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Review

Most relevant genetic factors in ovarian cancer development

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Abstract: Ovarian cancer (OC) represents a significant challenge in the realm of gynecological cancers, characterized by poor survival rates and complex etiology. This review delves into the genetic, environmental, and hormonal factors underpinning OC development, shedding light on both well-established contributors and emerging influences. We reviewed scientific databases searching for OC genetic and epigenetic factors and included studies based on their relevancy. As a result of exploring ovarian carcinogenesis, this systematic review contains data collected from 102 works. The role of prominent genetic players, such as *BRCA* mutations and DNA repair mechanisms, underscores the intricate landscape of OC susceptibility. Furthermore, we explore Li-Fraumeni and Lynch syndrome, which result in a heightened predisposition to OC development. Hormonal factors such as estrogen, progesterone, and androgens are also discussed in detail. Environmental alterations, ranging from lifestyle influences to microbiome dysbiosis add layers of complexity to OC pathogenesis. Lifestyle factors such as obesity, alcohol consumption, and physical activity intersect with genetic and epigenetic pathways, shaping the risk landscape for OC. This review provides a nuanced understanding of the multifactorial nature of OC through a meticulous examination of current literature, emphasizing the need for holistic approaches to prevention, diagnosis, and treatment.

Keywords: Ovarian cancer; Genetic factors; Hormonal factors; Environmental factors; BRCA mutations; DNA repair mechanisms; Hormone therapy; Tumor suppressor genes; Gynecologic cancer

Abbreviations

OC: ovarian cancer
LFS: Li-Fraumeni syndrome
PR: progesterone receptor
PCOS: polycystic ovary syndrome
COCPs: combined oral contraceptive pills
DSB: double-strand break repair
LPS: lipopolysaccharides

1. Introduction

Ovarian cancer (OC) is one of the most common gynecological cancers, being associated with poor survival rates [1,2]. According to the Ovarian Cancer Research Alliance, in 2023, there were 19,710 new estimated cases of OC in the United States, contributing to 1% of all new cancers. OC was responsible for 13,270 deaths in 2023, representing 2.2% of all cancer deaths. The five-year survival rates for ovarian cancer in the USA is approximately 50.8% [2]. In 2020, in Central Eastern Europe, there were 28,530 new cases and 17,565 deaths [3]. OC occurs more often in postmenopausal white women older than 63 years [4] (Figure 1). Non-specific symptoms make early diagnosis more difficult. A broad spectrum of factors contributes to carcinogenesis, which supports a more profound analysis.

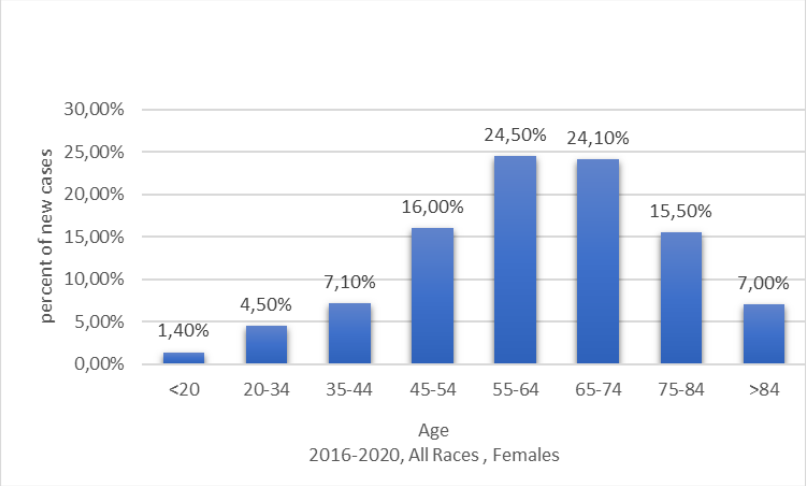

Figure 1. Percentage distribution of ovarian cancer incidence divided into age groups [2]. The number of new ovarian cancer cases in the United States increased significantly in the 45–54-year-old age group. The highest frequency occurs in the 55–64-year-old age group, constituting 24.5% of the new cases. https://ocrahope.org/for-patients/gynecologic-cancers/ovarian-cancer/ovarian-cancer-statistics/.

Type I tumors, accounting for 30% of the tumors, are low-grade tumors characterized by slow growth and large cystic formations, with mutations in *KRAS, BRAF, PTEN, CTNNB1, PIK3CA, PPP2R1A*, and *ARID1A* genes. Type II tumors, constituting 70% of all ovarian malignancies, are aggressive, high-grade cancers that almost always present at an advanced stage with high mortality.

Type II tumors have altered *TP53*, *BRCA1*, and *BRCA2* genes and are genetically unstable [5] (Figure 2). This study focuses mainly on factors related to type II tumors, as they are considered a significant medical concern requiring extensive knowledge and quick action. Figure 2 presents several important genes in ovarian carcinogenesis and the prevalence of their mutations in hereditary ovarian cancer cases. According to this, *BRCA* gene mutations represent 73% of all cases.

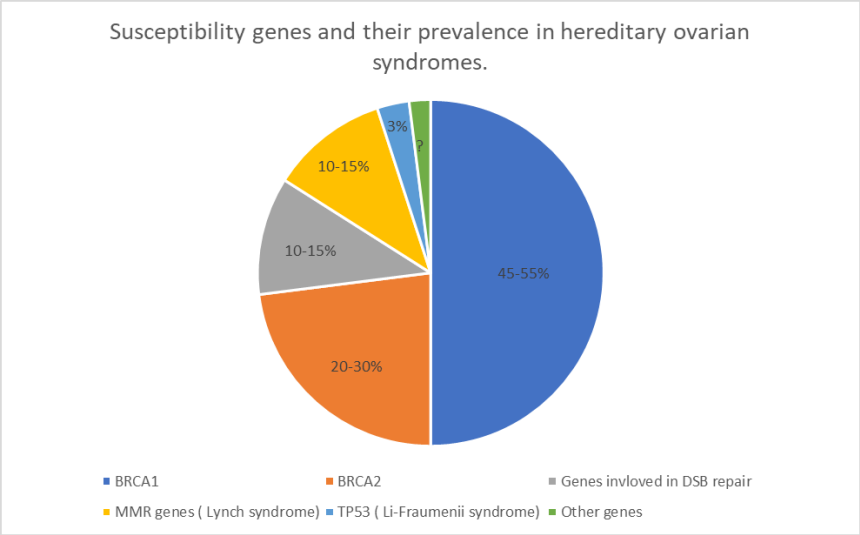

Figure 2. Frequency of mutations of particular genes in hereditary ovarian cancer [5]. Figure was created by the authors. https://pubmed.ncbi.nlm.nih.gov/26075229/.

We will discuss in detail the mutations of *BRCA1/2* genes, the DSB system and the consequences of its failure, the prevalence of OC in the Li-Fraumeni and Lynch syndromes, and the expression of the protein phosphatase and tensin homolog and its role in carcinogenesis. We advocate that knowledge about gene aberrations leading to OC has excellent value, as well as about processes influencing gene expression. We believe that including these two aspects in this work enables a comprehensive look at OC carcinogenesis and may be helpful in OC prevention and treatment. We select and describe several factors affecting gene expression that seem to contribute significantly to the development of OC. Hormonal and environmental factors are discussed here to analyze in a broader context the genetic intricacies behind OC: androgens, estrogens, and progesterone have been proven to affect the development of ovarian cancer, and several environmental factors may be related to OC, such as late menopause, hormone therapy, polycystic ovary syndrome, pregnancy, and breastfeeding. Also, we discuss the effect that microbiota and viruses, such as HPV, have on the development of ovarian cancer. In this review, the most critical factors for OC are described, as understanding them is essential from a prevention perspective. Numerous studies have confirmed the role of epigenetic changes in the development of OC. In OC, as in many cancer types, two opposing epigenetic phenomena have been identified: a global decrease in DNA methylation, leading to the demethylation of several oncogenes and repetitive elements, and specific CpG island hypermethylation associated with the promoters of tumor suppressor genes, deactivating these genes [6].

