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Review

Carcinogenic potential of ovulation stimulation in BRCA1/2 gene mutation carriers in assisted reproductive technology programs

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Abstract: Mutations of the BRCA1/2 genes constitute a fundamental and independent risk factor in the genesis of both breast cancer and ovarian cancer. The specifics of the infertility treatment effect on the risk of developing cancer in carriers of mutations in the BRCA1/2 genes remain unclear and require a comprehensive investigation. In this review, we analyzed published sources on the possible relationship between the infertility treatment and the risk of ovarian and breast cancer in BRCA1/2 mutation carriers.

Keywords: breast cancer, ovarian cancer, ovulation stimulation, assisted reproductive technologies, BRCA1/BRCA2 mutations.

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Introduction

Rationale

The worldwide prevalence of female infertility steadily increases instigating the necessity for a growing number of women to seek help from assisted reproductive technologies (ART) in order to successfully implement their reproductive function. In developed countries, infertility affects approximately 15-20% of married couples, with female infertility accounting for about 40% of the total infertility cases [1]. In the Russian Federation, the values of these indicators are 10–20% and 60%, respectively. Using medications stimulating ovarian function either as an independent therapy, or as part of a combination therapy, is essential to in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) protocols, depending on the cause of the fertility disorder, as well as the protocol [2]. To date, over five million children worldwide have been born owing to ART methods. However, the first results of international studies on the risk of potentiation of oncological disease treatment, especially malignant neoplasms of the female reproductive system, with the use of ovulation inductors were published only several decades after their introduction.

Given these facts, it is only expected to ask whether ovulation induction is oncologically safe, and whether ovulation induction is an independent trigger for the development of malignant neoplasms of the female reproductive system. However, the assessment of the ovulation induction effect on the carcinogenic risk of the reproductive system organs is a rather complicated issues, since it is difficult to single out infertility as an independent risk factor for the development of the reproductive system cancer and the possible carcinogenic effect of ovulation inductors as independent triggers.

A long-term study of the possible carcinogenic effect of ovulation inductors currently does not give a clear idea about the factors of malignant transformation of cells that these pharmaceutical drugs may cause. However, researchers around the world proposed a number of potential carcinogenesis mechanisms, taking into account the use of ovulation inductors.

Incessant ovulation theory

The ovulation process is accompanied by repeated microtrauma of the ovarian surface epithelium (mesothelium); and medications stimulating ovarian function via contributing to simultaneous ovulation of several follicles cause substantial mechanical injury of the ovarian mesothelium, long with an increase in epithelial inclusions [3].

It was established that the ovulation induction cycle can be equivalent to two years of normal menstrual cycles in terms of peak estrogen concentrations and the number of formed follicles [4]. Repeated multiple microtraumas of the mesothelium and high mitotic activity accompanying ovulation can lead to genetic disorders and autonomous growth of malignant cells [5].

Elevated gonadotropin level theory

Up to 90% of all ovarian cancer cases develop from cells of the ovarian surface epithelium. According to a study by B.E. Henderson et al., high levels of pituitary gonadotropins stimulate the ovarian surface epithelium directly or via an estrogen concentration increase, or else in combination with increased concentrations of estrogens, thereby provoking the carcinogenesis in ovarian mesothelium [6].

This hypothesis is supported by a study by Burdette et al., during which it was revealed that there was a significant increase in the proliferation of ovarian surface epithelial cells in response to the introduction of equine gonadotropin and human chorionic gonadotropin in the CD-1 group of mice, compared with the control group [7]. Increased proliferation, in turn, causes mutations in deoxyribonucleic acid (DNA) followed by progressive cell transformation and the development of ovarian cancer [7].

Oxidative stress

Exogenous gonadotropins have a stimulating effect on follicular iron content, which is a powerful oxidizer catalyzing the formation of free radicals in the Haber-Weiss reaction [8]. The product of oxidative DNA damage caused by reactive oxygen species (ROS), 8-hydroxy-2-deoxyguanosine (8-OH-dG) is monitored as a known marker of excessive ROS levels and oxidative stress leading to carcinogenesis [9]. It is important to note that 8-OH-dG content in primary breast tumors is 8-17 times higher than in normal tissues [9].

ROS cause a number of potentially carcinogenic mutations, such as oxidation of all four nucleotide bases, single-strand and double-strand breaks, mutations in alkaline-labile sites, which could subsequently lead to DNA breaks and its overall instability [10]. DNA base substitutions are much more common than deletions or translocations [10].

Loss of heterozygosity (LOH)

Inactivation of heterozygous loci of suspected oncogenes or suppressor genes leads to the development of a malignant tumor. Loss of heterozygosity of the PTEN/MMAC suppressor gene located at 10q23 is most often observed in endometrioid ovarian cancer (43%) as well as in 18% of cases of papillary serous ovarian cancer [11]. In breast cancer, the loss of heterozygosity in the BRCA1 gene is detected in 50% of cases.

