transvaginal ultrasound in LS, as well as high false-positive rates [71–73]. In contrast, regular endometrial sampling appears more effective for women with this condition [72, 74]. National Comprehensive Cancer Network guidelines suggest consideration of annual endometrial sampling among LS-affected women [24]. Existing evidence does not support surveillance for ovarian cancer among those with LS.

There are limited data that address the efficacy of chemopreventive agents to reduce gynecologic cancers among those with LS. Nevertheless, oral contraceptives decrease the risk of both endometrial cancer and ovarian cancer in the general population [75, 76].

Risk-reducing surgery

Given the high risk for endometrial cancer and the moderately increased risk for ovarian cancer, women with mismatch repair gene mutations must decide between surveillance and surgical prophylaxis. There are incomplete data regarding the efficacy of risk-reducing gynecologic surgery among Lynch syndrome-affected women [77]. Schmeler et al. reported on a retrospective cohort of 315 women followed for approximately 10 years who had MMR gene mutations. Sixty-one of the 315 women underwent prophylactic surgery. No endometrial or ovarian cancers developed in those who had surgery, whereas 33 % of those without surgery developed endometrial cancer and 5.5 % developed ovarian cancer. National Comprehensive Cancer Network recommenda-

tions cite that the risks and benefits of prophylactic hysterectomy and BSO after childbearing should be discussed with LS-affected women [24].

Psychosocial issues

The long-term psychological impact of genetic testing for gynecologic cancer risk is incompletely studied. One 5-year follow-up study of 65 cancer unaffected women who underwent *BRCA* testing showed that those who tested positive did not differ from those who tested negative on several distress measures. However, anxiety and depression increased in both groups from 1 to 5 years after testing. Higher long-term distress was associated with greater hereditary cancer-related anxiety at the time of genetic testing, having young children, loss of a relative to breast or ovarian cancer, limited test result communication within the family, and changes in relationships with relatives. Although those women with documented *BRCA* mutations who underwent prophylactic surgery were less satisfied with their body image and noted more changes in sexual relationships than noncarriers, those who elected risk-reducing surgery had reduced fears of developing cancer and noted satisfaction with their surgical decision [78].

Inherent in genetic testing for cancer risk is the burden of making serious medical management decisions. There are few studies that investigate which factors play a role in these decisions. One study reported that age and having children were significant predictors of the choice for risk-reducing mastectomy for cancer unaffected women with *BRCA1/2* mutations. Women ages 40–54 years and those with more than a high school education were more likely to opt for prophylactic oophorectomy [79]. In addition to decisions about their own healthcare, younger women that have hereditary cancer syndromes may face difficult decisions about family planning, including the option of preimplantation genetic diagnosis. Although one qualitative study found that the majority of women with documented *BRCA* mutations preferred not to have a detailed description of preimplantation genetic diagnosis (PGD) at the time of genetic test results disclosure, nearly all agreed that PGD should be addressed during genetic counseling [80].

Both women who test positive, as well as those from HBOC-affected families who test negative (true negative result) experience distress. A qualitative study revealed that those who test negative for the genetic alteration identified in the family report experiencing (i) feelings of isolation, (ii) difficulty with family communication, and (iii) ongoing cancer-related anxiety despite a true negative result [81]. These studies demonstrate the need for ongoing medical and emotional support for those with documented genetic risk, as well as those with true negative results.

Diet and lifestyle

There is incomplete information on the impact of diet and other lifestyle factors on cancer penetrance among those with or at risk for hereditary gynecologic

cancers. However, the widely recognized benefits of a healthy diet that is rich in fruits and vegetables, optimum weight control, regular physical activity, and avoidance of known carcinogens, such as cigarettes [82], are considered important for quality of life and longevity. Therefore, it is recommended that HBOC and LS-affected women be advised of the potential benefits of dietary and lifestyle modifications as they relate to overall health and potentially to cancer risk.