2. Materials and methods

2.1. Overview

Two autonomous researchers performed a systematic review of online scientific literature to uncover valuable publications, analyze the quantity and quality of research, and assess the availability of the materials.

A multistep search through the online databases PubMed, Google Scholar, and Science Direct was performed to identify scientific publications suitable for analysis. Two separate review sessions were conducted using the keywords "ovarian cancer genetic factors" and "ovarian cancer epigenetic factors", selecting articles published since 2000. Based on the most suitable results, a list of records was organized. All types of scientific papers that met the criteria were analyzed.

2.2. Exclusion and inclusion criteria

The research methodology employed exclusion criteria to accurately identify pertinent scientific papers. We decided to search only for journal articles published in or after the year 2000 as essential works began to appear in this year, which contained information confirmed in the subsequent works included.

While searching PubMed, Embase, and Google Scholar, we utilized the "sort by relevancy" function provided by those databases. We decided to cut the number of publications screened to the first 200 results in each search in every database. Papers that were inaccessible or works other than journal articles were excluded. We read only articles in English and Polish, as those were the only languages used by the authors. We relied on studies using both human samples and mice. We included only papers on genetic factors connected to OC etiology. If a paper was included by one reviewer and excluded by another, then the paper's relevancy was discussed among all authors until reaching a unanimous decision on the inclusion of that article.

2.3. Records retrieval

After entering the keyword "ovarian cancer genetic factors" in the three databases, we obtained 89,468 works. The keyword "ovarian cancer epigenetic factors" produced 20,375 results. The first 200 records from all three databases were analyzed by title and abstract. In the next step, 729 works were chosen from the most relevant as sorted by database. After this selection process, duplicates were removed to prevent redundancy and uphold data integrity. Duplication exclusion was based on publication identifiers or an analysis of titles, authors, and other metadata. As a result, 619 publications remained.

Publications focusing mainly on other types of cancers linked to the described genes, as well as articles discussing methods of treatment and causes of cancer resistance for specific chemotherapeutics, were excluded.

To uphold the credibility of the results, inaccessible papers and those containing inaccurate data that met the rejection criteria were eliminated. 102 papers met the criteria and were included in this work (Figure 3).

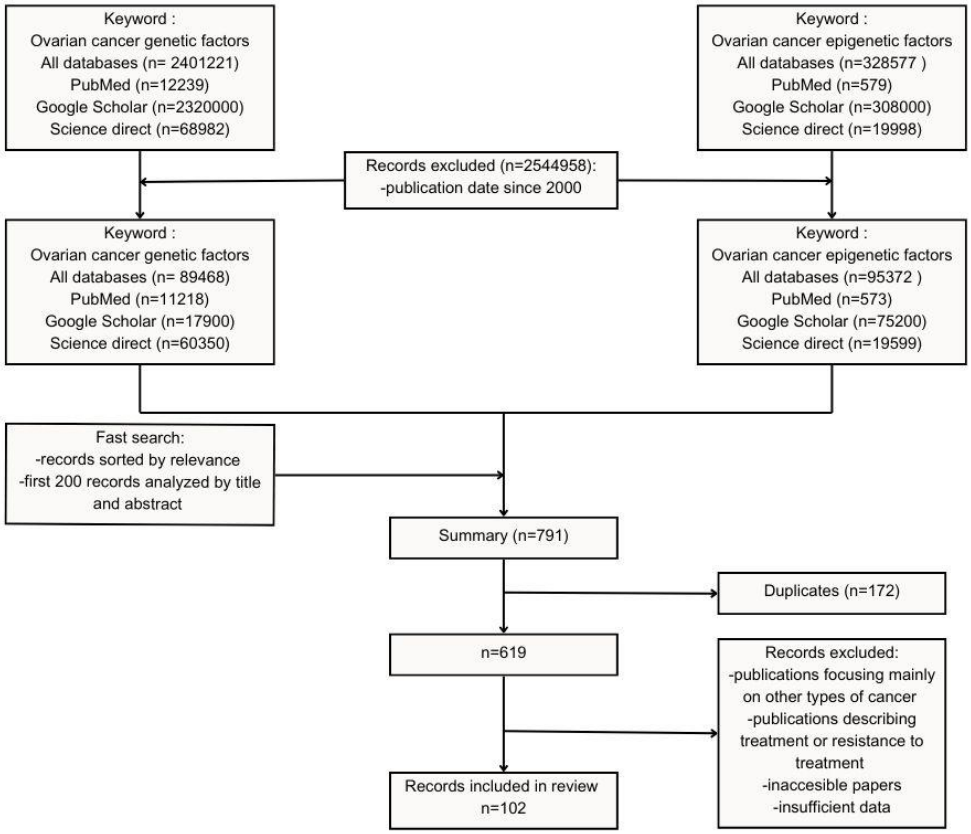

Figure 3. Exclusion criteria and number of works excluded and included in research.

2.4. Data analysis

Two authors independently examined all articles. Each author analyzed the title, structure, materials, methods, and results, including figures and tables. Works that were unusual or problematic in any way were also fully read.

2.5. Data compilation

The analysis emphasized commonalities among the papers, comparing various aspects such as the form of the articles, scientific discipline, concepts and types of research, choice of research methods, objectives, and subject matter to identify global tendencies. On this basis, an initial categorization of the papers was carried out. The articles within each category were then analyzed and compared to ensure alignment with the established criteria, enhancing the method's sensitivity. A subset of articles was selected from each group for discussion in the review. Our team has experience in systematic reviews in morphological sciences and associated disciplines [7–9].

3. Results

3.1. Selected genetic factors in ovarian carcinogenesis

3.1.1. *BRCA1/2* and double-strand break repair

BRCA1 and *2* are tumor suppressor genes, in which mutations can lead to breast and ovarian cancer [10]. *BRCA1* mutations are associated with an 18%–54% increased risk of developing OC by age 70. *BRCA2* mutations provide a 2.4%–19% increased risk of developing OC by age 70 [11]. *BRCA1* gene mutations have been found in 40%–50% of families with both breast and ovarian cancer [12].

More than 400 mutations have been detected in *BRCA1/2* genes, and many remain unexplored. At the same time, most human mutations are unique, and each family can present specific mutations. Most (80%) occur as point or deletion/insertion mutations. Due to this, the P53-dependent DNA breakdown is activated, which may lead to cell cycle arrest and apoptosis [12]. *BRCA* genes, through their proteins, support chromosome stability [13].

Cells deficient in the murine *BRCA2* homolog appear to sustain spontaneous aberrations in chromosome structures during cell division. The abnormalities include broken chromosomes and chromatids, triradial and quadradial structures, translocations, deletions, and fusions. In *BRCA1*-deficient mouse cells and *BRCA1* and *BRCA2*-deficient human cells, structural abnormalities were similar and abnormality in chromosomal structure occurred [13].

The second crucial evidence of *BRCA*'s role in carcinogenesis is that mammalian cells deficient in *BRCA* have gross chromosomal rearrangement resulting from inappropriate double-strand break repair (DSB) during the S and G2 phase when the *BRCA* proteins are maximally expressed. The leading cause is that these cells lack homologous recombination (HR), the only error-free way to repair DSB. Without HR, the altered cells use error-prone DSB repair mechanisms. This implies that chromosomal instability in *BRCA*-deficient cells is generated by incorrect directing of DSB processing down inappropriate pathways, rather than the failure of repair [14,15] (Figure 4).