Disorder of DNA repair processes

ROS can promote the expression of methyltransferases, which leads to the methylation of several genes essential for the cell cycle regulation (CDKN2), DNA mismatch repair (hMLH1), thereby contributing to the induction of carcinogenesis [10].

Hormonal metabolism disorder

Exogenous administration of gonadotropins stimulates simultaneous maturation of several follicles, triggering a significant increase in estradiol content [2]. The metabolites of estrogens have different ability for cell proliferation: multiple studies demonstrated that the concentration of 2-hydroxyestrone (2-OHE1) should typically be at least twofold of 16-hydroxyestrone (16-OHE1) content [12]. It was revealed that pathological proliferative processes in organs and tissues of the reproductive system were repeatedly intensified with an increased content of 16-OHE1 in a woman's body [12].

Mutations of BRCA1/BRCA2 genes

Mutations of BRCA1 and BRCA2 genes are independent risk factors for breast cancer and ovarian cancer. According to the literature, the cumulative risk of breast cancer in people under 70 years old ranges 40–87% for BRCA1 mutation carriers, and 27–84% for BRCA2 mutation carriers [13]. In relation to ovarian cancer, such risk varies from 16% to 68% for BRCA1 mutation carriers, and from 11% to 30% for BRCA2 mutation carriers [13]. Oktay et al. discovered that carriers of BRCA mutations had a significantly higher frequency of poor ovarian response to ovulation induction, compared with women without these mutations (33.3% vs. 3.3%; p=0.14) [14]. At the same time, a poor response to ovulation induction was observed in BRCA1 mutation carriers, while it was not recorded among BRCA2 carriers. Hence, it was proposed that the presence of BRCA1 gene mutation may be associated with a latent primary ovarian insufficiency.

Receptor status of steroid hormones

According to Lakhani et al. (2000), in 64–92% of cases, malignant neoplasms caused by germinal mutations of the BRCA1/2 genes did not have estrogen and progesterone receptors, especially in the presence of BRCA1 gene mutations [15]. In support of this pattern, a group of researchers, Flippo-Morton et al. (2016), established that breast cancer associated with a mutation of BRCA1 gene was usually characterized by a negative status of steroid hormone receptors, and, consequently, had hormone-independent growth [16]. This finding allows substantiating the ineffectiveness of ovariectomy in such group of women [16].

In our review, we analyze the studies published to date, in which the relationship between ovulation induction and the risk of breast cancer and ovarian cancer in carriers of BRCA1/BRCA2 gene mutations was examined.

Material and Methods

Original studies were searched in the PubMed and Cochrane Library databases for the period of 2000-2021. Our search was based on the following keywords: breast cancer, ovarian cancer, ovulation stimulation, assisted reproductive technologies, and BRCA1/BRCA2 mutations. As a result, we found five original studies: in three studies (a case-control study and two retrospective cohort studies), the risk of breast cancer was assessed; in two other studies (a case-control study and a retrospective cohort study), the results of examining the possible risk of invasive epithelial ovarian cancer were published.

Results

Breast cancer

The results of the search for published studies on the possible relationship between infertility treatment and breast cancer risk in carriers of BRCA1/2 gene mutations are presented in *Table* 1.

One of the studies, conducted in 2008 by Kotsopoulos et al. [17], was a case-control study that involved 1,380 carriers of BRCA1/2 mutations (1054 BRCA1 and 326 BRCA2). In the main group, 61 women were previously treated for infertility with clomiphene citrate, CC (n=24), or gonadotropin preparations, GT (n=16). The rest of the women were treated with medications of other groups. In several women, it was not possible to establish additional information about the type of medication. The mean age of women in the main group was 46.0 years vs. 46.2 years in the control group. According to the results of that study, there was no relationship between infertility treatment and breast cancer risk: odds ratio (OR)=1.21; 95% confidence interval (CI): 0.81; 1.82. When adjusted for the type of mutation, the results were similar:

OR=1.22; 95% CI 0.76; 1.94 (for BRCA1) vs. OR=1.25; 95% CI 0.56;2.78 (for BRCA2). Even when adjusted for the type of medication used for treating infertility, no association was revealed in that study: CC (OR=0.96; 95% CI 0.54; 1.72, p=0.89); GT (OR=2.32; 95% CI 0.91;5.95, p=0.08). The authors did not clarify the causes of infertility, the dosages of medications, the number of ovulation stimulation cycles, and the duration of treatment in carriers of BRCA1/2 mutations.

