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Review and Meta-analysis

Hereditary Breast and Ovarian Cancer Syndromes

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Women who inherit a mutation in the BRCA1 or BRCA2 gene are much more likely to develop breast and ovarian cancer. A woman’s specific risk depends on many factors including her age, whether she has a BRCA1 or BRCA2 mutation, and her medical and family history. Most women with breast or ovarian cancer have a sporadic cancer. The majority of women with inherited breast and/or ovarian cancers carry a pathogenic variant (ie, deleterious or harmful mutation) in breast cancer susceptibility gene 1 (BRCA1) or breast cancer susceptibility gene 2 (BRCA2), some hereditary breast cancers are due to other rare hereditary syndromes, such as Li-Fraumeni and Cowden syndromes, which are associated with pathogenic variants in the tumor protein p53 (TP53) and phosphatase and tensin homolog tumor suppressor (PTEN) genes, respectively. Pathogenic variants in other genes also confer a heightened risk of breast and/or ovarian cancer.hereditary breast and ovarian cancer syndromes associated with genes other than BRCA1/2.

Introduction

High-Penetrance Genes for Breast and/or Ovarian Cancer [1]

Breast cancer is a common cancer affecting a large number of patients. Notably, 5-10% of all breast cancer patients are genetically predisposed to cancers. Although the most common breast cancer susceptibility genes are BRCA1 and BRCA2, which are also associated with the risk of developing ovarian and pancreatic cancer, advances in next-generation sequencing (NGS) analysis technology enabled the discovery of several non-BRCA genes responsible for breast and ovarian cancers. Taking advantage of knowing predisposition of susceptibility to cancer, it is important to continue and update cancer management protocols, which includes the adoption of preventive measures, countermeasures, and treatments, to accurately assess and prevent the impact of cancer on the quality of life of the next generation of patients. The following are syndromes which you may don’t hear about it in relation with cancers:

TP53 (Li-Fraumeni syndrome), PTEN (PTEN hamartoma tumor syndrome), STK11 (LKB1, Peutz-Jegher Syndrom), CDH1(Hereditary diffuse gastric cancer syndrome), MSH, MLH1, MSH6, PMS2 and EPCAM (lynch syndrome), MODERATE-PENETRANCE GENES FOR BREAST, AND/OR OVARIAN CANCER CHEK2, ATM ,OTHER genes, BARD1, BRIP1, RAD51 paralogs, MUTYH, NF1, NBN.

TP53 (Li-Fraumeni) syndrome [2]

Germline pathogenic variants in the tumor protein p53 gene (TP53) multiple primary cancers in childhood or young adulthood lifetime cancer risk approaching 100 percent, specially breast cancer risk.sarcomas, brain cancer, leukemias, medulloblastoma, and adrenocortical cancers offered risk-reducing mastectomy (RRM) some may opt instead for early breast cancer screening supplemented with magnetic resonance imaging (MRI). ovarian, fallopian tube, and peritoneal cancers have reported in families with LFS, TP53 mutations. TP53 (Li-Fraumeni) syndrome.

Women with LFS are at high risk for premenopausal breast cancer. The lifetime risk of breast cancer for female mutation carriers 50 percent by age 60 years [3].

The mean age of onset is under 35 years, and a first diagnosis of breast cancer is rare over age 50 years .

Between 64 and 83 percent of breast cancers in these carriers are positive for human epidermal growth factor receptor 2 (HER2) carriers are at increased risk to develop secondary malignancies in radiation fields female carriers with breast cancer who receive radiotherapy are at increased risk for new primaries, especially within the breast, as well as radiation-induced cancers. Women with LFS who develop breast cancer are generally recommended to undergo mastectomy, rather than lumpectomy and radiation, given the risks of radiation-induced malignancies in this syndrome. Other clinical manifestations of LFS are discussed separately [4].