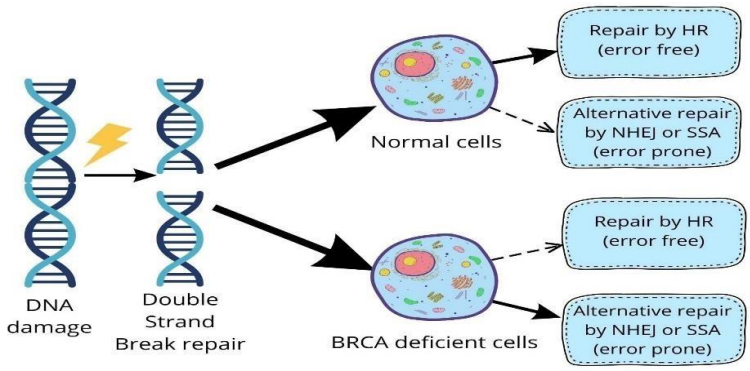

Figure 4. Preferred repair methods of DSB in normal cells with no DNA damage and in *BRCA*-deficient cells. *BRCA*-deficient cells are directed to the error-prone paths. The figure was created by the authors.

Another role of *BRCA2* is that it binds directly to RAD51, a key agent for DSB repair by HR [16]. Studies show that *BRCA2* directly regulates the availability and activity of RAD51. This mechanism

is responsible for creating a nucleoprotein filament that invades and pairs with a homologous DNA duplex, initiating strand exchange between the paired DNA molecules [13,17]. In the presence of BRC peptides, recombinant RAD51 spontaneously becomes largely monomeric instead of polymerizing.

Both nonhomologous ends joining (NHEJ) and single-strand annealing (SSA) are processes independent from RAD51 and error-prone [16]. *BRCA2*-deficient cells use NHEJ and SSA to repair site-specific DSBs [13,15]. In *BRCA1*-deficient cells, NHEJ predominates. This explains why BRCA proteins' role in the repair process relies on directing them to the wrong pathways [13,16]. BRCA2 participates in DNA repair and can regulate the cell cycle (G2/M phase) by interacting with the protein BRAF35, which binds in vitro to the branched DNA structures [8].

What about *BRCA1*?

BRCA1 can also inhibit the activity of MRE11—a protein essential for generating ssDNA (needed for HR and SSA repair)—at sites of DNA breakage and interact with enzymes that alter chromatin and DNA structures. *BRCA1* interacts with SWI/SNF, which remodels chromatin, histone acetylation/deacetylation regulators, and DNA helicases [13].

BRCA1 may be responsible for sensing DNA damage: when damage occurs in dividing cells, BRCA1 is rapidly phosphorylated. As implicated in several checkpoint events, *BRCA1*-deficient cells fail to arrest scheduled DNA synthesis in the S and G2 phases. It can also cohabit in high-molecular-weight complexes with many proteins that bind to abnormal DNA structures. *BRCA1*'s precise role remains to be clarified. However, it makes sense to assume that it works as a signal "processor" to coordinate DNA damage-sensing mechanisms with appropriate biological responses. On the one hand, *BRCA1* participates in protein complexes that have functions intrinsic to the sensing and signaling of different types of DNA lesions. On the other hand, it works as a sequence-specific transcriptional regulator of genes, whose expression affects checkpoint enforcement and other downstream biological responses [13].

Evidence shows that P53 mutations are more frequent in cancers with *BRCA* alterations. The spectrum of mutations is also different [13].

Women who are carriers of *BRCA1* and *BRCA2* mutations are more susceptible to breast, ovary, colon, stomach, pancreas, and gallbladder cancer. In patients with known *BRCA* mutations, more frequent monitoring is indicated. The main goal is early detection of malignancy or lesions. A positive *BRCA* mutation suggests a higher probability of cancer growth, but not every mutation must end that way. Likewise, a negative mutation result is not an exclusion for the development of breast or ovarian cancer in a lifetime [11].

3.1.2. Li-Fraumeni syndrome

The Li-Fraumeni syndrome (LFS) is a hereditary predisposition factor to cancers. It is also known as the sarcoma, breast, leukemia, and adrenal gland (SBLA) cancer syndrome [18], being related to the development of OC. We can distinguish three types of the disease. LFS1, the most common variant, is associated with a mutation in *TP53*. *TP53* is the genetic blueprint for the P53 protein and most commonly causes this condition by mutations or alterations in the gene. All families with LFS1 sequencing have shown mutations in the P53 DNA binding domain caused by germline missense [19]. Several subsequent studies have confirmed these initial findings, but mutations in the *TP53* gene have

also been shown to be distributed throughout the germline. Missense mutations account for 74% of germline *TP53* mutations, followed by nonsense mutations (9%) and splice mutations (8%) [19]. Most mutations occur in the highly conserved DNA-binding domain, and the six most common "hotspot" mutations are found in codons 175, 245, 248 (two common substitutions), 273, 282, and 337 [19,20]. Mutations can occur in the parent germ cell and be inherited or develop de novo during embryogenesis. There is a lack of data on the frequency of de novo mutations in LFS patients, although estimates range from 7% to 20% [21] (Figure 5).

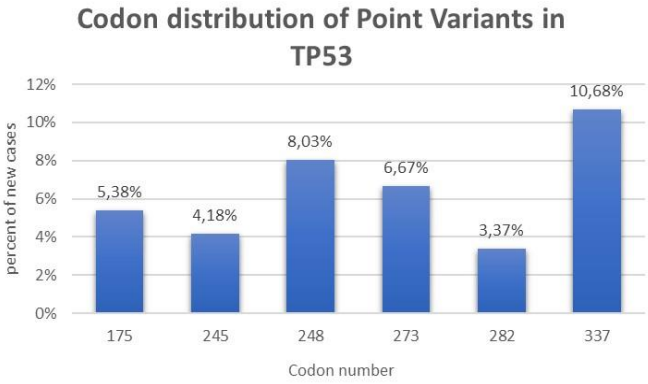

Figure 5. Distribution of point variants in the *TP53* gene at specific codon numbers [22]. The figure was created by the authors.

Two other less frequent types of the disease are LFS2 and LFS-L. LFS-L individuals do not have detectable mutations in P53. LFS2 is associated with a mutation in *CHEK2* (checkpoint kinase two), which regulates the activity of P53 [21].

P53 plays an essential role in cancer prevention mechanisms. It controls apoptosis, inhibits angiogenesis, and helps maintain genomic stability [23]. It participates in fixing DNA by activating DNA repair proteins. Mutations in LFS lead to the loss of functional P53 protein, which decreases the cell's defense against genetic changes.

Although only about 3% of cases of OC are associated with LFS, it increases its risk by 47% [5]. Also, they occur much earlier than expected. The median age for patients diagnosed with ovarian cancer is 39.5 years, compared to an average of almost 65 years for those who do not suffer from LFS. The probability of individuals with LFS developing any cancer in their lifetime is 75% for men and almost 100% for women [21].

3.1.3. Lynch syndrome

Lynch syndrome is a hereditary cancer syndrome that is passed down in an autosomal dominant manner. It may lead to various types of cancer, including OC. It is caused by pathogenic variants (PVs) in the DNA mismatch repair system [24]. These genes include mutL homolog 1 *(MLH1),* mutS homolog 2 *(MSH2),* mutS homolog 6 *(MSH6),* and PMS1 homolog 2 *(PMS2*). Deletions in the epithelial cell adhesion molecule (EpCAM) can result in the downstream epigenetic silencing of *MSH2*. The loss of this gene causes a point or frameshift mutation, which can lead to the creation of a non-functioning protein. These mutations accumulate in the areas of microsatellites that can be easily

recognized when compared with the microsatellite regions of normal cells [25]. Loss of *MSH6* or *MSH3* alone does not result in cancer formation, as the genes share redundant function. If both genes are non-functional, mutations can accumulate with subsequent cancer development [25]. In rarer cases, the inherited inactivation of the MMR system can occur from germline hypermethylation of the promoter region of *MLH1* [23]. MLH1 forms a heterodimer with PMS2 to participate in the mismatch repair system. However, its exact function has yet to be discovered. MLH1 also likely dimerizes with MLH3 [25] (Figure 6).