We also found two retrospective cohort studies. The first major study of the kind was published in 2018 by Derks-Smeets et al. [18]; it included a total of 2,514 BRCA1/2 mutation carriers (1550 BRCA1 and 964 BRCA2). Breast cancer was verified in 938 of 2,514 women: 630/1550 BRCA1 and 308/964 BRCA2. The average age at breast cancer diagnosis was 40.1 years among BRCA1 mutation carriers vs. 44.4 years in BRCA2 mutation carriers. Ovulation induction was performed in 76 carriers of BRCA1/2 mutations: 41 BRCA1 and 35 BRCA2. Breast cancer in the group of women undergoing ovulation induction was verified in 15 carriers: 12 BRCA1 and 3 BRCA2. The authors concluded that there was no association between the ovulation induction in BRCA1/2 mutation carriers and the risk of breast cancer: hazard ratio (HR)=0.79, 95% CI 0.46;1.36. However, the study did not provide data on the type of medication, its dosage, number of ovulation stimulation cycles, and causes of infertility.

In 2021, Perri et al. [19] published the results of their research, in which the risk of breast cancer after infertility treatment by various procedures was studied on 1,824 carriers of BRCA1/2 mutations. All carriers of mutations in these genes were distributed among two groups: 1,492 women who were not treated for infertility, and 332 who were treated for infertility by one of the methods: CC (n=134), GT (n=119), in vitro fertilization (IVF) (n=183), or a combination of these methods (n=89). As stated by the results, breast cancer was verified in 687 carriers of the BRCA1/2 mutation. The researchers revealed no association between infertility treatment and breast cancer risk, when adjusted for the medication used for infertility treatment or the treatment method. Regarding the former, the statistics were as follows: HR=0.77, 95% CI 0.49; 1.19 for CC; HR=0.54, 95% CI 0.28;1.01 for GT. Regarding the latter, the statistics were as follows: HR=0.65, 95% CI 0.39; 1.08 for IVF; HR=1.23, 95% CI 0.49; 3.06 for combined treatment. The authors did not specify medication dosages, number of ovulation stimulation cycles, and the type of mutation (BRCA1 or BRCA2).

Ovarian cancer

Table 2 presents an analysis of publications that investigated the possible relationship between infertility treatment and the risk of breast cancer in carriers of the BRCA1/2 mutations. A retrospective cohort study by Perri et al. 2015 [20] encompassed 1,073 carriers of BRCA1/2 mutations (718 BRCA1 and 331 BRCA2). There were 164 women were treated for infertility with CC (n=82), GT (n=69), IVF (n=66), or a combination of these methods (n=50). Also, there were 909 carriers of BRCA1/2 mutations who did not receive the treatment. In a group of 164 women who underwent infertility treatment, 105 carriers of the BRCA1 mutation, 54 carriers of the BRCA2 mutation, 1 carrier of the BRCA1/2 mutation and 4 women with unknown mutations were identified. The total of 175 BRCA1/2 carriers had verified ovarian cancer: 139 with BRCA1, 33 with BRCA2, and 3 with unknown mutations. In the group of women treated for infertility, ovarian cancer was verified in 3 carriers of BRCA1/2 mutations who were treated with CC, as well as in 1 carrier treated with GT. The mean age of women was 47.1 years in the infertility treatment group; 50.4 years in the group without infertility treatment; 53.6 years in women with verified ovarian cancer; and 49.1 years in women without such pathology. Even after the adjustment for age, the researchers did not detect an association between infertility treatment and ovarian cancer risk: OR=0.81; 95% CI 0.43; 1.53 in BRCA1; OR=1.01; 95% CI 0.31; 3.30 in BRCA2. When adjusted for the type of medication, still no relationship was revealed: OR=0.87; 95% CI 0.46;1.63 for CC; OR=0.59; 95% CI 0.26; 1.31 for GT; OR=1.08, 95% CI 0.57; 2.06 for IVF. The authors did not provide information on the causes of infertility, medication dosages, number of ovulation stimulation cycles, and treatment duration in carriers of BRCA1/2 mutations.

In 2016, Gronwald et al. [21] published the results of a case-control study conducted on 941 carriers of BRCA1/2 mutations: 791 with BRCA1 and 150 with BRCA2. There were 45 women treated for infertility: 34 with selective estrogen receptor modulators (SERM), 3 with gonadotropin preparations, and 8 with medications of other groups. The mean age of women in the main group was 63 years vs. 64 years in the control group. Ovarian cancer was detected in 12 subjects who received SERM, 2 patients who received gonadotropin preparations, and 4 women who were treated with medications of other groups. The authors detected no association between infertility treatment in BRCA1/2 mutation carriers and the risk of ovarian cancer (OR=0.66; 95% CI 0.18; 2.33, p=0.52). When adjusted for the type of medication, still no relationship was revealed: SERM (OR=0.55 95% CI=0.27; 1.10, p=0.09) vs. GT (OR=1.35 (95% CI 0.11; 16.62, p=0.82) vs. medications of other groups (OR=1.00 95% CI 0.25; 4.00, p=1.0). The peculiarities of this research were attributed to the fact that such indicators, as the cause of infertility, medication dosage, number of stimulation cycles, and their duration, were not studied. Also, according to the results of this study, no risk analysis for developing ovarian cancer was presented separately for carriers of BRCA1 vs. BRCA2 mutations.

