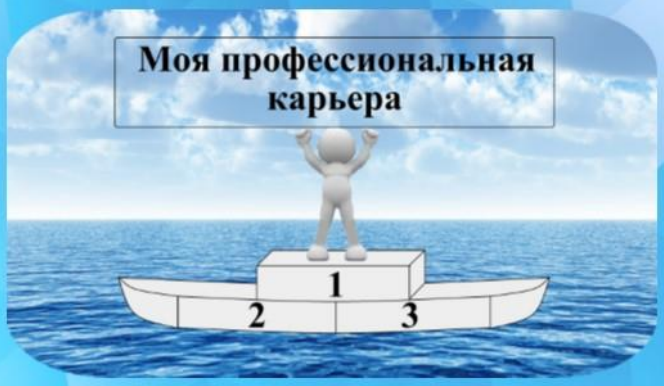
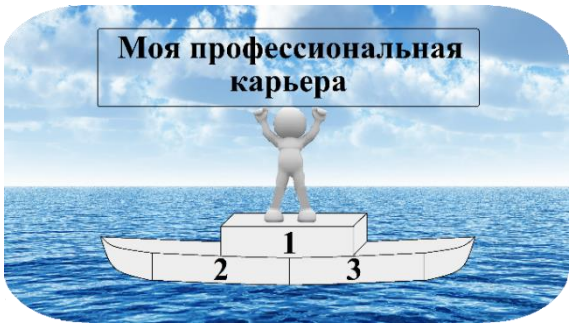


Научно-образовательный электронный журнал

ОБРАЗОВАНИЕ И НАУКА В XXI ВЕКЕ

Выпуск №24 (том 2)
(март, 2022)



Международный научно-образовательный электронный журнал
«ОБРАЗОВАНИЕ И НАУКА В XXI ВЕКЕ»

УДК 37
ББК 94

Международный научно-образовательный электронный журнал «ОБРАЗОВАНИЕ И НАУКА В XXI ВЕКЕ». Выпуск №24 (том 2) (март, 2022). Дата выхода в свет: 31.03.2022.

Сборник содержит научные статьи отечественных и зарубежных авторов по экономическим, техническим, философским, юридическим и другим наукам.

Миссия научно-образовательного электронного журнала «ОБРАЗОВАНИЕ И НАУКА В XXI ВЕКЕ» состоит в поддержке интереса читателей к оригинальным исследованиям и инновационным подходам в различных тематических направлениях, которые способствуют распространению лучшей отечественной и зарубежной практики в интернет пространстве.

Целевая аудитория журнала охватывает работников сферы образования (воспитателей, педагогов, учителей, руководителей кружков) и школьников, интересующихся вопросами, освещаемыми в журнале.

Материалы публикуются в авторской редакции. За соблюдение законов об интеллектуальной собственности и за содержание статей ответственность несут авторы статей. Мнение редакции может не совпадать с мнением авторов статей. При использовании и заимствовании материалов ссылка на издание обязательна.

ФИО авторов: *Nodira I. Tursunova1, Dilbar M. Almuradova2, Khadicha Kh. Turayeva3, Dilsora I. Mukimova4*

1 PhD, Assistant, Department of Oncology, Tashkent Medical Academy, Tashkent, Uzbekistan

2 PhD, Assistant, Department of Oncology, Tashkent Medical Academy, Tashkent, Uzbekistan

3Master of the Department of Oncology, Tashkent Medical Academy, Tashkent, Uzbekistan

4Master of the Department of Oncology, Tashkent Medical Academy, Tashkent, Uzbekistan

Название публикации: «HEREDITARY BREAST AND OVARIAN CANCER»