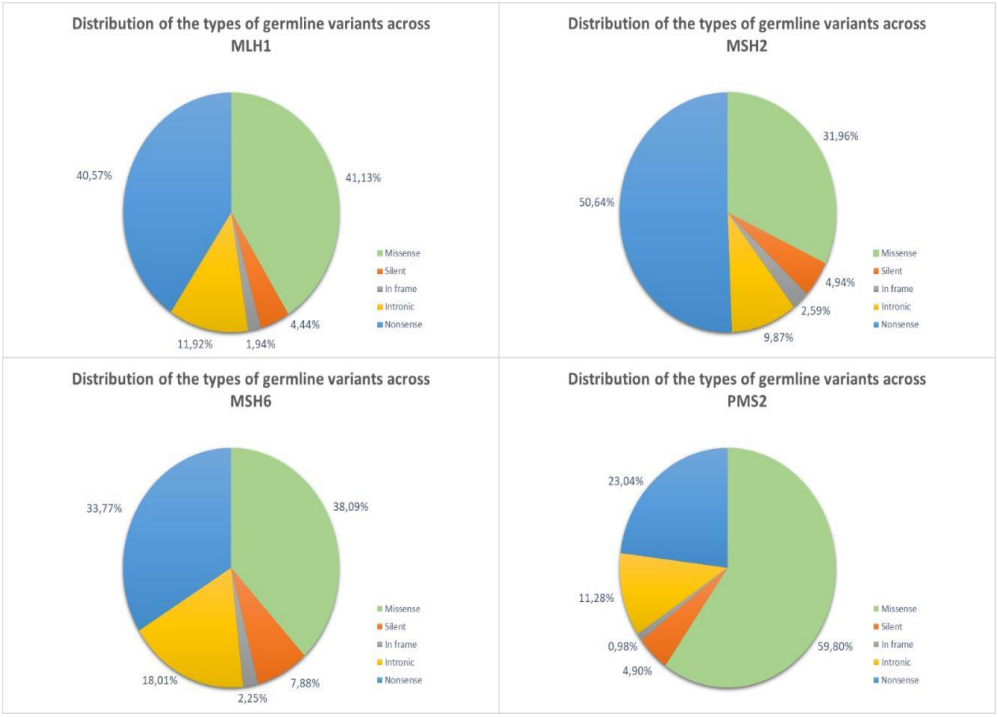

Figure 6. Distribution of types of germline variants across a) *MLH1*, b) *MSH2*, c) *MSH6*, and d) *PMS2* genes. Each chart represents variants: missense, silent, in-frame, intronic, and nonsense [22]. The figure was created by the authors.

MLH1 and *MSH2* are two of the most frequently mutated genes in Lynch syndrome tumors. This accounts for approximately 75% of mutations in patients diagnosed with Lynch syndrome [26]. This syndrome is believed to affect 1 in every 278 individuals, but more than 95% of people remain undiagnosed [26]. It increases a lifetime cancer risk by 10%–90% [27], which varies based on the specific variant and type of cancer. It also exhibits a lack of uniformity. The penetrance level, range of disease, and the age at which cancer begins can differ based on the specific gene mutation [24] (Figure 7).

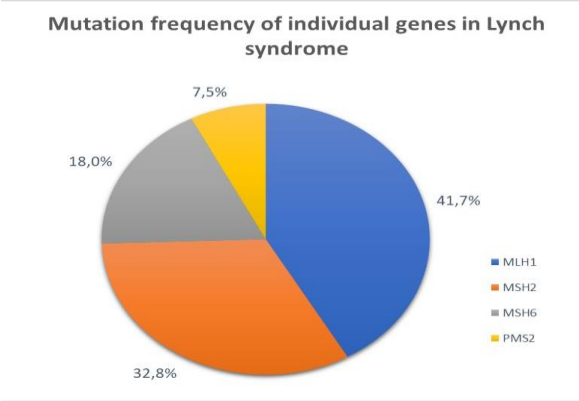

Figure 7. Overview of mutation frequency of individual genes associated with Lynch syndrome [22]. The figure was created by the authors.

Additionally, specific variants that cause Lynch syndrome have been shown to increase the risk of OC [24]. A lifetime cumulative risk of OC for women with Lynch syndrome is approximately 10% [28], which is exceptionally high for *MSH2*-mutation carriers [29]. They constitute 2% of all OC cases [28]. Cancers associated with Lynch syndrome are typically diagnosed at a younger age than similar cases in the general population [30]. On average, ovarian cancer is diagnosed in individuals with Lynch syndrome between the ages of 43 and 46 years, compared to 60 years in patients without Lynch syndrome (Table 1–3).

Table 1. Comparative analysis of the lifetime risk and average age of diagnosis for ovarian, colorectal, and endometrial cancers in the general population versus individuals with *MLH1* mutation [22].

Cancer type	Lifetime risk in general population	Lifetime risk with *MLH1* mutation	Average age of diagnosis in general population	Average age of diagnosis with *MLH1* mutation
Ovarian	1.10%	4%–20%	63	46
Colorectal	4.10%	46%–61%	68–72	44
Endometrial	3.10%	34%–54%	60	49

Table 2. Comparative analysis of the lifetime risk and average age of diagnosis for ovarian, colorectal, and endometrial cancers in the general population versus individuals with *MSH2* mutation [22].

Cancer type	Lifetime risk in general population	Lifetime risk with *MSH2* mutation	Average age of diagnosis in general population	Average age of diagnosis with *MSH2* mutation
Ovarian	1.10%	8%–38%	63	4
Colorectal	4.10%	33%–52%	68–72	44
Endometrial	3.10%	21%–57%	60	47–48

Table 3. A comparative analysis of the lifetime risk and average age of diagnosis for ovarian, colorectal, and endometrial cancers in the general population versus individuals with MSH6 mutation [22].

Cancer type	Lifetime risk in general population	Lifetime risk with *MSH6* mutation	Average age of diagnosis in general population	Average age of diagnosis with *MSH6* mutation
Ovarian	1.10%	1%–13%	63	46
Colorectal	4.10%	10%–44%	68–72	42–69
Endometrial	3.10%	16%–49%	60	53–55

Ovarian cancer associated with LS is primarily endometroid and has a better prognosis than the ones linked to *BRCA* mutations [23]. It is preferable for women diagnosed with Lynch syndrome to consult with a gynecologist around the age of 25 years to understand the warning signs of cancer, discuss family planning, and consider strategies to reduce risk [31].

There's limited evidence on how lifestyle impacts the risk of gynecological cancer in women with Lynch syndrome. The oral contraceptive pill is known to lower the risk of sporadic endometrial and ovarian cancer, as well as ovarian cancer associated with *BRCA1/2* [32]. Aspirin has been proven to decrease the risk of all Lynch syndrome–associated cancers. This suggests aspirin's effect on OC should be further investigated [33]. Individuals with Lynch syndrome may also be more susceptible to cancer due to lifestyle factors [34]. As a risk-reducing measure, the National Comprehensive Cancer Network (NCCN) now advises that *MLH1* and *MSH2/EPCAM* carriers should decide whether to individually have a BSO (bilateral salpingo-oophorectomy). The date ought to be determined by factors such as family history, specific variants, medical comorbidities, menopausal status, and completion of childbearing. According to NCCN, *MSH6* carriers should make their own decisions, because there is not enough information to advocate for BSO in this case. They offer even more specific advice for *PMS2* carriers, noting that they seem to have no increased risk of OC, and can legitimately decide for no oophorectomy [24].