STK11 (LKB1, Peutz-Jeghers syndrome)

Pathogenic variants in the serine/threonine kinase 11 gene (STK11, also called LKB1). Mucocutaneous pigmented lesions occur in about 95 percent of affected patients [5]. Hamartomatous polyps in the gastrointestinal tract are hallmark features very elevated risks for gastrointestinal cancers, including cancers of the colon and rectum, stomach, small intestine, and pancreas , breast and ovarian cancers, ovarian cancers are often sex-cord stromal tumors, which are nonepithelial in origin STK11 (LKB1, Peutz-Jeghers syndrome).Women with PJS are offered early breast cancer screening with supplemental MRI.The evidence is insufficient to uniformly recommend RRM, although for those with a concerning family history (>20 percent risk of breast cancer by a model), PRM be reasonable STK11 (LKB1, Peutz-Jeghers syndrome) pathogenic variants in the serine/threonine kinase 11 gene (STK11, also called LKB1) . Mucocutaneous pigmented lesions occur in about 95 percent of affected patients hamartomatous polyps in the gastrointestinal tract are hallmark features .very elevated risks for gastrointestinal cancers, including cancers of the colon and rectum, stomach, small intestine, and pancreas, as well as breast and ovarian cancers ovarian cancers are often sex-cord stromal tumors, which are nonepithelial in origin. STK11 (LKB1, Peutz-Jeghers syndrome) [6].

Women with PJS are offered early breast cancer screening with supplemental MRI.The evidence is insufficient to uniformly recommend RRM, although for those with a concerning family history (>20 percent risk of breast cancer by a model), it may be reasonable for carriers to consider this option (STK11 (LKB1, Peutz-Jeghers syndrome) [7].

Screening for endometrial and ovarian cancer in women with PJS iscontroversial. The absolute risk of breast cancer is approximately 55 percent and, in general, the diagnosis tends to occur in younger women, with a mean age of 37 years (range, 9 to 48 years). For ovarian cancer, the prevalence in one study was 21 percent among patients with PJS, diagnosed at a mean age of 28 years (range, 4 to 5years) [8].

PTEN (PTEN hamartoma tumor syndrome)

The phosphatase and tensin homolog tumor suppressor gene (PTEN) hamartoma tumor syndrome (PHTS) includes Cowden syndrome, which is the predominant disorder. All are associated with germline pathogenic variants in the PTEN gene. Carriers have elevated risks for breast, endometrial, and thyroid cancer, particularly follicular cancer. Women with PHTS are typically offered RRM, although some may opt instead for early breast cancer screening supplemented with MRI. Pathogenic variants in PTEN do not appear to confer a significantly increased risk for ovarian cancer, PTEN (PTEN hamartoma tumor syndrome). In a prospective study of almost 3400 patients meeting relaxed International Cowden Consortium PHTS criteria, including 368 individuals with a pathogenic variant, the estimated lifetime risk of developing breast cancer was 85 percent. Most cancers are diagnosed premenopausally between the ages of 38 and 46 years in one study, 50 percent were impacted by age 50. It is estimated that up to 67 percent of women with a PTEN pathogenic variant also have an increased risk of benign breast changes (eg, intraductal papillomatosis, adenosis, lobular atrophy, and fibroadenomas) [9].

CDH1 (Hereditary diffuse gastric cancer syndrome)

Characterized by a susceptibility to diffuse, highly invasive gastric cancer (also called signet ring carcinoma or isolated cell-type carcinoma). It is associated with germline pathogenic variants in the cadherin 1 gene (CDH1). Germline CDH1 mutations are also associated with development of lobular breast cancer in women, with a cumulative lifetime risk estimated to be as high as 50 to 60 percent. For those with pathogenic variants in CDH1, we typically initiate annual mammography with tomography and annual breast MRI, starting at age 30 years. Use of tomography is preferred in this population to increase cancer detection rates relative to mammography alone. The evidence is insufficient to uniformly recommend RRM, although for those with a concerning family history (>20 percent risk of breast cancer by a model), it is reasonable to consider this option. CDH1 (Hereditary diffuse gastric cancer syndrome) pathogenic variants in CDH1 do not appear to confer a significantly increased risk for ovarian cancer. CDH1 pathogenic variants can cosegregate with invasive lobular breast cancer in the absence of diffuse gastric cancer, suggesting that gastric cancer is not an obligatory hallmark of families with CDH1 mutations. Most CDH1 mutation carriers develop cancer before age 40 CDH1 pathogenic variants have been identified in up to 50 percent of affected kindreds who meet the clinical criteria for HDGC. with increased testing by multigene panels, several individuals with pathogenic variants in CDH1 have been identified who do not meet diagnostic testing criteria for hereditary diffuse gastric cancer [10, 11].

