# АКТУАЛЬНЫЕ ВОПРОСЫ ДИАГНОСТИКИ И ЛЕЧЕНИЯ ЗЛОКАЧЕСТВЕННЫХ НОВООБРАЗОВАНИЙ


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## BREAST CANCER AND GENETICS

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**Breast cancer and genetics**

A Role for Common Genomic variants in the assessmrnt of familial breast cancer

Breast cancer is a common disorder with a significant heritable component. Clinical service dedicated to the management of familial breast cancer risk have principally focused on the identification of families segregating rare high-penetrance breast cancer genes, such as BRCA1 and BRCA2, which are associated with the highest lifetime cancer risks. Together, the known high and moderate risk genes are thought to account for no more than 25 % of the familial aggregation of breast cancer. Consequently, the majority of diagnostic genetic tests performed in the clinical setting yield uninformative results that provide minimal assistance in the clinical management of the individual and do not contribute to an understanding of the familial breast cancer risk in the family.

Major efforts have been made to explain the remaining heritable risk of breast cancer through large genome-wide association studies (GWAS) that seek to identify common variants in the genome associated with increased breast cancer risk. To date, more than 20 risk alleles have been identified in large, high-quality studied that reach the stringent standards of genome wide significance. These studies provide clear evidence that common variants have a role in

the etiology of breast cancer, but the integration of this information into clinical practice is yet to be resolved.

**Evaluating Breast Cancer Risk With Genome-Wide Association Studies: is This Approach Patient Ready?**

In contrast to mutation analysis, Genome-Wide Association Studies (GWASs) involve the identification of single-nucleotide polymorphisms (SNPs) in large cohorts of patients, with the goal of discovering variants that may identity or contribute to risk of different traits of diseases. Through this approach, multiple SNPs have been identified with possible risk associations for breast cancer using advanced biostatistics and sound scientific methods. Through the use of GWASs, there is promise of further refining risk models to aid in counseling patients and making risk reduction interventions.

However, GWASs of individual SNPs have not yet been able to propel this technology to a clinically meaningful use for patients, even in the setting of high-risk BRCA mutation carriers. Although risk has been identified, often only modest increases have been seen, and the level of increased risk has not yet reached a threshold to rule in or rule out preventative measures in high-risk persons. Therefore, given the polygenic nature of breast cancer, harnessing this technology to find a potential SNP panel that is clinically meaningful is ongoing and important

**Risk of Asynchronous Contralateral Breast Cancer in Noncarriers of BRCA1 and BRCA2 Mutations with a Family History of Breast Cancer: A Report from the Women's Environmental Cancer and Radiation**

*Epidemiology Study*

A family history of breast cancer is a well-established and significant risk factor for breast cancer. Relative risks vary depending on the age at diagnosis of the affected relative(s) and the number of affected relatives, ranging from two-fold for one affected first-degree relative to three-fold for two affected first-degree relatives and fourfold for three affected first-degree relatives. Young ages at diagnosis and bilaterality in first-degree relatives further increased risk.

After diagnosis of a first primary breastcancer, women with an intact contralateral breast are at risk of developing contralateral breast cancer (CBC). The majority of studies, but not all, have identified family history as a risk factor for CBC. From the few studies presenting risk by detailed family history, there is evidence that a family history of bilateral breast cancer, multiple affected relatives, and early-onset disease significantly increase risk of CBC.

We and others have shown that CBC risk is greatly increased in women carrying deleterious mutations in BRCA1 or BRCA2 and that the magnitude of this association is modified by age at diagnosis of the first breast cancer. Graeser et al. found that women who were carrying a deleterious mutation in BRCA1 or BRCA2 and who were older than 50 years at first breast cancer diagnosis had a 10-year CBC risk of 8.4 %, whereas carries younger than 40 years had



a 10-year CBC risk of 28.3 %. In the Women's Environmental Cancer and Radiation Epidemiology (WECARE) Study, we previously reported that the youngest women (25 to 29 years) who were carrying a deleterious BRCA1 or BRCA2 mutation had a 10-year CBC risk of 28.2 % and those older than 50 years had an analogous risk of 10.8 %.