Table 1. Ovulation induction and breast cancer risk in women with BRCA1/BRCA2 mutations

Study	*Study design*	*Sample sizes*	*Number of women using ovulation inductors*	*Ovulation inductors*	*Results*
Kotsopoulos, et al. 2008 [17]	Case-control study	*Main cohort*: n=1,054 BRCA1 n=326 BRCA 2 *Control group*: n=1,054 BRCA1 n=326 BRCA2	*Main cohort*: n=61 BRCA1/2 *Control group*: n=56 BRCA1/2	1.Clomiphene citrate (CC) 2.Gonadotropins (GT)	BRCA1/2: OR=1.21; 95% CI 0.81; 1.82. CC, BRCA1/2: OR=0.96; 95% CI 0.54; 1.72; p=0.89. GT, BRCA1/2: OR=2.32; 95% CI 0.91; 5.95; p=0.08.
Derks-Smeets, et al. 2018 [18]	Retrospective cohort study	n=1,550 BRCA1 n=964 BRCA2	n=76 BRCA1/2	–	BRCA1/2: HR=0.79; 95% CI 0.46; 1.36.
Perri, et al. 2021 [19]	Retrospective cohort study	n=1,824 BRCA1/2	n=332 BRCA1/2	1.Clomiphene citrate (CC) 2.Gonadotropins (GT)	CC, BRCA1/2: HR=0.77; 95% CI 0.49; 1.19. GT, BRCA1/2: HR=0.54; 95% CI 0.28;1.01.

Table 2. Ovulation induction and ovarian cancer risk in women with BRCA1/BRCA2 mutations

Study	*Study design*	*Sample sizes*	*Number of women using ovulation inductors*	*Ovulation inductors*	*Results*
Perri, et al. 2015 [20]	Retrospective cohort study	n=718 BRCA1 n=331 BRCA2 n=3 BRCA1/2	n=164 BRCA1/2 n=105 BRCA1 n=54 BRCA2 n=1 BRCA1/2	1.Clomiphene citrate (CC) 2.Gonadotropins (GT)	Not adjusted for the type of treatment BRCA1: OR=0.81; 95% CI 0.43; 1.53. BRCA2: OR=1.01; 95% CI 0.31; 3.30. CC, BRCA1/2: OR=0.87; 95% CI 0.46; 1.63 GT, BRCA1/2: OR=0.59; 95% CI 0.26; 1.31.
Gronwald, et al. 2016 [21]	Case-control study	n=791 BRCA1 n=150 BRCA2	n=45 BRCA1/2	1. Selective estrogen receptor modulators (SERM) 2. Gonadotropins (GT) 3. Preparations of other groups	Not adjusted for the type of treatment BRCA1/2: OR=0.66; 95% CI 0.18; 2.33; p=0.52. SERM, BRCA1/2: OR=0.55; 95% CI 0.27; 1.10; p=0.09. GT, BRCA1/2: OR=1.35; 95% CI 0.11; 16.62; p=0.82. Drugs of other groups, BRCA1/2: OR=1.00; 95% CI 0.25; 4.00; p=1.0.

Discussion

The association between infertility, methods of its treatment, and the risk of developing breast and ovarian cancers arouses augmented interest among researchers worldwide. To date, little work has been done to study this issue. However, its relevance in clinical practice continuously increases. This is due to an increase in the prevalence of female infertility and the need to solve this problem using ART methods, and also due to an increase in the number of women of reproductive age with a verified diagnosis of breast and ovarian cancers.

According to some researchers, there is a negative effect of medications used in ART programs on the risk of developing breast and ovarian cancers [22, 23, 24]; on the contrary, other practicing scientists are convinced that there is no such risk [25, 26, 27].