Abstract. Prevalence of germline *BRCA* mutations has been estimated to be about 1:1,600 women in the general population. Rate of *BRCA1/2* mutations in Ashkenazi Jews population is 98-99%. Rate of *BRCA1/2* mutations in Russian population is high – 28.4%. The average woman's lifetime risk of developing breast cancer is about 12%. In women with the BRCA1 mutation, the risk rises to about 72%, and in women with the BRCA2 mutation, to about 69%. They are also at a higher risk of getting cancer of a second breast after the first - the risk of developing contralateral breast cancer is about 40%. Ovarian cancer is less common: 1.3% of women in the general population. Women with the BRCA1 mutation have a risk of about 44%, and those with the BRCA2 mutation have a risk of about 17% before the age of 80. 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. Studies on hereditary breast and ovarian cancer (HBOC) involve not only determining the predisposition to developing cancer, but also considering the current treatment for breast cancer, prevention of next cancer, risk diagnosis, and adoption of protective measures for relatives. We present a comprehensive review of HBOC, which will be a useful resource in the clinical setting. Many hereditary tumors, including HBOC, are syndromes characterized by the development of different types of cancer in succession. 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, toaccurately assess and prevent the impact of cancer on the quality of life of the next generation of patients.

Keywords: Hereditary breast and ovarian cancer , *BRCA1/2* mutations, genetic test.

Introduction. Families with a history of multiple breast or ovarian cancers approximately account for 15% of all patients with breast cancer [10], and the disease is termed familial breast cancer (FBC). FBC includes people who are genetically predisposed to cancer. According to the National Cancer Institute, HBOC is defned as "An inherited disorder in which the risk of breast cancer (especially before the age of 50 years) and ovarian cancer is higher than normal." Most cases of HBOC syndrome are caused by certain mutations in *BRCA1* or *BRCA2* HBOC patients are prone to the development of malignant neoplasms in multiple organs including the breast, ovary, and fallopian tube. From a pathological perspective, a number of morphological features have been described in *BRCA*-associated breast and tuboovarian cancers. People with HBOC syndrome may also have an increased risk of developing other types of cancer, including melanoma, pancreatic and prostate cancers. This review will discuss the current knowledge regarding hereditary breast and ovarian cancer syndrome [29]

Characterization of BRCA1 and BRCA2. Fifteen years of analysis of large multigenerational families with a strong history of breast cancer led in 1990 to the identification of a gene on chromosome 17q12–21 that conferred a greatly increased risk of breast cancer in an autosomal-dominant manner. The gene itself, BRCA1, was cloned in 1994. The discovery of the complete sequence of a second such gene, BRCA2 on 13q12-13, was reported in 1995. The protein-coding region of BRCA1 consists of 5592 bp in 22 exons that encode a protein of 1863 amino acids, and the proteincoding region of BRCA2 consists of 10,254 bp in 26 exons that encode a protein of 3418 amino acids. Studies of the interactions of these proteins led to the conclusion that they are involved in the regulation of genomic stability and DNA repair. The BRCA1 and BRCA2 proteins interact through a third breast cancer tumor suppressor, PALB2 (partner and localizer of BRCA2) that serves as a major link. A key function of the BRCA1–PALB2–BRCA2 pathway is to secure proper and stable loading of the RAD51 protein at sites of DNA lesions such as DNA double-strand breaks. RAD51 is crucial for homologous recombination repair as well as for the protection of exposed DNA from undergoing excessive degradation during DNA replication. Mice lacking Brca1 and BRCA2 (the murine homologues of BRCA1 and BRCA2) undergo developmental arrest during embryogenesis. Furthermore, the modeling of mice with mutations in BRCA1 and BRCA2 revealed that such genetic changes

display enhanced tumorigenesis. This can be modeled to take place in the murine breast tissue, particularly when combined with the TP53 loss. Mice homozygous for a truncating mutation of BRCA2 that survive to adulthood have a wide range of defects, including improper tissue differentiation, absence of germ cells, and the development of lethal thymomas, and cultured embryonic fibroblasts from these mice are unable to repair radiation-induced DNA damage. Other studies suggest that mouse embryonic stem cells deficient in Brca1 are unable to carry out a transcription-coupled repair of oxidative DNA damage and are hypersensitive to ionizing radiation and hydrogen peroxide. Human BRCA2-defective cancer cells are also deficient in the repair of double-strand DNA breaks induced by ionizing radiation, although individuals with germline mutations in BRCA1 and BRCA2 do not appear to be hypersensitive to ionizing radiation.[1,14]