3.1.4. Phosphatase and tensin homolog protein expression

Alterations in the *PTEN* gene are significant contributors to ovarian cancer pathogenesis, with studies indicating that approximately 6% of primary ovarian cancer samples exhibit mutations in *PTEN*. In a comprehensive analysis involving 117 ovarian adenocarcinomas, the frequency of loss of heterozygosity (LOH) at loci flanking and within the *PTEN* gene ranged from 30% to 50%, while somatic mutations were identified in 6% of cases, encompassing various types such as missense and frameshift mutations [35]. The study highlighted that 11% of tumors showed absent *PTEN* expression despite lacking detectable mutations, suggesting that mechanisms such as epigenetic silencing play a crucial role in *PTEN* inactivation, which is associated with increased phosphorylated Akt (P-Akt) levels, thereby implicating *PTEN* loss in enhanced cell survival and proliferation pathways in ovarian cancer [35]. Furthermore, it has been demonstrated that there is a link between *PTEN* (phosphatase and tensin homolog deleted on chromosome 10) protein expression and estrogen receptor expression in EOC (epithelial ovarian cancer). *PTEN* expression is low in EOC tissues, and estrogen inhibits it through EOC cells' estrogen receptor 1 (*ESR1*) [36]. Knocking down *PTEN* boosts the proliferation and migration of estrogen-driven EOC cells. In addition, estrogen stimulation activates the G protein-

coupled receptor 30 (GPR30)-protein kinase C (PKC) signaling pathway, which phosphorylates *PTEN*. Inhibiting *PTEN* phosphorylation inhibits estrogen-induced EOC cell proliferation and migration while lowering AKT and mTOR phosphorylation. These findings reveal that estrogen lowered *PTEN* expression levels via the ESR1 genomic pathway and phosphorylated *PTEN* via the GPR30-PKC non-genomic pathway, triggering the PI3K/AKT/mTOR [phosphoinositide three kinase/protein kinase B/mammalian (or mechanistic) target of rapamycin] signaling cascade and influencing the fate of EOC cells [37,38].

3.2. Hormonal factors

3.2.1. Estrogens

The majority of ovarian tumors are thought to emerge in the surface epithelium because of hormonal changes. Prolonged treatment with hormone replacement treatment (HRT) is considered a contributing factor [39]. A 22% increased risk of OC was seen in postmenopausal women using unopposed estrogen as HRT [39]. The risk was still significantly increased (approximately by 10%) by applying a combination of estrogen and progestin [40]. Women who have early menarche and late menopause and women who are taking fertility drugs (gonadotropin-releasing hormone antagonists or clomiphene) are at increased risk of developing OC [41]. This is caused by a high concentration of estrogen after stimulation of the sex-steroid hormone synthesis in the ovary [42]. Early menarche increases its risk by 4% in Europe and 5%–9% in the USA [43].

3.2.2. Androgens

Several studies have reported the expression of androgen receptors (AR) in OC cells, particularly in hormone-sensitive subtypes, such as endometrioid and low-grade serous ovarian carcinomas [44]. AR suggests that these tumors may be responsive to androgen signaling, which could influence their growth and progression. Preclinical studies have demonstrated that androgen stimulation can promote the proliferation and survival of AR-positive ovarian cancer cells in vitro and in vivo [44,45]. This androgen-driven tumor growth is mediated by activating various signaling pathways, including the PI3K/AKT and MAPK pathways, which are known to play crucial roles in cancer cell proliferation and survival [45].

According to global cancer statistics from the World Health Organization (WHO), OC accounts for approximately 3% of all new cancer cases and 5% of cancer-related deaths among women worldwide [45]. The incidence and mortality rates vary across different regions, with higher rates observed in developed countries compared to developing nations. This variation may be attributed to factors such as differences in risk factors, access to screening and early detection programs, and the availability of effective treatment options [46].

3.2.3. Progesterone

Numerous studies have suggested that progesterone may play a protective role against OC. A study published in the Journal of the National Cancer Institute in 2013 found that women who used progesterone-only contraceptives had a significantly lower risk of developing OC compared to non-

users [47]. Similarly, a 2015 study in the International Journal of Cancer reported that higher levels of progesterone were associated with a reduced risk of OC [48].

The proposed mechanisms by which progesterone may inhibit OC development include its ability to induce apoptosis in OC cells, suppress cell proliferation, and inhibit angiogenesis, which is crucial for tumor growth. Additionally, progesterone has been shown to modulate the immune system, potentially enhancing the body's ability to recognize and eliminate cancer cells [37,38,49].

However, the relationship between progesterone and OC is not entirely straightforward. Some studies have suggested that progesterone may also have a stimulatory effect on OC cells under certain conditions. Another study has found that progesterone could promote the growth and invasion of OC cells in the presence of specific genetic alterations [50].

In conclusion, the current scientific evidence suggests that progesterone may play a complex and multifaceted role in the development and progression of OC. While many studies have reported a protective effect of progesterone, the specific mechanisms and the influence of various factors, such as genetic and hormonal profiles, require further investigation to fully understand the relationship between this hormone and ovarian cancer.

3.2.4. Progesterone receptor

The type of progesterone receptor (*PR*) and its genetic variations have been implicated in the development of OC. One significant factor is the loss of heterozygosity (LOH) at the 11q23.3-24.3 locus, where the *PR* gene is located [51]. LOH at 11q23.3-24.3 has been frequently observed in OC cases, suggesting that this region harbors tumor suppressor genes crucial for ovarian carcinogenesis [52,53]. The loss of one functional copy of the *PR* gene in this region may contribute to the dysregulation of progesterone signaling, potentially promoting OC development.

Regarding specific *PR* gene polymorphisms, scientists have identified four variants: +44C/T, +331G/A, G393G, and V660L [49,50]. After extensive research, it was found that the +44C/T, +331G/A, and G393G polymorphisms did not appear to be associated with an increased risk of OC [52,53]. However, an inverse relationship was observed between the V660L variant and OC risk (odds ratio = 0.70, 95% confidence interval: 0.57, 0.85) [52,53]. This suggests that individuals carrying the V660L variant may have a reduced risk of developing OC compared to those without this genetic variation. The V660L polymorphism is thought to potentially alter the biological functions of the progesterone receptor, which could influence the development and progression of ovarian cancer[52-54]. However, the specific mechanisms by which this variant confers a protective effect are not fully understood and require further investigation. The association between *PR* gene variations and OC risk may be influenced by various factors, such as OC histology, reproductive history, and other risk factors [55]. Further research is needed to fully elucidate the complex interplay between progesterone receptor genetics, hormone signaling pathways, and the development of OC.

3.3. Environmental factors

3.3.1. PCOS and age of menopause

The direct correlation between polycystic ovary syndrome (PCOS) and ovarian malignancies is not yet confirmed. Even so, many studies have shown that they share the same risk factors, such as

obesity and hormonal imbalances [56]. Because of that, it is now believed that PCOS may lead to ovarian cancer. Endometriosis is also one of the risk factors.

The proof for age-at-menopause as a risk factor is conflicting [6]. In the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, ages above 52 years were associated with an increased risk of OC by 5.7% (HR = 1.57, 95% CI 1.16–2,13) compared with age-of-menopause under 45 years. However, when excluding women who were diagnosed with OC within their first 2 years of follow-up, the risk decreased slightly and amounted to 4% (HR = 1.40, 95% CI 0.98–2.00) [57].