PALB2

Partner and localizer of BRCA2 (PALB2) is a breast cancer susceptibility gene that encodes a BRCA2-interacting protein. The BRCA2-PALB2 interaction is crucial for key BRCA2 DNA damage response functions as well as tumor suppression activity. Women who carry a monoallelic PALB2 pathogenic variant have a risk of breast cancer by age 70 that ranges from 33 to 58 percent depending on family history. Given this range of risk, and that the upper risk range can overlap with BRCA2 risks, PALB2 is considered to be a moderate to high-risk gene associated with hereditary breast cancer. For women with pathogenic variants in PALB2, we typically initiate annual mammography with tomography and annual breast MRI, starting at age 30 years. RRM may be an appropriate option for some patients, depending on their preferences, especially for those with a concerning family history (>20 percent risk of breast cancer by a model). Although pathogenic variants in PALB2 do not appear to confer a significantly increased risk for ovarian cancer, we discuss the potential risks and benefits of rrBSO with carriers who have a family history of ovarian cancer. For women with pathogenic variants in PALB2 [12, 13]. We typically initiate annual mammography with tomography and annual breast MRI, starting at age 30 years. RRM may be an appropriate option for some patients, depending on their preferences, especially for those

with a concerning family history (>20 percent risk of breast cancer by a model). Pathogenic variants in PALB2 do not appear to confer a significantly increased risk for ovarian cancer. The cumulative lifetime breast cancer risk to age 80 for all female carriers is approximately 44 percent,Whereas the cumulative risk to age 49 is about 14 percent [14]. In comparison with the general population, the relative risk of breast cancer for a woman with a PALB2 pathogenic variant based upon her age is

●Under 40 years – Eight- to ninefold increase

●40 to 60 years – Six- to eightfold increase

●Over 60 years – Fivefold increase

Breast cancer risk associated with a PALB2 pathogenic variant appears to be influenced by a family history of breast cancer and other as yet unidentified environmental and lifestyle factors. In a study of 362 members of 154 families with a PALB2 pathogenic variant, the absolute lifetime risk to age 70 years for the development of female breast cancer was dependent upon family history of breast cancer, as follows [15].

●No family history of breast cancer – 33 percent (95% CI 25-44)

●Two or more family members with breast cancer – 58 percent (95% CI 50-66)

Although rare, monoallelic deleterious PALB2 pathogenic

Although rare, monoallelic deleterious PALB2 pathogenic variants are present in a small but substantial proportion of patients with breast cancer including approximately 1 percent of patients with breast cancer and approximately 1 percent of patients with triple-negative breast cancer [16]. In high-risk families, pathogenic PALB2 variants were identified in 3.9 percent (13 of 409) of breast and/or ovarian cancer patients in the Czech Republic who were negative for BRCA1/2 mutations. Several studies have shown that PALB2 pathogenic variants also appear to be associated with an increased risk of pancreatic cancer,although the absolute risk is unclear. In addition, PALB2 pathogenic variants may also be associated with increased risk for breast cancer in men prostate cancer medulloblastoma, ovarian cancer [17].