Cancer Risk Due to Mutations in BRCA1 and BRCA2. The risk for the development of breast and tubo-ovarian cancer is approximately 10–15%. In *BRCA1* and *BRCA2* mutation carriers, the risk increases to approximately 45–65% and 20–50%, respectively [2,5,8,14]. Germline mutations in other homologous recombination genes including *BARD1, BRIP1, PALB2, RAD51C, RAD51D,* and others (all encoding proteins involved in BRCA protein stability and/or function), have also been identified to varying degrees in breast and tubo-ovarian cancer patients. Studies evaluating the lifetime risk of disease development in these patients have estimated a range of at least 15–35% for breast cancer [3, 9] and 5–10% for tubo-ovarian cancer [4,33,38]. Mutations in some of these genes impart an increased risk for either breast or tubo-ovarian cancer with minimal to no increased risk for the development of the other tumor type (i.e., increased risk of breast cancer without risk of tubo-ovarian cancer, and vice versa) [39,42]. For example, *BRIP1, RAD51C*, and *RAD51D* mutation carriers have an increased risk for tubo-ovarian cancer, while there is insufficient evidence for an increased risk for breast cancer development. In contrast, *BARD1* and *PALB2* mutation carriers have an increased risk for breast cancer development without an associated increased risk for tubo-ovarian cancer [7]. Genetic alterations are also observed at a high frequency in groups that are or were geographically or culturally isolated, in which one or more of the ancestors harbored the altered gene. This is often called the founder efect or founder variant [3]. Founder mutations of *BRCA1/2* have been widely reported in diferent regions and ethnic groups. However, genetic testing for *BRCA1/2* should include uniform sequence analysis along with deletion/duplication analysis, except for in Ashkenazi Jews. Ashkenazi Jews can undergo targeted analysis of three *BRCA1* and *BRCA2* pathogenic founder mutations; 98–99% of the PVs identifed in Ashkenazi Jews are

c.68_69delAG and c.5266dupC for *BRCA1*, and c.5946delT for *BRCA2* [11,12,13]. If any PV cannot be identifed using target analysis, sequence analysis, and deletion/duplication analysis, multiple gene panel analysis should be performed. Recently, many founder mutations have been reported in Asia (Tables 1, 2).

Table 1. [10,32]

Population	Proportion of *BRCA1/2*
Ashkenazi Jews	98–99% of *BRCA1/2* mutations Vast majority of *BRCA1/2*
Poland	80% of *BRCA1/2* mutations, 91% of *BRCA1* mutations
Germany	38% of *BRCA1* mutations
Hungary	80% of *BRCA1* mutations, 48% of *BRCA2* mutations
Norway	68% of *BRCA1* mutations 3% of ovarian cancer
Finland	84% of *BRCA1/2* mutations
Sweden	70% of *BRCA1/2* mutations in West Sweden
Denmark	35% of *BRCA1/2* mutations
French	52% of *BRCA1/2* mutations

Table 2.

Population	Proportion of *BRCA1/2*
Southern Chinese	23% of *BRCA1/2* [37]
Japanese	16% of *BRCA1/2* [30, 35]
Koreans	10% of *BRCA1/2* [36, 19]
Malaysians	6% of *BRCA1* [40]
Filipinos	13% of *BRCA1/2* [38]
Russia	28,4% of *BRCA1/2* [41]
Uzbekistan	18% of *BRCA1/2* [43]

Characteristics of *BRCA*-related breast and ovarian cancer. The Western Consortium of Investigators of Modifers of BRCA1/2: the CIMBA reports on the pathological fndings of *BRCA1/2* breast cancer as follows [18,21]: *BRCA1*- related