3.3.2. Pregnancy and breastfeeding

Pregnancy has a great impact on decreasing the risk of OC. It has been proven that women who had given birth had 30%–40% lower chances of developing OC [58-60]. Some other studies calculated the risk of OC decreasing by 8% with every pregnancy and another one calculated a decline of 18%, 26%, 33%, and 42% for the first, second, third, and fourth pregnancy, respectively [59]. In Finland, scientists have proven that the odds ratio (OR) between pregnancy and developing OC for serous cancer was 0.65 (95% confidence interval, 0.56–0.77), for mucinous cancer was 0.66 (0.52–0.83), for endometrioid cancer was 0.52 (0.40–0.68), for clear-cell cancer was 0.30 (0.19–0.46), and for other cancer types was 0.59 (0.43–0.80). In women aged 55 or older, the respective ORs were 0.86 (0.75–0.99), 0.78 (0.57–1.07), 0.61 (0.47–0.79), 0.44 (0.29–0.66), and 0.74 (0.57–0.95), adjusted for hormone therapy [60].

The number of childbirths was associated with a trend toward reduction of risk, especially in serous and clear-cell cancers. Higher age at first birth was associated with a higher risk of clear-cell cancer; otherwise, age at first or last birth did not have an impact on the incidence of cancer subtypes [60]. Breastfeeding decreases the risk of OC, especially with long-term duration [61], but some studies have proven that prolactin may induce carcinogenesis by regulating gene expression or by activating signaling pathways associated with proliferation and inhibition of apoptosis [61].

3.3.3. Combined oral contraceptive pills

Combined oral contraceptive pills (COCPs) are unquestionably the strongest protective factor and play an important role in preventing OC. Substantial reduction in epithelial OC risk was observed among women who used COCPs for <1 year if they were recent users (time since first or last COCP use within 20 years); each year of COCP use provided an average 5% reduction in the odds ratio (OR 0.95; CI 0.92–0.98) [62]. The greatest reduction in risk was observed in women who started COCPs use before being 20 years old and stopped after being 30 years old [6,62].

3.3.4. Role of microbiome

Our microbiome can impact a lot of different parts of our body. More and more scientific papers are being published on the higher risk of developing cancer caused by dysbiosis [63-66]. There is evidence that dysbiosis, also called oncobiosis, may also contribute to the carcinogenesis of ovarian malignancies [67-69]. Many different factors can cause the transformation of the microbiome. The most common are lifestyle choices such as smoking, obesity, type of diet, changes to the diurnal rhythm, aging, underlying diseases, exercise, and antibiotic and probiotic use [70].

Women who have vaginal colonies poor in *Lactobacillus* spp. are proven to be carriers of *BRCA1* mutations. Deficiency of *Lactobacillus* is also observed in women with OC. This relation is more observable in the group of patients who are less than 40 years old [71]. Nevertheless, dysbiosis is not only caused by a decrease but also an increased number of other species. The tumor tissue is enriched in gram-negative bacteria such as Proteobacteria and Fusobacteria [70]. Potentially pathogenic microorganisms such as *Brucella*, *Mycoplasma*, and *Chlamydia* spp. were found in 60%–76% of ovarian tumors, as well as HSV virus, cytomegalovirus, or *C. trachomatis* [72].

Presumably, changes in the microbiome affect carcinogenesis by inducing inflammation and regulating immune responses. Bacterial metabolites and components play a major role in these processes. Specifically, lipopolysaccharides, lysophosphatides, tryptophan metabolites, short-chain fatty acids, secondary bile acids, and polyamines are shown to participate in OC pathogenesis [70]. First, lipopolysaccharides (LPS), which are the components of gram-negative bacteria's outer membrane, can activate cancer cells and tumor-associated macrophages; also, tumor tissue is more reactive to the LPS than normal tissue. LPS also drives inflammation in cancer cells by activating TLR4 receptors [73,74]. Lysophosphatides can also induce cell proliferation, migration, and invasion of cancer cells and increase the expression of elements essential for cancer angiogenesis [70]. Other bacterial metabolites have been shown to engage in carcinogenesis; however, their impact on ovarian cancer specifically is still ambiguous.

3.3.5. Role of viruses

Our analysis found that potentially tumorigenic viruses were present in more than 50% of the analyzed tumor tissues. In this group, the herpesviruses and human papillomaviruses represent the highest group [75].

Human herpesvirus-6a (HHV6a) is present in 50% of tumor samples and may exhibit two oncogenic mechanisms. The first is its ability to block insulin growth factor binding protein, which causes a great share of free and active growth factors with potentially mitogenic consequences. The second mechanism consists of the activation of some oncogenic genes like *SH3RF2* [76].

Viruses of the human papillomavirus group are one of the most common sexually transmitted viruses in the world. HPV16, 18, 31, and 45 have high oncogenic potential; these types cause intraepithelial neoplasia, which can lead to invasive cancers. The early region of HPV genomes encodes six proteins participating in viral replication: E1, E2, E3, E4, E6, and E7. E6 and E7 act as oncogenes by promoting tumor growth and malignant transformation [77]. In cells expressing high-risk HPV E7 proteins, the steady-state levels and metabolic half-life of the retinoblastoma tumor suppressor protein (pRB) are reduced [78]. E7 binds to the human pRb and E2F transcription factors, resulting in the dissociation of pRb from E3F and premature cell progression into the S-phase of the cell cycle [79]. These proteins target several negative regulators of the cell cycle, including P53. The HR-HPV E6 oncoprotein supports proteasomal degradation of P53, removes the trophic sentinel response for viral DNA synthesis, and increases telomerase activity to elude cell senescence [77]. Some reports have confirmed the presence of HPV in malignant ovarian cancer [67,80,81]. However, the frequency of occurrence varies significantly by geographical region with a prevalence of zero in most studies from Western Europe and North America and an HPV prevalence reaching almost 19% in Eastern Europe and 67% in Asia. This may be the result of environmental and genetic factors or differences in lifestyle factors such as smoking [82].

3.3.6. Obesity, physical activity, and metabolic basis of ovarian cancer

It is indisputable that obesity and physical activity are important factors in carcinogenesis in general. There are studies describing the correlation between these aspects and the risk of OC [83-86]. Evidence associates a small amount of physical activity with a higher risk of OC [87]. Obesity is a risk factor for 13 different cancers including OC. According to the Sook Bae meta-analysis, the presence of obesity 5 years before the diagnosis of OC and at a young age is related to a poor prognosis [87].

The main biological mechanism whereby these components are related to cancer incidence is the fact that a high concentration of adipocytes in the human organism can lead to adipose tissue impairment, which affects immune and hormonal alternations in the microenvironment, which is an important part of carcinogenesis [88]. The other participating factors may be altered adipokine expression, increased levels of circulating growth factors, and chronic inflammation [89]. Obesity and lack of physical activity are linked to pathways related to oxidative stress, DNA methylation, telomere length, immune function, and gut microbiome [87].

Adipose tissue produces several interleukins (IL) such as Il-6 and Il-8, as well as leptin, C reactive protein, IFNs, monocyte chemotactic protein 1 (MCP1), and tumor necrosis factor α (TNF-α). It has been proven that IL-6 is increased in ovarian patient's serum and is related to poor outcomes and chemotherapy resistance. IL-6 activates the JAK-STAT3 pathway and enables ovarian cancer cell invasion and metastasis. Moreover, IL-6 induces Mcl-1 antiapoptotic protein expression, which happens to be overexpressed in OC. Higher levels of IL-8, TNF-α, and CRP are also related to increased risk of ovarian carcinogenesis [90].

Adipose tissue also produces leptin, which is related to estradiol secretion from the ovaries. Furthermore, in OC patients, reduced serum leptin levels have been observed. On the other hand, overexpression of leptin receptors in OC tissue indicates aggressive disease [91].

There is some evidence showing adiponectin to be a factor in ovarian carcinogenesis. Adiponectin has been shown to have antiangiogenic, anti-inflammatory, and anti-neoplastic properties, and its levels are decreased in obesity. Increased levels of Il-6, leptin, and VEGF (vascular endothelial growth factor) and decreased levels of adiponectin have been observed to be caused by hypoxia [87]. Hypoxia itself is closely connected with higher fatty mass [92]. IGF-1 (insulin growth factor), which is also related to obesity, can activate HIF 1 (hypoxia-inducible factor) in conditions of lower oxygen availability. Increased level of IGF-1 is inversely linked with the survival of epithelial OC [89].