It is believed that from 5-10% of all cases of breast cancer and 10-17% of all cases of ovarian cancer are hereditary, and mutations in the BRCA1/2 genes are the essential factor in their development [28, 29]. Mutations of the BRCA1/2 genes cause about 20-50% of hereditary forms of breast cancer and 90-95% of ovarian cancer [28, 29]. These genes are present in healthy human cells and initiate carcinogenesis only with mutational changes. Oncological diseases associated with BRCA1/2 gene mutations have been studied since their discovery in 1994–1995 [30, 31]. The association of mutations in these genes with the risk of developing breast and ovarian cancers was initially detected among women living in Europe and North America [32, 33, 34]. BRCA mutations lead to chromosomal instability and malignant transformation of breast and ovarian cells. However, a distinctive feature of the BRCA2 gene mutation is a greater risk of developing breast-ovarian syndrome [35]. BRCA-associated breast cancer is characterized by early manifestation of the disease: according to the published data, the mean age is 41 years in the presence of BRCA1 mutation and 44 years in BRCA2 [36]. Also, BRCA1/2 mutation carriers are statistically significantly more likely to have sclerosing adenosis and microcalcifications, cysts and intraductal papillomas. Therefore, when assessing the risk of breast cancer and ovarian cancers in women prior to initiating their infertility treatment, it is also important to consider the presence of mutations in these genes and benign breast pathologies.

To date, there are the following basic indications for conducting molecular genetic analysis for the presence of mutations in genes associated with breast and ovarian cancers: 1) three or more cases of breast or ovarian cancers in the family history (one of which is <50 years of age); 2) two cases of breast cancer in the family under the age of 40 years old; 3) breast cancer in a man and ovarian cancer at an early age in a woman among blood relatives; 4) ethnic background of Ashkenazi Jews and breast cancer under the age of 60 years; 5) breast cancer at an early age and/or hereditary breast-ovarian cancer syndrome in one patient [37].

The studies analyzed by us do not focus on the infertility causes. Similarly, none of the studies examined the association with the medication dosage, number of ovulation stimulation cycles, and the duration of treatment. These factors are important to consider because there is published evidence of a possible increase in the risk of breast cancer by ≥40% among women who received injections of chorionic gonadotropin (HCG) in 6 or more IVF cycles [38]. Pappo et al. [39] reported that ≥IVF attempts increase the risk of developing breast cancer, even though statistical significance of the pattern was not established (HR=1.9; 95% CI 0.95; 3.81).

It is equally important to take into account the contribution of various types of mutations to the carcinogenesis. Germline mutations are present in gametes and are passed on to the next generation via inheritance [40]. The assessment of the contribution of these mutations in the BRCA1/2 genes to the risk of developing ovarian cancer varies from 5% to 20% [41]. Somatic mutations arise spontaneously in the body cells and gradually accumulate throughout life. Such mutations in BRCA1/2 genes are less common: they present only in 2-8% of patients [42, 43].

Ovarian neoplasms represent histologically heterogeneous group of tumors. The most common ovarian cancer is invasive epithelial ovarian cancer with five common histological subtypes: high-grade serous (70%), endometrioid (10%), clear-cell (10%), low-grade serous (5%) and mucinous (3%) [44]. According to our data, none of the included studies identified histological subtypes of ovarian cancer in the study groups. Therefore, it is necessary to conduct studies aimed at assessing the association of fertility with histological subtypes of ovarian cancer [45].

Lifestyle factors can have an equally significant impact on the risk of developing breast and ovarian cancers in carriers of mutations. Their analysis needs to be carried out taking woman's age into account. Reproductive factors (early menarche, decreased fertility, lack of hormonal contraceptives and pregnancies, breastfeeding) affect ovulatory cycles, and, consequently, the cumulative effect of gonadotropins [46]. Irwin et al. (2020) analyzed the association of follicle-stimulating hormone (FSH), inhibin B, and anti-mullerian hormone (AMH) levels with the risk of developing the breast cancer. According to the results of the study, high levels of FSH (HR=2.78, 95% CI 1.05; 7.38) and inhibin B (HR=1.97, 95% CI 1.14; 3.39) may be associated with an increased risk of various histological subtypes [47].

Until the carcinogenic potential of various infertility factors, along with lifestyle factors, is studied in carriers of BRCA

mutations, we would not be able to undertake a comprehensive study on the association between infertility treatment and the risk of developing breast and ovarian cancers. Despite the recognition of high effectiveness of ART, the issue of oncological safety of this method regarding breast and ovarian cancers in carriers of BRCA mutations remains unresolved.

Conclusion

The results of published studies do not let us completely excluding a possible increase in the risk of breast and ovarian cancers among the carriers of BRCA mutations undergoing infertility treatment. Carriers of BRCA gene mutations should be informed about a possible increase in the risk of breast and ovarian cancers developing in association with various methods of infertility treatment. A long period of observation, the factor of infertility, lifestyle, as well as all features of infertility therapy, would contribute to a more in-depth study of the relationship between the development of breast and ovarian cancers in carriers of BRCA mutations, and methods actively used today in reproductive medicine.