breast cancer has the following features: (1) histopathological image of medullary carcinoma, which develops in a globular manner in peripheral tissues, (2) high histological nuclear grade, (3) a high proportion of negative for the expression of both estrogen and progesterone receptors and HER2 overexpression. The histology of the *BRCA2*-mutated breast cancer tissue is almost similar to those without *BRCA* mutations, and the histological nuclear grade is generally high . In addition, high-grade serous adenocarcinoma has been reported as a pathological feature of *BRCA1/2* ovarian cancer [25, 28]. Both *BRCA1/2*-related breast and ovarian cancers are typically highly aggressive. Germline *BRCA1/2* mutations are found in approximately 15% of women with ovarian epithelial neoplasms, the most common tubo-ovarian tumor subtype [20]. The hallmark histopathologic diagnosis of HBOC-related tubo-ovarian cancer due to *BRCA* mutations is that of high-grade serous carcinoma [19,35], and the frequency of *BRCA1* and *BRCA2* germline mutations increases to approximately 25% in patients diagnosed with these neoplasms [6,27]. In addition to high-grade serous carcinoma, other ovarian tumor histotypes including those with endometrioid, mucinous and clear cell differentiation (and others) have also been described to varying degrees in *BRCA*-associated cohorts [22, 23,26,30, 31], although some of these studies did not have central review of all pathological specimens [15]. Morphologically, classical high-grade serous carcinoma shows expansile and infiltrative growth of glands and papillae with slit-like spaces. Tumor nuclei are generally enlarged and irregular with prominent nucleoli and brisk mitoses, including atypical forms.

Specific Tumor Characteristics. A variety of specific morphological characteristics have been described in the context of *BRCA*-associated high-grade serous carcinoma (Table 3).

Table 3. Morphological features of *BRCA1* and *BRCA2* associated high-grade serous carcinoma.

Morphological features	*BRCA1*	*BRCA2*
Architecture	Frequent SET morphology	
Nuclear atypia	Marked	
Necrosis	Abundant	Relatively deficient
TILs	Abundant	Relatively deficient
Morphology of metastases	Pushing invasion or infiltrative invasion composed exclusively of micropapillae	
Immunophenotype	CK7 +, PAX8 +, WT-1 +, ER +, PR +/-, aberrant expression pattern of p53, and diffuse p1	

In addition to morphological features identified at the primary tumor site, specific architectural patterns (metastatic deposits with rounded and pushing contours/“medullary-like” invasion or infiltrative invasion composed exclusively of micropapillae) identified at metastatic sites have also been found to be highly concordant with *BRCA1/2* mutation status and display a high level of agreement among observers (kappa > 0.9) [34] Cases which displayed those features at metastatic sites most commonly also exhibited SET features in both the metastatic and primary tumors. Distinction between these two patterns appears to be prognostically relevant as an infiltrative micropapillary pattern has been more commonly identified in metastatic tumor foci from patients who suffered recurrence or death from disease, compared to those with pushing pattern metastases [17]. Interestingly, it has been hypothesized that metastatic tumor architecture may influence the ease of resection of these deposits and thus may contribute to surgeons ability to achieve optimal tumor debulking in these patients [34, 53]

How is HBOC identified? Mutations in the *BRCA1* or *BRCA2* genes can be identified through a blood or saliva test. The usual method of testing, called standard gene sequencing, can find most *BRCA* mutations. There are other types of mutations called rearrangements, which include deletions or duplications in *BRCA1* and *BRCA2* that also may cause an increased risk for these cancers. Testing is also available for large rearrangements in *BRCA1* and *BRCA2*.

After initial *BRCA1* and *BRCA2* genetic testing, additional testing may be recommended if:

- The results were “negative,” meaning no genetic mutation was detected
- A variant of uncertain significance was detected, which means that there is a genetic change, but it is not known how that change could affect cancer risk

Risk-reducing surgery. A prophylactic, bilateral mastectomy, which is the preventive surgical removal of both breasts, can lower the risk of breast cancer by more than 90%. Only about 3% of breast cancers associated with *BRCA* mutations are diagnosed before age 30, so most women with a *BRCA* mutation could consider surgery after 30. However, bilateral mastectomy is an invasive and irreversible procedure. A prophylactic salpingo-oophorectomy, which is the preventive surgical removal of the ovaries and fallopian tubes, can lower the risk of ovarian cancer by approximately 90%. It may also help lower the risk of breast cancer by 50% for women who have not been through menopause. A special procedure to look for microscopic cancer in the ovaries and fallopian tubes is recommended after this surgery. Deciding whether to have preventive surgery to lower your risk of developing breast or ovarian cancer is a very personal decision. Your health care team and genetic counselor can help you understand the risks and benefits, based on your health, type of *BRCA* mutation, and family history of cancer.[16]