Metabolic derangements can also contribute to the progress of OC by influencing levels of sex hormones important in ovarian carcinogenesis. As mentioned, several processes potentially connected with obesity may increase OC risk. A cohort study of 461,646 women (≤49 years of age) registered in the Danish Medical Birth Registry found that the risk of premenopausal OC increased by 23% per 5 kg/m^2 increase in BMI [84].

3.3.7. Alcohol

There is increasing evidence showing that alcohol consumption may induce epigenetic changes such as the suppression of the DNAm mechanism [93]. DNAm alterations are an early step in ovarian carcinogenesis [94], which is why there may be an association between drinking alcohol and the development of epithelial OC. Despite this, several studies describe no such relation [93,95,96]

3.3.8. Caffeine

Although coffee is proven to have a few antioxidant and anti-carcinogenic compounds, we also know that it correlates with a higher level of sex hormones (testosterone, estradiol), which is associated with an enhanced risk of OC [97]. Coffee contains acrylamide, which can also affect carcinogenesis [98]. Previous studies have shown an increased risk of ovarian cancer associated with caffeine intake in premenopausal women and no or slight association in postmenopausal women [99].

4. Discussion

Evaluation of available global literature regarding genetic and epigenetic factors of OC revealed significant aspects influencing the development of this cancer, which remain unclear. Our article focused solely on factors of the highest importance to the etiology of ovarian cancer.

Crucial factors are *BRCA1*/2 gene variations, which have already been proven to be a significant etiologic factor in various cancers. Knowledge about processes related to these mutations is essential for discovering new, effective treatments. Furthermore, we have found cancer-related syndromes, such as Li-Fraumeni syndrome and Lynch syndrome, to be serious factors in the development of ovarian cancer. 5000–20,000 people present Li-Fraumeni syndrome [21]. Lynch syndrome is estimated to affect from 1 in 280 to 1 in 2000 people in the general population [100]. This creates a considerable group of patients who require better prevention, diagnostics, and treatment options.

Epigenetic factors related to the reproductive system play an essential role in the field of OC. Many relationships have been established, such as the effects of contraception, childbirth, breastfeeding, hormonal factors, and even coffee and alcohol. However, there is still much research to be done, and many relationships remain uncertain. For example, polycystic ovary syndrome (PCOS) represents a complex scenario. While it is now believed that there is a potential association between PCOS and an increased risk of OC, the data remains inconclusive and varies across different studies [56,101]. Further research is needed to clarify the relationship between PCOS and ovarian cancer development. In Lynch syndrome, the data on gynecological surveillance is of low quality, with most studies being single-center and retrospective. The results are inconsistent, with some showing benefits and others not. The United Kingdom Familial Ovarian Cancer Screening Study (UKFOCS) found that a combination of serum CA125 testing and transvaginal ultrasound scanning was sensitive and resulted in a shift in disease stage in women with a lifetime risk of OC greater than 10% [102]. Human papillomavirus (HPV) infection is also the subject of increasing publications, including it as a possible OC factor. However, the results are different in various geographic regions. Regrettably, there is no substantial evidence to verify its impact. HPV infection is a significant issue on a broad scale, showing the need for further work.

5. Conclusions

Our review shows that ovarian cancer is a multifactor disease. We attempted to summarize our knowledge about ovarian carcinogenesis's most important genetic and epigenetic factors.

Knowledge about the described genes is crucial for early diagnosis and treatment of OC. While exploring the available articles about the genetics and epigenetics of OC, we also came across the influence of some substances and lifestyles on mutation development and the development of OC.

Although many remain ambiguous, awareness of their potential role in ovarian carcinogenesis can also be a vital element of OC prevention (Figure 8).

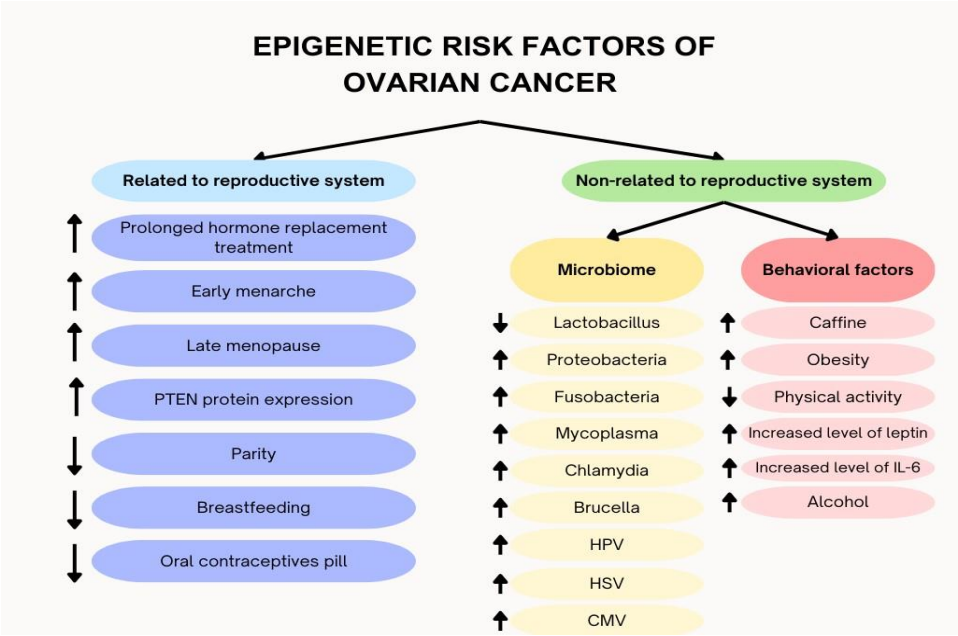

Figure 8. Differentiation of epigenetic factors into related and non-related to the reproductive system. Figure 8 presents factors discussed in the text, divided into related and non-related to the reproductive system. Non-related factors were divided into behavioral and those connected with microbiome. The figure was created by the authors.

Please remember that our research discusses only the most important factors and sheds some light on this subject, which is still shrouded in darkness. In search of answers to one of the most critical questions of today's oncologic gynecology, we hope to aid frontline researchers who are constantly searching laboratories and clinics for solutions to this problem.

Use of Generative-AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Author contributions

Alicja Florczak was responsible for the investigation, data curation, formal analysis, writing the original draft, and visual preparation of the manuscript. She was a leading contributor to materials and methods and preparation of the final manuscript. **Aleksandra Królikowska** was responsible for the investigation, data curation, formal analysis, and writing of the original draft. She was also a leading contributor to the materials and methods and final manuscript preparation. **Mateusz Mazurek** was responsible for the visual preparation of the manuscript, a supporting contributor in materials and methods and final manuscript preparation, and a supporting contributor in the supervision of work.

Sławomir Woźniak, MD, PhD, was responsible for conceptualizing the study and supporting its supervision. **Zygmunt Domagała MD, PhD,** was the leading supervisor and supporting contributor in the final manuscript preparation.

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Conflict of interest

The authors declare no conflict of interest.