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Disclosure

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Szabo CI, King MC. Population genetics of BRCA1 and BRCA2. Am J Hum Genet. 1997;60(5):1013–20.
2. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: recommendation statement. Ann Intern Med. 2005;143(5):355–61.
3. Tung N. Management of women with BRCA mutations: a 41-year-old woman with a BRCA mutation and a recent history of breast cancer. JAMA. 2011;305(21):2211–20.
4. Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Loman N, Olsson H, Johannsson O, Borg A, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2003;72(5):1117–30.
5. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 2007;25(11):1329–33.
6. Panchal S, Bordeleau L, Poll A, Llacuachaqui M, Shachar O, Ainsworth P, Armel S, Eisen A, Sun P, Narod SA. Does family history predict the age at onset of new breast cancers in BRCA1 and BRCA2 mutation-positive families? Clin Genet. 2010;77(3):273–9.
7. Goodwin PJ, Phillips KA, West DW, Ennis M, Hopper JL, John EM, O'Malley FP, Milne RL, Andrulis IL, Friedlander ML, et al. Breast cancer prognosis in BRCA1 and BRCA2 mutation carriers: an International Prospective Breast Cancer Family Registry population-based cohort study. J Clin Oncol. 2012;30(1):19–26.
8. Weissman SM, Weiss SM, Newlin AC. Genetic testing by cancer site: ovary. Cancer J. 2012;18(4):320–7.
9. Petrucelli N, Daly MB, Feldman GL. BRCA1 and BRCA2 Hereditary Breast and Ovarian Cancer. In: Pagon RABT, Dolan CR, et al., editors. GeneReviews™ [Internet], 2010/03/20 edn. Seattle (WA): University of Washington; 1993, 1998 Sep 4 [Updated 2011 Jan 20].
10. Metcalfe K, Lynch HT, Ghadirian P, Tung N, Olivotto I, Warner E, Olopade OI, Eisen A, Weber B, McLennan J, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol. 2004;22(12):2328–35.
11. Malone KE, Begg CB, Haile RW, Borg A, Concannon P, Tellhed L, Xue S, Teraoka S, Bernstein L, Capanu M, et al. Population-based study of the risk of second primary contralateral breast cancer associated with carrying a mutation in BRCA1 or BRCA2. J Clin Oncol. 2010;28(14):2404–10.
12. Graeser MK, Engel C, Rhiem K, Gadzicki D, Bick U, Kast K, Froster UG, Schlehe B, Bechtold A, Arnold N, et al. Contralateral breast cancer risk in BRCA1 and BRCA2 mutation carriers. J Clin Oncol. 2009;27(35):5887–92.
13. Hampel H, de la Chapelle A. The search for unaffected individuals with Lynch syndrome: do the ends justify the means? Cancer Prev Res (Phila). 2011;4(1):1–5.

14. Vasen HF. Clinical diagnosis and management of hereditary colorectal cancer syndromes. J Clin Oncol. 2000;18(21 Suppl):81S–92S.
15. Resnick KE, Hampel H, Fishel R, Cohn DE. Current and emerging trends in Lynch syndrome identification in women with endometrial cancer. Gynecol Oncol. 2009;114(1):128–34.
16. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. Genet Med. 2009;11(1):35–41.
17. Hendriks YM, Wagner A, Morreau H, Menko F, Stormorken A, Quehenberger F, Sandkuijl L, Moller P, Genuardi M, Van Houwelingen H, et al. Cancer risk in hereditary nonpolyposis colorectal cancer due to MSH6 mutations: impact on counseling and surveillance. Gastroenterology. 2004;127(1):17–25.
18. Kohlmann W, Gruber SB. Lynch Syndrome. In: Pagon RA BT, Dolan CR, et al., editors. GeneReviews™ [Internet] Seattle (WA): University of Washington, Seattle; 1993. Seattle; 2004 Feb 5 [Updated 2012 Sep 20].
19. Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, Timmerman MM, Brody LC, Tucker MA. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med. 1997;336 (20):1401–8.
20. Venkitaraman AR. Cancer susceptibility and the functions of BRCA1 and BRCA2. Cell. 2002;108(2):171–82.
21. Tutt A, Ashworth A. The relationship between the roles of BRCA genes in DNA repair and cancer predisposition. Trends Mol Med. 2002;8(12):571–6.
22. Bougie O, Weberpals JI. Clinical Considerations of BRCA1- and BRCA2-Mutation Carriers: A Review. Int J Surg Oncol. 2011;2011:374012.
23. Chung DC, Rustgi AK. The hereditary nonpolyposis colorectal cancer syndrome: genetics and clinical implications. Ann Intern Med. 2003;138(7):560–70.
24. [http://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf] [http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf]
25. Domchek SM, Eisen A, Calzone K, Stopfer J, Blackwood A, Weber BL. Application of breast cancer risk prediction models in clinical practice. J Clin Oncol. 2003;21 (4):593–601.
26.• Amir E, Freedman OC, Seruga B, Evans DG. Assessing women at high risk of breast cancer: a review of risk assessment models. J Natl Cancer Inst. 2010;102 (10):680–91.