References

1. Cetin I, Cozzi V, Antonazzo P. Infertility as a cancer risk factor – A review. *Placenta* 2008; 29 Suppl B: 169-177. https://doi.org/10.1016/j.placenta.2008.08.007.
2. Korneeva IE, Kovalchuk AI. Preventing the premature luteinizing hormone surge produced by gestagen in the modified ovarian stimulation protocol in assisted reproductive technology programs. *Obstetrics and Gynecology* 2020; 11: 39-43. Russian. https://doi.org/10.18565/aig.2020.11.39-43.
3. Meirow D, Schenker JG. The link between female infertility and cancer: Epidemiology and possible aetiologies. *Hum Reprod Update* 1996; 2(1): 63-75. https://doi.org/10.1093/humupd/2.1.63.
4. Attia A. EBM in action: Does ovulation induction increase the risk of ovarian cancer? *Middle East Fertil Soc J* 2006; 11(2): 135-139. http://www.bioline.org.br/pdf?mf06025.
5. Fathalla MF. Incessant ovulation: A factor in ovarian neoplasia? *Lancet* 1971; 2(7716): 163. https://doi.org/10.1016/s0140-6736(71)92335-x.
6. Henderson BE, Ross R, Bernstein L. Estrogens as a cause of human cancer: The Richard and Hinda Rosenthal Foundation Award lecture. *Cancer Res* 1988; 48(2): 246-253. https://pubmed.ncbi.nlm.nih.gov/2825969.
7. Burdette JE, Kurley SJ, Kilen SM, Mayo KE, Woodruff TK. Gonadotropin-induced superovulation drives ovarian surface epithelia proliferation in CD1 mice. *Endocrinology* 2006; 147(5): 2338-2345. https://doi.org/10.1210/en.2005-1629.
8. Reubinoff BE, Har-El R, Kitrossky N, Friedler S, Levi R, Lewin A, et al. Increased levels of redox-active iron in follicular fluid: A possible cause of free radical-mediated infertility in β-thalassemia major. *Am J Obstet Gynecol* 1996, 174(3): 914-918. https://doi.org/10.1016/s0002-9378(96)70325-3.
9. Malins DC, Haimanot R. Major alterations in the nucleotide structure of DNA in cancer of the female breast. *Cancer Res* 1991; 51(19): 5430–5432. https://pubmed.ncbi.nlm.nih.gov/1655250.
10. Dasari K, Madu CO, Lu Y. The role of oxidative stress in cancer. *Novel Approaches in Cancer Study* 2020; 4(2): 350-355. https://doi.org/10.31031/NACS.2020.04.000585.
11. Obaka K, Morland SJ, Watson RH, Hitchcock A, Chenevix-Trench G, Thomas EJ, et.al. Frequent PTEN/MMAC mutations in endometrioid but not serous or mucinous epithelial ovarian tumors. *Cancer Res* 1998; 58(10): 2095-2097. https://pubmed.ncbi.nlm.nih.gov/9605750.
12. Babaeva NA, Ashrafyan LA, Antonova IB, Aleshikova OI, Ivashina SV. The role of hormonal disbalance in the carcinogenesis of tumors of the female reproductive system. *Obstetrics and gynecology. News. Views. Education* 2017; (1(15)): 76-82. Russian. https://doi.org/10.24411/2303-9698-2017-00021.
13. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA* 2017; 317(23): 2402-2416. https://doi.org/10.1001/jama.2017.7112.
14. Oktay K, Kim JY, Barad D, Babayev SN. Association of BRCA1 mutations with occult primary ovarian insufficiency: A possible explanation for the link between infertility and breast/ovarian cancer risks. *J Clin Oncol* 2010; 28(2): 240-244. https://doi.org/10.1200/JCO.2009.24.2057.