Moderate-Penetrance Genes for Breast and/or Ovarian Cancer

In a case-control study of over 65,000 patients with breast cancer undergoing germline genetic testing using a multigene panel, after exclusion of BRCA1, BRCA2, and syndromic breast cancer genes cadherin 1 (CDH1), phosphatase and tensin homolog (PTEN), and tumor protein p53 (TP53), pathogenic variants in partner and localizer of BRCA2 (PALB2) were associated with the highest risks of breast cancer (odds ratio [OR] 7.46) variants in checkpoint kinase 2 (CHEK2; OR 1.48), ataxia-telangiectasia mutated(ATM; OR 2.78), BRCA1-associated RING domain 1 (BARD1; OR 2.16), and RAD51 paralog D (RAD51D; OR 3.07) were associated with moderate risks of breast cancer.variants in MRE11A, RAD50, nibrin (NBN), BRCA-interacting protein 1 (BRIP1), RAD51 paralog C (RAD51C), mutL homolog 1 (MLH1), and neurofibromatosis type 1 (NF1) were not associated with an increased risk of breast cancer [18]. A study of over 11,000 patients with breast and/or ovarian cancer and almost 4000 controls from the same database found that pathogenic variants in MSH6 in addition to PALB2, ATM, and CHEK2 were associated with an increased risk of breast cancer, and in MSH6, RAD51C, TP53, and ATM genes, were associated with an increased risk of ovarian cancer [19]. A study of over 11,000 patients with breast and/or ovarian cancer and almost 4000 controls from the same database found that pathogenic variants in MSH6 in addition to PALB2, ATM, and CHEK2 were associated with an increased risk of breast cancer and in MSH6, RAD51C, TP53, and ATM genes, were associated with an increased risk of ovarian cancer [20].

CHEK2

The checkpoint kinase 2 (CHEK2) gene is associated with the DNA damage repair response Fanconi anemia (FA)-BRCA1/2 pathway Several CHEK2 variants have been identified including one polymorphism (1100delC) that appears to be associated with a low- to moderate-penetrance breast cancer susceptibility allele. The 1100delC protein-truncating variant is associated with a two- to threefold increased risk of breast cancer, predominantly among white women of Northern or Eastern European descent [One study suggested that of those with this mutation, there is a 37 percent (95% CI 26 to 56 percent) risk of breast cancer by age 70 years. The lifetime cumulative risk of breast cancer to age 80 in women with this variant is about 32 percent, whereas the cumulative risk to age 49 is about 6 percent [21].

● Cancer risks associated with most missense variants in CHEK2 are unclear however, the breast cancer risk associated with some variants appears to be lower. For example, I157T is associated with only a modest increase in breast cancer risk (OR 1.58, 95% CI 1.42-1.75). Estimated age-specific risks for the I157T variant indicate that the cumulative lifetime risk of breast cancer to age 80 is about 18 percent, [22] whereas the cumulative risk of breast cancer to age 49 is about 3 percent. CHEK2 mutation carriers are significantly more likely to Be younger at the time of diagnosis (mean age, 50 versus 54; p <0.001)

•Have a family history of breast cancer (13 versus 10 percent; p <0.001)

•Develop estrogen receptor-positive breast cancers (63 versus 57 percent; p <0.001)

•Develop a second primary breast cancer (hazard ratio [HR] 3.52, 95% CI 2.35-5.27)

•Have a higher risk of an earlier death (HR 1.43, 95% CI 1.12-1.82)

•Have a higher breast cancer-specific death risk (HR 1.63, 95% CI 1.24-2.15)

The risks for other CHEK2-associated cancers are not well defined [23, 24].

However, the 1100delC variant appears to be associated with an increased risk for colorectal cancer, particularly in the setting of a family history of colon cancer. For example, the cumulative risk of colorectal cancer for 1100delC carriers to age 49 is estimated to be

0.6 percent, with a cumulative lifetime risk to age 85 for all carriers of about 12 percent]. This compares with a lifetime risk in the general population of about 6 percent.Studies have also found that CHEK2 carriers have increased risks for male breast cancer as well as stomach, prostate, kidney, and thyroid cancer and sarcoma. At present, there is no strong evidence that CHEK2 mutations confer an increased risk of ovarian cancer given how infrequently they are identified in women with ovarian cancer [25].