This is an excellent review of models for estimating the probability of an individual carrying a BRCA1/2 mutation and models for estimating the risk of developing breast cancer.

27. Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology. 1999;116(6):1453–6.
28. Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Ruschoff J, Fishel R, Lindor NM, Burgart LJ, Hamelin R, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst. 2004;96(4):261–8.
29. Green RC, Parfrey PS, Woods MO, Younghusband HB. Prediction of Lynch syndrome in consecutive patients with colorectal cancer. J Natl Cancer Inst. 2009;101(5):331–40.
30. Mercado RC, Hampel H, Kastrinos F, Steyerberg E, Balmana J, Stoffel E, Cohn DE, Backes FJ, Hopper JL, Jenkins MA, et al. Performance of PREMM(1,2,6), MMRpredict, and MMRpro in detecting Lynch syndrome among endometrial cancer cases. Genet Med. 2012;14(7):670–80.
31. Mavaddat N, Rebbeck TR, Lakhani SR, Easton DF, Antoniou AC. Incorporating tumour pathology information into breast cancer risk prediction algorithms. Breast Cancer Res. 2010;12(3):R28.
32. Evans DG, Lalloo F, Cramer A, Jones EA, Knox F, Amir E, Howell A. Addition of pathology and biomarker information significantly improves the performance of the Manchester scoring system for BRCA1 and BRCA2 testing. J Med Genet. 2009;46 (12):811–7.
33. Kwon JS, Gutierrez-Barrera AM, Young D, Sun CC, Daniels MS, Lu KH, Arun B. Expanding the criteria for BRCA mutation testing in breast cancer survivors. J Clin Oncol. 2010;28(27):4214–20.
34. Brekelmans CT, Tilanus-Linthorst MM, Seynaeve C, vd Ouweland A, Menke-Pluymers MB, Bartels CC, Kriege M, van Geel AN, Burger CW, Eggermont AM, et al. Tumour characteristics, survival and prognostic factors of hereditary breast cancer from BRCA2-, BRCA1- and non-BRCA1/2 families as compared to sporadic breast cancer cases. Eur J Cancer. 2007;43 (5):867–76.
35.•• Alsop K, Fereday S, Meldrum C, de Fazio A, Emmanuel C, George J, Dobrovic A, Birrer MJ, Webb PM, Stewart C, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol. 2012;30(21):2654–63.

This work correlated BRCA mutation rates with serous histology and demonstrated that BRCA mutation status (germline and somatic) influences treatment response and survival among women with nonmucinous ovarian carcinoma.

36.•• Palomaki GE, McClain MR, Melillo S, Hampel HL, Thibodeau SN. EGAPP supplementary evidence re-

view: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. Genet Med. 2009;11(1):42–65.

This important paper summarizes the evidence-based review process done by the independent Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group that resulted in a recommendation to offer a series of genetic tests for Lynch syndrome to all individuals with newly diagnosed colorectal cancer, to reduce morbidity and mortality in family members.

37.• Bellcross CA, Bedrosian SR, Daniels E, Duquette D, Hampel H, Jasperson K, Joseph DA, Kaye C, Lubin I, Meyer LJ, et al. Implementing screening for Lynch syndrome among patients with newly diagnosed colorectal cancer: summary of a public health/clinical collaborative meeting. Genet Med. 2012;14(1):152–62.

In follow up to [Palomaki] authors explore issues surrounding implementation of the EGAPP recommendation for universal Lynch syndrome testing. This paper acknowledged that effective implementation of this strategy will require multilevel and multidisciplinary approaches built on public health and clinical partnerships.

38.• Robson ME, Storm CD, Weitzel J, Wollins DS, Offit K. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. J Clin Oncol. 2010;28(5):893–901.

This statement, by members of American Society of Clinical Oncology's (ASCO's) Cancer Prevention and Ethics Committees, is an update of previous ASCO genetic testing policy statements. It reviews progress in priority areas identified previously and addresses how new developments, including the availability of genetic tests for low-penetrance genetic variants and direct-to-consumer genetic testing, impact the practice of oncology and preventive medicine.

39. Epplein M, Koon KP, Ramsey SD, Potter JD. Genetic services for familial cancer patients: a follow-up survey of National Cancer Institute Cancer Centers. J Clin Oncol. 2005;23(21):4713–8.