The role of chemotherapy in BRCA 1/2 positive. Abnormality in the *BRCA* gene impairs the DNA repair pathway, resulting in the accumulation of damaged DNA. Reportedly, patients with *BRCA* mutations are highly sensitive to drugs that cause DNA damage, such as platinum doublet and PARP (poly (ADP-ribose) polymerase) inhibitors. Importantly, the identification of an germline-associated *BRCA1/2*-mutated tumor indicates not only an underlying germline defect (in the patient and perhaps also in her family members), but also implies certain important prognostic and treatment connotations. For example, mutations involving genes whose protein products are involved in homologous recombination have been shown to be associated with chemotherapeutic platinum sensitivity and improved survival in both breast and tubo-ovarian cancer patients Similarly, triple-negative breast cancer patients harboring defects in homologous recombination proteins have been shown to exhibit increased sensitivity to both platinum-based and standard chemotherapy regimens, although the effect on prognosis is more complex. The underlying molecular abnormalities due to homologous re combination deficiency indic ate t hat t hese malignancies c an be tre ated wit h novel poly ADP-ribose polymerase (PARP) inhibitors which act to limit repair of single strand breaks and thus lead to tumor cell death due to the overwhelming genetic instability .[24]

Cancer chemoprevention is the use of drugs to stop or keep cancer from developing. Tamoxifen (available as a generic drug) taken for 5 years by women with a high risk of breast cancer lowers this risk by 50%. Some research suggests that tamoxifen can help lower breast cancer risk for women with *BRCA1* and *BRCA2* mutations. However, because women with *BRCA1* mutations are more likely to develop hormone receptor-negative cancers, it may not be as effective for these women. Risk-reducing

tamoxifen is a reasonable option for women with *BRCA1* or *BRCA2* mutations to consider in addition to screening (see below). Raloxifene (Evista) and aromatase inhibitors (AIs) can also help lower breast cancer risk for women with higher risk of the disease. [16]

Conclusion. In this review, we have discussed the HBOC syndrome from a pathological perspective and have described specific characteristics of *BRCA1* and *BRCA2*-associated breast and tubo-ovarian neoplasms. Pathologists play a critical role in the identification and triage of affected patients, particularly those without a known family history, as a number of morphological features associated with these *BRCA*-mutated tumors have been reproducibly described and are easily recognized. Accurate and timely pathological assessment and interpretation is critical given the implications for prognosis, therapy and genetic testing. Ongoing research will continue to refine our understanding of HBOC syndrome pathology, including how non-*BRCA* gene mutations affect tumor morphology, behavior and prognosis.

References.

1. Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, 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) 30:2654–63. doi: 10.1200/ jco.2011.39.8545

2. Antoniou A, Pharoah PDP, Narod S, Risch HA, Eyfjord JE, Hopper JL, 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) 72:1117–30. doi:10.1086/375033

3.Antoniou AC, Casadei S, Heikkinen T, Barrowdale D, Pylkäs K, Roberts J, et al. Breast-cancer risk in families with mutations in PALB2. *N Engl J Med*. (2014)371:497–506.doi:10.1056/NEJMoa1400382 15

4. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature*. (2011) 474:609–15. doi: 10.1038/nature 10166

5. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol*. (2007) 25:1329–33. doi: 10.1200/JCO.2006.09.1066

6. Choi MC, Heo J-H, Jang J-H, Jung SG, Park H, Joo WD, et al. Germline mutations of *BRCA1* and *BRCA2* in Korean ovarian cancer patients. Int J Gynecol Cancer. 2015;25:1386–91.