No studies to date have examined the predictive contribution of various components of family history in relation to the risk of CBC for women in whom no mutation in BRCA1 or BRCA2 has been identified. Our goal in this study is to more clearly define risk prediction for women with a first primary breast cancer who test negatively for deleterious BRCA1 and BRCA2 mutations.

**Screening of 185DelAG, 1014DelGT and 3889DelAG BRCA1 Mutations in Breast Cancer Patients from North-East India**

Globally, breast cancer is the most common cause of cancer-related death in women, with around 327,000 deaths each year. Around 1.35 million cases of breast cancer have been found each year and 4.4 million women are believed to be live with breast cancer worldwide. It has been speculated that in 2020, around 1.7 million women will be diagnosed with breast cancer, which is an increased of about 26 % in the developing world from current levels (Wong et al., 2009). In India, almost 100,000 women are diagnosed every year with breast cancer, and a rise to 131,000 cases is predicted by 2020 (Agarwal et al., 2008; Mangtani et al., 2010).

And in North-East India breast cancer has always been a hotspot in comparison to rest part of the India because of genotoxic stress from tobacco exposure (Sunita et al., 2010).

Several environmental risk factors that may contribute to or hasten the development of breast cancer have been identified, including mainly lifestyle and reproductive factors. The factor with the strongest breast cancer risk association is a family history of breast and/or ovarian cancer, the associated risk being even higher for family history of early-onset disease (< age 40) (Datta et al., 2009). Genetic susceptibility to breast cancer is triggered in several ways; the best understood causal mechanism being due to germline mutations in tumor suppressor genes. Together, mutations in BRCA1and BRCA2 genes account for the great majority of families with hereditary susceptibility to breast and ovarian cancer (Ford et al., 1998).

Among breast cancer patients, up to 5 % ~ 10 % are considered directly relating to the inheritance of mutation in BRCA1 (MIM 113705, Genbank accession no. U14680) and BRCA2 (MIM 600185, Gene bank accession no. U43746), which accounts for most of the hereditary breast cancers (Claus et al., 1994). Moreover, women carrying these mutations have 60 % ~ 80 % prone to breast cancer and ovarian cancer (Wooster et al., 2003). The BRCA1 gene is located on long arms of chromosomes 17 and it encodes a protein of 1863 amino acids (Hall et al., 1990). The protein physically associates with p53 and involved

in homologous recombination (HR) and double-strand break repair in response to DNA damage (Greenberg, 2008; Zhang et al., 2010). Miki et al. describes that BRCA1 is a strong candidate for the breast and ovary cancer (Miki et al., 1994). The spectrum of BRCA1 mutations has been characterized in different populations worldwide, with significant variation of the relative contribution of this genes to hereditary cancer between populations (Brozek et al., 2011). However, the contribution of mutations in these two genes to breast cancer patients in the Indian population remains relatively unexplored apart from a few small studies (Saxena et al., 2006). Thus, the screening of prevalence of mutations in BRCA1 gene will serve as a molecular predictor for women with breast cancer along with ovarian cancer in North-East Indian population.

**Three deleterious nonsense mutations resulting in a premature termination codon were identified in BRCA1: 185DelAG in exon 2; 1014DelGT and 3889Del AG in exon 11, rather absent in the observed control group**

Worldwide population studies have revealed that the 185DelAG mutation predates the severance of Sephardi and Ashkenazi Jewish populations and is probably 2000 years old (Bar-Sade et al., 1998).

Genetic variants associated with breast cancer risk for Ashkenazi Jewish women with strong family histories but on identifiable BRCA1/2 mutation.

Breast cancer continues to be the most common gender-specific malignancy and a leading cause of death in the United States, accounting for nearly one-third of all new cancer in females (Jemal et al., 2010; Siegel et al., 2011). Breast cancer ranks as the most common cause of cancer deaths among women between the ages of 20 and 59 years, highlighting the need for accurate risk assessment for women in this age group.