40. Cass I, Baldwin RL, Varkey T, Moslehi R, Narod SA, Karlan BY. Improved survival in women with BRCA-associated ovarian carcinoma. Cancer. 2003;97(9):2187–95.

41. Boyd J, Sonoda Y, Federici MG, Bogomolniy F, Rhei E, Maresco DL, Saigo PE, Almadrones LA, Barakat RR, Brown CL, et al. Clinicopathologic features of BRCA-linked and sporadic ovarian cancer. JAMA. 2000;283(17):2260–5.

42. Chetrit A, Hirsh-Yechezkel G, Ben-David Y, Lubin F, Friedman E, Sadetzki S. Effect of BRCA1/2 mutations on long-term survival of patients with invasive ovarian cancer: the national Israeli study of ovarian cancer. J Clin Oncol. 2008;26(1):20–5.

43. Tan DS, Rothermundt C, Thomas K, Bancroft E, Eeles R, Shanley S, Ardern-Jones A, Norman A, Kaye SB, Gore ME. "BRCAness" syndrome in ovarian cancer: a case–control study describing the clinical features and outcome of patients with epithelial ovarian cancer associated with BRCA1 and BRCA2 mutations. J Clin Oncol. 2008;26(34):5530–6.

44. Ben David Y, Chetrit A, Hirsh-Yechezkel G, Friedman E, Beck BD, Beller U, Ben-Baruch G, Fishman A, Levavi H, Lubin F, et al. Effect of BRCA mutations on the length of survival in epithelial ovarian tumors. J Clin Oncol. 2002;20(2):463–6.

45. Popat S, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. J Clin Oncol. 2005;23(3):609–18.

46. Sinicrope FA, Sargent DJ. Molecular pathways: microsatellite instability in colorectal cancer: prognostic, predictive, and therapeutic implications. Clin Cancer Res. 2012;18(6):1506–12.

47. Scheuer L, Kauff N, Robson M, Kelly B, Barakat R, Satagopan J, Ellis N, Hensley M, Boyd J, Borgen P, et al. Outcome of preventive surgery and screening for breast and ovarian cancer in BRCA mutation carriers. J Clin Oncol. 2002;20(5):1260–8.

48. Komenaka IK, Ditkoff BA, Joseph KA, Russo D, Gorroochurn P, Ward M, Horowitz E, El-Tamer MB, Schnabel FR. The development of interval breast malignancies in patients with BRCA mutations. Cancer. 2004;100(10):2079–83.

49.•• Pijpe A, Andrieu N, Easton DF, Kesminiene A, Cardis E, Nogues C, Gauthier-Villars M, Lasset C, Fricker JP, Peock S, et al. Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations: retrospective cohort study (GENE-RAD-RISK). BMJ. 2012;345:e5660.

This study examined the impact of diagnostic radiation, including mammography, before age 30 years on breast cancer risk among those with BRCA mutations, revealing exposure to diagnostic radiation before the age of 30 was associated with an increased risk of breast cancer. The results of this study support the use of non-ionizing radiation imaging modalities, i.e., magnetic resonance imaging, as the main tool for surveillance in young HBOC-affected women.

50. Kriege M, Brekelmans CT, Boetes C, Besnard PE, Zonderland HM, Obdeijn IM, Manoliu RA, Kok T, Peterse H, Tilanus-Linthorst MM, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med. 2004;351(5):427–37.

51. Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. Ann Intern Med. 2008;148(9):671–9.

52. Sardanelli F, Podo F, D'Agnolo G, Verdecchia A, Santaquilani M, Musumeci R, Trecate G, Manoukian S, Morassut S, de Giacomi C, et al. Multicenter comparative multimodality surveillance of women at genetic-familial high risk for breast cancer (HIBCRIT study): interim results. Radiology. 2007;242(3):698–715.