7. Domchek SM, Robson ME. Update on genetic testing in gynecologic cancer. *J Clin Oncol*. (2019) 37:2501–9. doi: 10.1200/jco.19.00363
8. Easton DF, Ford D, Bishop DT. Breast and ovarian cancer incidence in BRCA1-mutation carriers. Breast cancer linkage consortium. *Am J Hum Genet*. (1995)56:265–71.10
9. Evans MK, Longo DL. PALB2 mutations and breast-cancer risk. *N Engl J Med*. (2014) 371:566–8. doi: 10.1056/nejme1405784 16
10. Ferla R, Calò V, Cascio S, Rinaldi G, Badalamenti G, Carreca I, et al. Founder mutations in *BRCA1* and *BRCA2* genes. Ann Oncol. 2007;18(6):93–8.
11. Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE. Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Lancet. 1994;343:692–5
12. Frank TS, Defenbaugh AM, Reid JE, Hulick M, Ward BE, Lingenfelter B, Gumpper KL, et al. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. J Clin Oncol. 2002;20:1480–90.
13. GeneReview: https://www.ncbi.nlm.nih.gov/books/NBK1247/. Accessed 7 Sept 2020
14. Hereditary Risk of Breast and Ovarian Cancer: BRCA1 and BRCA2q Claus Storgaard Sørensen, University of Copenhagen, Copenhagen, Denmark © 2019 Elsevier
15. Hoang LN, Gilks BC. Hereditary breast and ovarian cancer syndrome: moving beyond BRCA1 and BRCA2. *Adv Anat Pathol*. (2018) 25:85–95. doi: 10.1097/pap.0000000000000177
16. https://www.cancer.net/about-us/cancernet-editorial-board
17. Hussein YR, Ducie JA, Arnold AG, Kauff ND, Vargas-Alvarez HA, Sala E, et al. Invasion patterns of metastatic extrauterine high grade serous carcinoma with BRCA germline mutation and correlation with clinical outcomes. *Am J Surg Pathol*. (2016) 40:404–9. doi: 10.1097/pas. 0000000000000556
18. Kang E, Kim SW. The Korean hereditary breast cancer study: review and future perspective. J Breast Cancer. 2013;16:245–53.
19. Kang E, Seong MW, Park SK, Lee JW, Lee J, Kim LS, et al. The prevalence and spectrum of *BRCA1* and *BRCA2* mutations in Korean population: recent update of the Korean hereditary breast cancer (KOHBRA) study. Breast Cancer Res Treat. 2015;151:157–68.
20. King M-C, Marks JH, Mandell JB. New York Breast Cancer study group. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and

BRCA2. *Science*. (2003) 302:643–6. doi: 10.1126/science.1088759
21. Kuchenbaecker KB, Neuhausen SL, Robson M, Barrowdale D, McGufog L, Mulligan AM, et al. Associations of common breast cancer susceptibility alleles with risk of breast cancer subtypes in *BRCA1* and *BRCA2* mutation carriers. Breast Cancer Res. 2014;16:3416.
22. Kwong A, Ng EK, Wong CL, Law FB, Au T, Wong HN, et al. Identifcation of BRCA1/2 founder mutations in Southern Chinese breast cancer patients using gene sequencing and high resolution DNA melting analysis. PLoS ONE. 2012;7:e43994
23. Lakhani SR, Manek S, Penault-Llorca F, Flanagan A, Arnout L, Merrett S, et al. Pathology of ovarian cancers in BRCA1 and BRCA2 carriers. *Clin Cancer Res*. (2004) 10:2473–81. doi: 10.1158/1078-0432.ccr-1029-3
24. Loveday C, Turnbull C, Ramsay E, Hughes D, Ruark E, Frankum JR, et al. Germline mutations in RAD51D confer susceptibility to ovarian cancer. *Nat Genet*. (2011) 43:879–82. doi: 10.1038/ng.893
25. Mavaddat N, Barrowdale D, Andrulis IL, Domchek SM, Eccles D, Nevanlinna H, et al. Pathology of breast and ovarian cancers among *BRCA1* and *BRCA2* mutation carriers: results from the Consortium of Investigators of Modifers of BRCA1/2 (CIMBA). Cancer Epidemiol Biomarkers Prev. 2012;21:134–47.
26. Mavaddat N, Peock S, Frost D, Ellis S, Platte R, Fineberg E, et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. *J Natl Cancer Inst*. (2013) 105:812–22. doi: 10.1093/jnci/djt095
27. McAlpine JN, Porter H, Köbel M, Nelson BH, Prentice LM, Kalloger SE, et al. BRCA1 and BRCA2 mutations correlate with TP53 abnormalities and presence of immune cell infiltrates in ovarian high-grade serous carcinoma. *Mod Pathol*. (2012) 25:740–50. doi: 10.1038/modpathol.2011.211
28. McLaughlin JR, Rosen B, Moody J, Pal T, Fan I, Shaw PA, et al. Long-term ovarian cancer survival associated with mutation in *BRCA1* or *BRCA2*. J Natl Cancer Inst. 2013;105:141–9.
29. National Cancer Institute Dictionary of Cancer Terms https ://www.cancer.gov/publications/dictionaries/cancer-terms. Accessed 7 Sept 2020
30. Norquist BM, Harrell MI, Brady MF, Walsh T, Lee MK, Gulsuner S, et al. Inherited mutations in women with ovarian carcinoma. *JAMA Oncol*. (2016) 2:482–90. doi: 10.1001/jamaoncol.2015.5495
31. Pennington KP, Walsh T, Harrell MI, Lee MK, Pennil CC, Rendi MH, et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and