Family history is an important risk factor for breast cancer. The risk of developing breast cancer for a woman with a first-degree affected relative is increased twofold (Easton et al., 2007). The risk is even greater for women with multiple cases in family members. Brest cancer risk may be attributable to mutations in high-penetrance genes such as BRCA1, BRCA2, p53 and PTEN, as well as moderate or low penetrance genes (e. g., CHEK2, ATM, HRAS1, BRIP1, and PALB2), but these mutations account for a relatively small proportion of the heritable risk in these breast cancer families (Easton, 1999; Walsh et al., 2006, 2010).

To date genome-wide association studies (GWAS) have used high-density genotyping successfully primarily in European-American populations identify SNPs associated with breast cancer risk in several genes including FGFR2, TNRC9, MAP3K1, LSP1, CASP8, SLC4A7, NEK10 and COX11 and the 8q and 2q35 chromosomal regions (Ahmed et al., 2009; Cox et al., 2007; Easton et al., 2007; Rahman et al., 2007; Stacey et al., 2007).

Variability of risk allele frequency and effect size has been observed among major ethnic groups (European, African and Asian) for a panel of com-



plex disease SNPs that had reached genome-wide significance in at least one of the groups (Ntzani et al., 2011).

The current study utilizes the Ashkenazi Jewish (AJ) population, the largest genetic isolate in the United States, comparising 2 % of the total population (Stacey et al., 2007).

The study of this group reduces the major confounding effect of population stratification and holds the promise of identifying founder mutations and less common mutations not easily identifiable in the general population.

**Hereditary breast cancer in the Han Chinese Population**

Breast cancer has an incidence rate of 16.39 per 100,000 Chinese women and seriously affects the lives and health of this population. Among women in economically developed Chinese provinces and cities, breast cancer has the highest incidence of all cancer and is the fourth most common cause of cancer death. Breast cancer also has a strong genetic background. Hereditary breast cancer tends to display familial aggregation and is associated with early age at onset and a high incidence of bilateral occurrence. Since the discovery of the breast cancer susceptibility genes BRCA1 and BRCA2 in 1994, a total of 18 breast cancer-associated susceptibility genes have been identified. These genes include breast cancer susceptibility genes with high penetrance (CDH1, NBS1, NF1, PTEN, TP53, and STK11), moderate penetrance (ATM, BRIP1, CHEK2, PALB2, and RAD50), and low penetrance (FGFR2, LSP1, MAP3K1, TGFB1, and TOX3).

China has 56 ethnic groups, but the Han ethnic group makes up more than 90 % of the country's population.

BRCA1 and BRCA2 are located on chromosomes 17q21 and 13q12.3, respectively. BRCA1 consists of 24 exons, of which exons 1 and 4 are non-coding. BRCA2 consists of 27 exons, of which exon 1 is non-coding. The BRCA1 and BRCA2 proteins have an important role in repairing DNA double-stranded breaks.

Germline mutations in these 2 genes contribute to the pathogenesis of 20 % to 40 % of familial breast cancer in whites, thus accounting for 5 % of all breast cancers.

In addition to BRCA1 and BRCA2, other breast cancer susceptibility genes have also been extensively studied in Chinese.

The protein of the TP53 gene has important roles in the control of cell cycle progression, repair of DNA damage, genomic stability, and apoptosis. TP53 mutations are found in 50 % to 70 % of individuals with Li–Fraumeni syndrome, an autosomal dominant inherited disease that was first reported in 1969 and is a rare cancer-predisposing syndrome.

The BRIP1 gene is also known as BACH1. Biallelic mutation carriers of this gene are susceptible to Fanconi anemia. The BACH1 protein binds with

the BRCT protein binding sites and has a key role in repair of DNA double-stranded breaks via the BRCA1 pathway.