53. Plevritis SK, Kurian AW, Sigal BM, Daniel BL, Ikeda DM, Stockdale FE, Garber AM. Cost-effectiveness of screening BRCA1/2 mutation carriers with breast magnetic resonance imaging. JAMA. 2006;295(20):2374–84.
54. Goff BA, Mandel LS, Melancon CH, Muntz HG. Frequency of symptoms of ovarian cancer in women presenting to primary care clinics. JAMA. 2004;291(22):2705–12.
55. Friedman GD, Skilling JS, Udaltsova NV, Smith LH. Early symptoms of ovarian cancer: a case–control study without recall bias. Fam Pract. 2005;22(5):548–53.
56. Hermsen BB, Olivier RI, Verheijen RH, van Beurden M, de Hullu JA, Massuger LF, Burger CW, Brekelmans CT, Mourits MJ, de Bock GH, et al. No efficacy of annual gynaecological screening in BRCA1/2 mutation carriers; an observational follow-up study. Br J Cancer. 2007;96(9):1335–42.
57. Olivier RI, Lubsen-Brandsma MA, Verhoef S, van Beurden M. CA125 and transvaginal ultrasound monitoring in high-risk women cannot prevent the diagnosis of advanced ovarian cancer. Gynecol Oncol. 2006;100(1):20–6.
58. Gaarenstroom KN, van der Hiel B, Tollenaar RA, Vink GR, Jansen FW, van Asperen CJ, Kenter GG. Efficacy of screening women at high risk of hereditary ovarian cancer: results of an 11-year cohort study. Int J Gynecol Cancer. 2006;16 Suppl 1:54–9.
59. Oei AL, Massuger LF, Bulten J, Ligtenberg MJ, Hoogerbrugge N, de Hullu JA. Surveillance of women at high risk for hereditary ovarian cancer is inefficient. Br J Cancer. 2006;94(6):814–9.
60.•• Iodice S, Barile M, Rotmensz N, Feroce I, Bonanni B, Radice P, Bernard L, Maisonneuve P, Gandini S. Oral contraceptive use and breast or ovarian cancer risk in BRCA1/2 carriers: a meta-analysis. Eur J Cancer. 2010;46(12):2275–84.

This meta-analysis of 2855 breast cancer cases and 1503 ovarian cancer cases reported the benefit of oral contraceptive use in hereditary ovarian cancer, with a summary relative risk for ovarian cancer of 0.5 found for oral contraceptive users compared with non-users, and no significant increased risk of breast cancer found (increased risk of breast cancer with oral contraceptive with formulations made prior to 1975 has been found, but not with more recent formulations). Thus previously-reported benefits of oral contraceptive use in ovarian cancer without regard to BRCA1/2 carrier status have shown benefit specifically in BRCA1/2 carriers in this study.

61. Narod SA, Risch H, Moslehi R, Dorum A, Neuhausen S, Olsson H, Provencher D, Radice P, Evans G, Bishop S, et al. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. N Engl J Med. 1998;339(7):424–8.
62. Narod SA, Dube MP, Klijn J, Lubinski J, Lynch HT, Ghadirian P, Provencher D, Heimdal K, Moller P, Robson M, et al. Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst. 2002;94(23):1773–9.
63. Jernstrom H, Loman N, Johannsson OT, Borg A, Olsson H. Impact of teenage oral contraceptive use in a population-based series of early-onset breast cancer cases who have undergone BRCA mutation testing. Eur J Cancer. 2005;41(15):2312–20.
64. Gronwald J, Byrski T, Huzarski T, Cybulski C, Sun P, Tulman A, Narod SA, Lubinski J. Influence of selected lifestyle factors on breast and ovarian cancer risk in BRCA1 mutation carriers from Poland. Breast Cancer Res Treat. 2006;95(2):105–9.
65. Milne RL, Knight JA, John EM, Dite GS, Balbuena R, Ziogas A, Andrulis IL, West DW, Li FP, Southey MC, et al. Oral contraceptive use and risk of early-onset breast cancer in carriers and noncarriers of BRCA1 and BRCA2 mutations. Cancer Epidemiol Biomarkers Prev. 2005;14(2):350–6.
66. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. J Natl Cancer Inst. 2009;101(2):80–7.
67. Gien LT, Mackay HJ. The Emerging Role of PARP Inhibitors in the Treatment of Epithelial Ovarian Cancer. J Oncol. 2010;2010:151750.
68.•• Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, Mortimer P, Swaisland H, Lau A, O'Connor MJ, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med. 2009;361(2):123–34.

This study summarizes the results of a phase I trial of a poly (adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitor, olaparib (AZD2281), in ovarian, breast, and prostate cancer patients, enriched for those with BRCA1 or BRC2 mutations. It found acceptable levels of toxicity and selective anti-tumor response in those with BRCA1/2 mutations. These early results were encouraging and subsequent phase II trials in advanced breast and ovarian cancer in BRCA1/2 carriers were undertaken.