15. Lakhani SR, Gusterson BA, Jacquemier J, Sloane JP, Anderson TJ, van de Vijver MJ, et al. The pathology of familial breast cancer: Histological features of cancers in families not attributable to mutations in BRCA1 or BRCA2. *Clin Cancer Res* 2000; 6(3): 782-789. https://pubmed.ncbi.nlm.nih.gov/10741697.
16. Flippo-Morton T, Walsh K, Chambers K, Amacker-North L, White B, Sarantou T, et al. Surgical decision making in the BRCA-positive population: Institutional experience and comparison with recent literature. *Breast J* 2016; 22(1): 35-44. https://doi.org/10.1111/tbj.12521.
17. Kotsopoulos J, Librach CL, Lubinski J, Gronwald J, Kim-Sing C, Ghadirian P, et al. Infertility, treatment of infertility, and the risk of breast cancer among women with BRCA1 and BRCA2 mutations: A case–control study. *Cancer Causes Control* 2008; 19(10): 1111-1119. https://doi.org/10.1007/s10552-008-9175-0.
18. Derks-Smeets IAP, Schrijver LH, de Die-Smulders CEM, Tjan-Heijnen VCG, van Golde RJT, Smits LJ, et al. Ovarian stimulation for IVF and risk of primary breast cancer in BRCA1/2 mutation carriers. *Br J Cancer* 2018; 119(3): 357-363. https://doi.org/10.1038/s41416-018-0139-1.
19. Perri T, Naor-Revel S, Eliassi-Revivo P, Lifshitz D, Friedman E, Korach J. Fertility treatments and breast cancer risk in Jewish Israeli BRCA mutation carriers. *Fertil Steril* 2021; 116(2): 538-545. https://doi.org/10.1016/j.fertnstert.2021.02.030.
20. Perri T, Lifshitz D, Sadetzki S, Oberman B, Meirow D, Ben-Baruch G, et al. Fertility treatments and invasive epithelial ovarian cancer risk in Jewish Israeli BRCA1 or BRCA2 mutation carriers. *Fertil Steril* 2015; 103(5): 1305-1312. https://doi.org/10.1016/j.fertnstert.2015.02.011.
21. Gronwald J, Glass K, Rosen B, Karlan B, Tung N, Neuhausen SL, et al. Treatment of infertility does not increase the risk of ovarian cancer among women with a BRCA1 or BRCA2 mutation. *Fertil Steril* 2016; 105(3): 781-785. https://doi.org/10.1016/j.fertnstert.2015.11.034.
22. Burkman R, Tang M, Malone K, Marchbanks PA, McDonald JA, Folger SG, et al. Infertility drugs and the risk of breast cancer: Findings from the National Institute of Child Health and Human Development Women's Contraceptive and Reproductive Experiences Study. *Fertil Steril* 2003; 79(4): 844-851. https://doi.org/10.1016/s0015-0282(02)04950-6.
23. Brinton LA, Scoccia B, Moghissi KS, Westhoff CL, Althuis MD, Mabie JE, et al. Breast cancer risk associated with ovulation stimulating drugs. *Hum Reprod* 2004; 19(9): 2005-2013. https://doi.org/10.1093/humrep/deh371.
24. van Leeuwen FE, Klip H, Mooij TM, van de Swaluw AM, Lambalk CB, Kortman M, et al. Risk of borderline and invasive ovarian tumours after ovarian stimulation for in vitro fertilization in a large Dutch cohort. *Hum Reprod* 2011; 26(12): 3456-3465. https://doi.org/10.1093/humrep/der322.
25. Lerner-Geva L, Keinan-Boker L, Blumstein T, Boyko V, Olmar L, Mashiach S, et al. Infertility, ovulation induction treatments and the incidence of breast cancer – A historical prospective cohort of Israeli women. *Breast Cancer Res Treat* 2006; 100(2): 201-212. https://doi.org/10.1007/s10549-006-9238-4.
26. Brinton LA, Trabert B, Shalev V, Lunenfeld E, Sella T, Chodick G. In vitro fertilization and risk of breast and gynecologic cancers: A retrospective