peritoneal carcinomas. *Clin Cancer Res*. (2014) 20:764–75. doi: 10.1158/1078-0432.ccr-13-2287
32. Ramus SJ, Gayther SA. The contribution of BRCA1 and BRCA2 to ovarian cancer. Mol Oncol. 2009;3:138–50.
33. Ramus SJ, Song H, Dicks E, Tyrer JP, Rosenthal AN, Intermaggio MP, et al. Germline mutations in the BRIP1, BARD1, PALB2, and NBN genes in women with ovarian cancer. *J Natl Cancer Inst*. (2015) 107:djv214. doi: 10.1093/jnci/djv214
34. Reyes MC, Arnold AG, Kauff ND, Levine DA, Soslow RA. Invasion patterns of metastatic high-grade serous carcinoma of ovary or fallopian tube associated with BRCA deficiency. *Mod Pathol*. (2014) 27:1405–11. doi: 10.1038/modpathol.2013.237
35. Sekine M, Nagata H, Tsuji S, Hirai Y, Fujimoto S, Hatae M, et al. Mutational analysis of *BRCA1* and *BRCA2* and clinicopathologic analysis of ovarian cancer in 82 ovarian cancer families: two common founder mutations of BRCA1 in Japanese population. Clin Cancer Res. 2001;7:3144–50.
36. Song H, Dicks E, Ramus SJ, Tyrer JP, Intermaggio MP, Hayward J, et al. Contribution of germline mutations in the RAD51B, RAD51C, and RAD51D genes to ovarian cancer in the population. *J Clin Oncol*. (2015) 33:2901–7. doi: 10.1200/JCO.2015.61.2408
37. Suszynska M, Kluzniak W, Wokolorczyk D, Jakubowska A, Huzarski T, Gronwald J, et al. BARD1 is a low/moderate breast cancer risk gene: evidence based on an association study of the Central European p.Q564X recurrent mutation. *Cancers (Basel)*. (2019) 11:740. doi: 10.3390/cancers11060740
38. Walsh T, Casadei S, Lee MK, Pennil CC, Nord AS, Thornton AM, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proc Natl Acad Sci USA*. (2011) 108:18032–7. doi: 10.1073/pnas.1115052108
39. Weber-Lassalle N, Hauke J, Ramser J, Richters L, Groß E, Blümcke B, et al. BRIP1 loss-of-function mutations confer high risk for familial ovarian cancer, but not familial breast cancer. *Breast Cancer Res*. (2018) 20:7. doi: 10.1186/s13058-018-0935-9
40. Walsh T, King M-C. Ten genes for inherited breast cancer. *Cancer Cell*. (2007) 11:103–5. doi: 10.1016/j.ccr.2007.01.010
41. web site: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.e13111
42. Yoshida R, Watanabe C, Yokoyama S, Inuzuka M, Yotsumoto J, Arai M, et al. Analysis of clinical characteristics of breast cancer patients with the Japanese founder mutation BRCA1 L63X. Oncotarget. 2019;10:3276–84.

43. Tillyashaikhov M.N., Ibragimova S.M., Janklich State of cancer care to the population of the republic of Uzbekistan in 2019.