69.•• Fong PC, Yap TA, Boss DS, Carden CP, Mergui-Roelvink M, Gourley C, De Greve J, Lubinski J, Shanley S, Messiou C, et al. Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. J Clin Oncol. 2010;28(15):2512–9.

This expansion trial to [Fong 68], reported the results of a study of olaparib in ovarian cancer patients with documented or strongly suspected BRCA1/2 mutations. Complete or partial response to the drug was found in 40% of the 50 patients treated, and 46% of patients showed clinical benefit, with response rate correlated with platinum sensitivity. While these early results of the drug were encouraging, a press release by AstraZeneca in 2011 (http://www.astrazeneca.com/Media/Press-releases/Article/20111220-az-updates-olaparib-TC5214-development) indi-

cated that phase III trials in maintenance treatment of serous ovarian cancer would not be undertaken due to interim analysis of phase II results suggesting that the previously reported progression-free survival benefit was not likely to translate into improved overall survival.

70. Edwards SL, Brough R, Lord CJ, Natrajan R, Vatcheva R, Levine DA, Boyd J, Reis-Filho JS, Ashworth A. Resistance to therapy caused by intragenic deletion in BRCA2. Nature. 2008;451(7182):1111–5.
71. Rijcken FE, Mourits MJ, Kleibeuker JH, Hollema H, van der Zee AG. Gynecologic screening in hereditary nonpolyposis colorectal cancer. Gynecol Oncol. 2003;91(1):74–80.
72. Renkonen-Sinisalo L, Butzow R, Leminen A, Lehtovirta P, Mecklin JP, Jarvinen HJ. Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. Int J Cancer. 2007;120 (4):821–4.
73. Dove-Edwin I, Boks D, Goff S, Kenter GG, Carpenter R, Vasen HF, Thomas HJ. The outcome of endometrial carcinoma surveillance by ultrasound scan in women at risk of hereditary nonpolyposis colorectal carcinoma and familial colorectal carcinoma. Cancer. 2002;94(6):1708–12.
74. Gerritzen LH, Hoogerbrugge N, Oei AL, Nagengast FM, van Ham MA, Massuger LF, de Hullu JA. Improvement of endometrial biopsy over transvaginal ultrasound alone for endometrial surveillance in women with Lynch syndrome. Fam Cancer. 2009;8(4):391–7.
75. Combination oral contraceptive use and the risk of endometrial cancer. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. *JAMA* 1987, 257(6):796–800.
76. van Leeuwen FE, Rookus MA. The role of exogenous hormones in the epidemiology of breast, ovarian and endometrial cancer. Eur J Cancer Clin Oncol. 1989;25(12):1961–72.
77. Schmeler KM, Lynch HT, Chen LM, Munsell MF, Soliman PT, Clark MB, Daniels MS, White KG, Boyd-Rogers SG, Conrad PG, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med. 2006;354(3):261–9.
78. van Oostrom I, Meijers-Heijboer H, Lodder LN, Duivenvoorden HJ, van Gool AR, Seynaeve C, van der Meer CA, Klijn JG, van Geel BN, Burger CW, et al. Long-term psychological impact of carrying a BRCA1/2 mutation and prophylactic surgery: a 5-year follow-up study. J Clin Oncol. 2003;21(20):3867–74.
79. Meijers-Heijboer EJ, Verhoog LC, Brekelmans CT, Seynaeve C, Tilanus-Linthorst MM, Wagner A, Dukel L, Devilee P, van den Ouweland AM, van Geel AN, et al. Presymptomatic DNA testing and prophylactic surgery in families with a BRCA1 or BRCA2 mutation. Lancet. 2000;355(9220):2015–20.
80. Hurley K, Rubin LR, Werner-Lin A, Sagi M, Kemel Y, Stern R, Phillips A, Cholst I, Kauff N, Offit K: Incorporating information regarding preimplantation genetic diagnosis into discussions concerning testing and risk management for BRCA1/2 mutations: A qualitative study of patient preferences. *Cancer* 2012.
81. Bakos AD, Hutson SP, Loud JT, Peters JA, Giusti RM, Greene MH. BRCA mutation-negative women from hereditary breast and ovarian cancer families: a qualitative study of the BRCA-negative experience. Health Expect. 2008;11(3):220–31.
82. Stein CJ, Colditz GA. Modifiable risk factors for cancer. Br J Cancer. 2004;90(2):299–303.