ATM

Monoallelic carriers of such pathogenic variants (ie, heterozygotes) are at approximately twofold higher risk of developing breast cancer than noncarriers, with a cumulative lifetime breast cancer risk of about 30 percent (and 6 percent to age 49). Rare pathogenic variants in the ataxia-telangiectasia mutated (ATM) gene may be associated with a substantially higher risk of breast cancer, so riskassessment based on genotype can be important. The risk of second primary breast cancer is not clear. Although it is also possible that there is an increased risk of ovarian cancer based on results of a case-control study these data need to be confirmed.It is estimated that

approximately 3 percent of Caucasians in the United States are ATM heterozygotes. In a retrospective study of 443 BRCA1/2-negative familial breast cancer patients and 521 control breast cancer patients, ATM mutations were more commonly identified in patients with familial breast cancer compared with the control population (12 versus 2 deleterious ATM mutations) [26]. Relatives of individuals with AT, especially obligate carrier mothers of affected children, should be informed about the elevated cancer risks and potential screening strategies. ATM pathogenic variants have also been associated with increased risks for pancreatic and ovarian cancer, but more data are needed to confirm these findings. The potential increased risk for this and other cancers has not been well characterized other genes [27-31].

●BARD1●BRIP1●RAD51 paralogs ●MUTYH ●NF1●NBN

Management of moderate-penetrance genes

Women who have pathogenic variants in NF1, ATM, CHEK2, BARD1, or NBN have a moderate lifetime risk of breast cancer those with mutations in BRIP1, RAD51C, or RAD51D have a moderate lifetime risk for breast or ovarian cancer, and as such are managed with surveillance and risk reduction strategies [28]. Pathogenic variants in NF1 initiate annual mammography with tomography and annual breast magnetic resonance imaging (MRI), starting at age 30 years [32]. Prophylactic risk-reducing mastectomy (RRM), depending on personal and family history risk factors. pathogenic variants in ATM, CHEK2, or NBN annual mammography with tomography and annual MRI, starting at age 40 years, given evidence of moderately increased lifetime risk of breast cancer. may consider prophylactic RRM, depending on personal and family history risk factors pathogenic variants in BRIP1, BARD1, and RAD51 paralogues. we do not perform early mammography or breast MRI unless their family history places them at increased risk [33]. Recommendations patient’s personal risk factors and family history screening modalities start (eg, 5 to 10 years before the earliest age of breast cancer diagnosis in the family) whether MRI is recommended ,whether mastectomy is offered. For women with pathogenic variants in other genes that are not known to be associated with increased risks for breast cancer, if models estimate their lifetime risk of breast cancer is 20 percent or higher, MRI screening is recommended. ovarian cancer screening in women with pathogenic variants in the moderate-penetrance genes do not recommend either imaging or cancer antigen (CA) 125 measurements given the limited efficacy; [29]. However we may recommend risk-reducing bilateral salpingo-oophorectomy (rrBSO) for some patients based on their genetic testing results, such as for RAD51C carriers. Women with CHEK2 mutations and MSH/MUTYH mutations require screening colonoscopy.

Risk reduction

For women with pathogenic variants in ATM, CHEK2, NBN, and NF1 (ie,moderate to high penetrance for breast cancer), the evidence is insufficient to uniformly recommend RRM, although for those with a concerning family history (>20 percent risk of breast cancer by a model), it may be reasonable for carriers to consider this option [32, 34].

● Given that breast cancer risks are not well defined, no guidelines exist about how to manage breast cancer risks in women with pathogenic variants in newly identified genes, including BARD1, BRIP1, and MUTYH.

In such cases, breast cancer risk may still be assessed based on personal and family history. Such women may wish to discuss the option of RRM, particularly if they have a strong family history musculoskeletal disorders [34-36].

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