Like the BRIP1 gene, individuals with biallelic mutations in PALB2 are susceptible to Fanconi anemia. The PALB2 protein can bind the N-terminal of the BRCA2 protein and has an important role in DNA stability. Rahman et al. reported truncating PALB2 mutations in 10/923 individuals with familial breast cancer and no such mutations in healthy controls, suggesting that such mutations conferred a relative risk of 2.3 for breast cancer.

The CDH1 gene encodes E-cadherin, the calcium-dependent cell-cell adhesion glycoprotein. CDH1 gene mutation is related to hereditary diffuse gastric cancer and lobular carcinoma of the breast. The risk of breast cancer was 50 % higher in women with a family history of diffuse gastric breast cancer.

The CHEK2 gene encodes a cell cycle checkpoint kinase. When DNA is damaged, CHEK2 is activated by ATM, resulting in phosphorylation of BRCA1, which has a role in the repair of DNA double-stranded breaks. The CHEK2 1100delC mutation has been found to double the risk of breast cancer in women.

**PTEN**

The PTEN gene codes a dual-specificity phosphatase with lipid and protein phosphatase activity. Mutations in the PTEN gene cause Cowden syndrome, a rare autosomal dominant inherited disease that predisposes affected individuals to breast cancer, thyroid carcinoma, endometrial carcinoma, and hamartoma with high fat content.

The protein expressed by the ATM gene plays a role in DNA double-stranded break repair pathways by upstreaming the BRCA1 gene. Biallelic mutation of the ATM gene cause ataxia telangiectasia, which manifests as cerebellar ataxia, immune deficiency, and a variety of tumors such as leukemia, lymphoma, glioma, medulloblastoma, and breast cancer.

**RAD50 and NBS1**

The proteins of the genes NBS1, RAD50, and MRE11 from MRN complex, which has a role in the identification and repair of DNA double-stranded breaks. Mutations in the NBS1 gene cause Nijmegen breakage syndrome, an autosomal recessive inherited disease that manifests as microcephaly, growth retardation, immunodeficiency, and cancer susceptibility.

**Management of Genetic Syndromes Predisposing to Gynecologic Cancer**

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.



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.

In the decade since publications 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 hereditary breast and ovarian cancer (HBOC) associated with mutations in BRCA1 and BRCA2, and 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.

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.

**Incidence**

Estimates of BRCA**1/2** 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, as well as in families with early-onset cancers or with multiple cases of breast and/or ovarian cancer. An estimated 3–5 % of breast cancer and 10–15 % of ovarian cancer has been attributed to BRCA**1/2** mutations.

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. 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 BRCA2 mutations, respectively. 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, 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. 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)

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 mutations versus a BRCA1 mutations (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). A most recent population-based, nested case control study of CBC risk reported cumulative 5- and 10-years 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). Long term CBC risk among those with BRCA1/2 mutations is reported as 47.4 % at 25 years.



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 rearrangement 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 617 del T.

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. 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 doublestranded DNA breaks and interstrand crosslinks. 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 neo-plastic transformation.

HBCO-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. 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 theme. The most widely applied models are BRCAPRO, Myriad II, and BOADICEA.

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. Genetic counseling facilitates informed decisions about genetic testing and medical management options, improves knowledge of cancer risk, provides information on available support resources (p. 94), 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. In response to growing demands for cancer genetic risk assessment, counseling, and testing, cancer genetic counseling services have recently increased nationally. The National Society of Genetic Counselors provides an up-to-date link to available genetic counseling services across the country.

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 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

Screening

The goal of 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 internal cancers (cancers detected between screening exams). Furthermore, data are limited regarding the safety of early mammograms among those with BRCA mutations. A recent retrospective cohort study of 1933 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.



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. 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 %).

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. 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, whereas other studies fail to show an elevated risk.

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.

**Emerging therapies**

Poly (ADP-ribose) polymerase (PARP) is a novel target for the management of those with HBCO-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.

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 group 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 relationship, those who elected risk-reducing surgery had reduced fears of developing cancer and noted satisfaction with their surgical decision.

**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 cancer. 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, 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.