cohort study within the Israeli Maccabi Healthcare Services. *Fertil Steril* 2013; 99(5): 1189-1196. https://doi.org/10.1016/j.fertnstert.2012.12.029.

27. van den Belt-Dusebout AW, Spaan M, Lambalk CB, Kortman M, Laven JS, et al. Ovarian stimulation for in vitro fertilization and long-term risk of breast cancer. *JAMA* 2016; 316(3): 300-312. https://doi.org/10.1001/jama.2016.9389.
28. Lalwani N, Prasad SR, Vikram R, Shanbhogue AK, Huettner PC, Fasih N. Histologic, molecular, and cytogenetic features of ovarian cancers: Implications for diagnosis and treatment. *Radiographics* 2011; 31(3): 625-646. https://doi.org/10.1148/rg.313105066.
29. Lyubchenko LN. Hereditary breast and/or ovarian cancer: DNA diagnosis, individual prognosis, treatment and prevention. DSc Dissertation. Moscow, 2009; 238 p. Russian. https://elibrary.ru/item.asp?id=19224711.
30. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994; 266(5182): 66-71. https://doi.org/10.1126/science.7545954.
31. Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, et al. Identification of the breast cancer susceptibility gene BRCA2. *Nature* 1995; 378(6559): 789-792. https://doi.org/10.1038/378789a0.
32. Bochkov NP, Ginter EK, Puzyrev VP. Hereditary diseases: National guidelines. Moscow, Russia: GEOTAR-Media. 2013; 936 p. Russian. https://www.rosmedlib.ru/book/ISBN9785970422311.html.
33. Williams MJ, Sottoriva A, Graham TA. Measuring clonal evolution in cancer with genomics. *Annu Rev Genomics Hum Genet* 2019; 20: 309-329. https://doi.org/10.1146/annurev-genom-083117-021712.
34. Nussbaum RL, McInnes RR, Willard HF, Hamosh A. Genetics in medicine. 8th Ed. Elsevier. 2007; 599 p. https://www.elsevier.com/books/thompson-and-thompson-genetics-in-medicine/nussbaum/978-1-4377-0696-3.
35. Chesire DR, Dunn TA, Ewing CM, Luo J, Isaacs WB. Identification of aryl hydrocarbon receptor as a putative Wnt/beta-catenin pathway target gene in prostate cancer cells. *Cancer Res* 2004; 64 (7):2523-2533. https://doi.org/10.1158/0008-5472.can-03-3309.
36. Lyubchenko LN, Bateneva EI. Medical Genetic Counseling and DNA Diagnostics for Hereditary Predisposition to Breast Cancer and Ovarian Cancer. Moscow, Russia: IG RONTS. 2014; 75 p. Russian. https://docplayer.com/27130325-Mediko-geneticheskoe-konsultirovanie-i-dnk-diagnostika-pri-nasledstvennoy-predraspolozhennosti-k-raku-molochnoy-zhelezy-i-raku-yaichnikov.html.
37. Cazzaniga M, Bonanni B. Prevention of ER-negative breast cancer: Where do we stand? *Eur J Cancer Prev* 2012; 21(2): 171-181. https://doi.org/10.1097/CEJ.0b013e32834c9c26.
38. Brzezinski A, Peretz T, Mor-Yosef S, Schenker JG. Ovarian stimulation and breast cancer: Is there a link? *Gynecol Oncol* 1994; 52(3): 292-295. https://doi.org/10.1006/gyno.1994.1051.
39. Pappo I, Lerner-Geva L, Halevy A, Olmer L, Friedler S, Raziel A,. The Possible Association between IVF and Breast Cancer Incidence. *Ann Surg Oncol* 2008; 15(4): 1048-1055. https://doi.org/10.1245/s10434-007-9800-2.
40. Mitsudomi T, Yatabe Y. Mutations of the epidermal growth factor receptor gene and related genes as determinants of epidermal growth factor receptor tyrosine kinase inhibitors sensitivity in lung cancer. *Cancer Sci* 2007; 98(12): 1817-1824. https://doi.org/10.1111/j.1349-7006.2007.00607.x.
41. Ramus, SJ, Gayther SA. The contribution of BRCA1 and BRCA2 to ovarian cancer. *Mol Oncol* 2009; 3(2): 138-150. https://doi.org/10.1016/j.molonc.2009.02.001.
42. Berchuck A, Heron KA, Carney ME, Lancaster JM, Fraser EG, Vinson VL, et al. Frequency of germline and somatic BRCA1 mutations in ovarian cancer. *Clin Cancer Res* 1998; 4(10): 2433-2437. https://pubmed.ncbi.nlm.nih.gov/9796975.
43. Foster KA, Harrington P, Kerr J, Russell P, DiCioccio RA, Scott IV, et al. Somatic and germline mutations of the BRCA2 gene in sporadic ovarian cancer. *Cancer Res* 1996; 56(16): 3622-3625. https://pubmed.ncbi.nlm.nih.gov/8705994.
44. Cunningham JM, Cicek MS, Larson NB, Davila J, Wang C, Larson MC, et al. Clinical characteristics of ovarian cancer classified by BRCA1, BRCA2, and RAD51C status. *Scientific Reports* 2014; 4: 4026. https://doi.org/10.1038/srep04026.
45. Gates MA, Rosner BA, Hecht JL, Tworoger SS. Risk factors for epithelial ovarian cancer by histological subtype. *Am J Epidemiol* 2010; 171(1): 45-53. https://doi.org/10.1093/aje/kwp314.
46. Sergentanis TN, Diamantaras AA, Perlepe C, Kanavidis P, Skalkidou A, Petridou ET. IVF and breast cancer: A systematic review and meta-analysis. *Hum Reprod Update* 2014: 20(1): 106-123, 2014. https://doi.org/10.1093/humupd/dmt034.
47. Irvin SR, Weiderpass E, Stanczyk FZ, Brinton LA, Trabert B, Langseth H, et al. Association of anti-mullerian hormone, follicle-stimulating hormone and inhibin B with risk of ovarian cancer in the Janus Serum Bank. *Cancer Epidemiol Biomarkers Prev* 2020; 29(3): 636-642. https://doi.org/10.1158/1055-9965.EPI-19-0675.

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