References

1. Gupta S, Rajappa S, Advani S, et al. (2021) Prevalence of BRCA1 and BRCA2 mutations among patients with ovarian, primary peritoneal, and fallopian tube cancer in India: A multicenter cross-sectional study, *JCO Glob Oncol* 7: 849–861. https://doi.org/10.1200/GO.21.00051
2. Ovarian Cancer Research Alliance (2024) Ovarian cancer, Available from: https://ocrahope.org/get-the-facts/statistics/.
3. Cabasag CJ, Fagan PJ, Ferlay J, et al. (2022) Ovarian cancer today and tomorrow: A global assessment by world region and Human Development Index using GLOBOCAN 2020, *Int J Cancer* 151: 1535–1541. https://doi.org/10.1002/ijc.34002
4. Ovarian Cancer Statistics (2024) Key Statistics for Ovarian Cancer, Available from: https://www.cancer.org/cancer/types/ovarian-cancer/about/key-statistics.html
5. Toss A, Tomasello C, Razzaboni E, et al. (2015) Hereditary ovarian cancer: Not only *BRCA* 1 and 2 Genes, *Biomed Res Int* 2015: 341723. https://doi.org/10.1155/2015/341723
6. Avramenko AS, Flanagan JM (2023) An epigenetic hypothesis for ovarian cancer prevention by oral contraceptive pill use, *Clin Epigenet* 15: 165. https://doi.org/10.1186/S13148-023-01584-9
7. Domański J, Domagala Z, Simmons JE, et al. (2023) *Terra Incognita* in anatomical museology–A literature review from the perspective of evidence-based care, *Ann Anat* 245: 152013. https://doi.org/10.1016/J.AANAT.2022.152013
8. Mateusz M, Oliwier P, Mateusz D, et al. (2024) Decoding the mysteries of the obturator nerve, *J Anat Soc India* 73: 64–69. https://doi.org/10.4103/JASI.JASI_122_23
9. Domagała D, Data K, Szylle H, et al. (2024) Cellular, molecular and clinical aspects of aortic aneurysm—vascular physiology and pathophysiology, *Cells* 13: 274. https://doi.org/10.3390/CELLS13030274
10. Xu K, Yang S, Zhao Y (2017) Prognostic significance of BRCA mutations in ovarian cancer: an updated systematic review with meta-analysis, *Oncotarget* 8: 285-302. https://doi.org/10.18632/ONCOTARGET.12306
11. Casaubon JT, Kashyap S, Regan JP (2023) BRCA1 and BRCA2 mutations. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470239/.
12. Varol U, Kucukzeybek Y, Alacacioglu A, et al. (2018) BRCA genes: BRCA 1 and BRCA 2, *J BUON* 23: 862–866.

13. Venkitaraman AR, Cancer susceptibility and the functions of BRCA1 and BRCA2, *Cell* 108: 171–182. https://doi.org/10.1016/S0092-8674(02)00615-3
14. Vergote I, González-Martínet A, Ray-Coquardal I, et al. (2022) European experts consensus: BRCA/homologous recombination deficiency testing in first-line ovarian cancer, *Ann Oncol* 33: 276–287. https://doi.org/10.1016/j.annonc.2021.11.013
15. Tutt ANJ, Lord CJ, Mccabe N, et al. (2005) Exploiting the DNA repair defect in BRCA mutant cells in the design of new therapeutic strategies for cancer, *Cold Spring Harb Symp Quant Biol* 70: 139–148. https://doi.org/10.1101/SQB.2005.70.012
16. KD Doig, AP Fellowes, SB Fox (2023) Homologous Recombination Repair Deficiency: An Overview for Pathologists, *Modern Pathol* 36: 100049. https://doi.org/10.1016/j.modpat.2022.100049
17. McCarthy N (2005) A positive defect, *Nat Rev Cancer* 5: 333, https://doi.org/10.1038/nrc1618
18. Villani A, Frebourg T, Malkin D (2021) Li-fraumeni syndrome, In: *The hereditary basis of childhood cancer*, Springer, Cham, 1–21. https://doi.org/10.1007/978-3-030-74448-9_1
19. Guha T, Malkin D (2017) Inherited *TP53* mutations and the Li-fraumeni syndrome, *Cold Spring Harb Perspect Med* 7: a026187. https://doi.org/10.1101/CSHPERSPECT.A026187
20. AD Sorrell, CR Espenschied, JO Culver, et al. (2013) Tumor protein p53 (TP53) testing and Li-Fraumeni Syndrome, *Mol Diagn Ther* 17: 31-47. https://doi.org/10.1007/S40291-013-0020-0
21. Kumamoto T, Yamazaki F, Nakano Y, et al. (2021) Medical guidelines for Li–Fraumeni syndrome 2019, version 1.1, *Int J Clin Oncol* 26: 2161-2178. https://doi.org/10.1007/S10147-021-02011-W
22. Genes by Name. Available from: https://www.facingourrisk.org/info/hereditary-cancer-and-genetic-testing/hereditary-cancer-genes-and-risk/genes-by-name.
23. Ryan NA, McMahon RF, Ramchander NC, et al. (2021) Lynch syndrome for the gynaecologist, *TOG* 23: 9-20. https://doi.org/10.1111/TOG.12706
24. Underkofler KA, Ring KL (2023) Updates in gynecologic care for individuals with lynch syndrome, *Front Oncol* 13: 1127683. https://doi.org/10.3389/FONC.2023.1127683
25. Bansidhar BJ, Silinsky J (2012) History and Pathogenesis of Lynch Syndrome, *Clin Colon Rectal Surg* 25: 63-66. https://doi.org/10.1055/S-0032-1313776
26. McRonald FE, Pethick J, Santaniello F, et al. (2024) Identification of people with Lynch syndrome from those presenting with colorectal cancer in England: baseline analysis of the diagnostic pathway, *Eur J Hum Genet* 32: 529–538. https://doi.org/10.1038/s41431-024-01550-w
27. Hampel H, De La Chapelle A (2011) The search for unaffected individuals with Lynch syndrome: Do the ends justify the means? *Cancer Prev Res (Phila)* 4: 1–5. https://doi.org/10.1158/1940-6207.CAPR-10-0345
28. Grindedal EM, Renkonen-Sinisalo L, Vasen H, et al. (2010) Survival in women with MMR mutations and ovarian cancer: A multicentre study in Lynch syndrome kindreds, *J Med Genet* 47: 99–102. https://doi.org/10.1136/JMG.2009.068130
29. Broaddus RR, Lynch HT, Chen L, et al. (2006) Pathologic features of endometrial carcinoma associated with HNPCC: A comparison with sporadic endometrial carcinoma, *Cancer* 106: 87–94. https://doi.org/10.1002/CNCR.21560
30. Christianson CA, Powell KP, Hahn SE, et al. (2012) The use of a family history risk assessment tool within a community health care system: views of primary care providers, *J Genet Couns* 21: 652–661. https://doi.org/10.1007/S10897-011-9479-1

31. Crosbie EJ, Ryan NA, Arends MJ, et al. (2019) The Manchester International Consensus Group recommendations for the management of gynecological cancers in Lynch syndrome, *Genet Med* 21: 2390–2400. https://doi.org/10.1038/S41436-019-0489-Y
32. Weiss JM, Gupta S, Burke C, et al. (2021) NCCN guidelines® insights: Genetic/familial high-risk assessment: Colorectal, version 1.2021, *J Natl Compr Canc Netw* 19: 1122–1132. https://doi.org/10.1164/jnccn.2021.0048
33. Burn J, Sheth H, Elliott F, et al. (2020) Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial, *Lancet* 395: 1855-1863.
34. Burton AM, Peterson SK, Marani SK, et al. (2010) Health and lifestyle behaviors among persons at risk for Lynch syndrome, *Cancer Causes Control* 21: 513-521. https://doi.org/10.1007/S10552-009-9482-0
35. Kurose K, Zhou XP, Araki T, et al. (2001) Frequent loss of PTEN expression is linked to elevated phosphorylated Akt levels, but not associated with p27 and cyclin D1 expression, in primary Epithelial ovarian carcinomas, *Am J Pathol* 158: 2097-2106. https://doi.org/10.1016/S0002-9440(10)64681-0
36. Li X, Miao C, Wang L, et al. (2023) Estrogen promotes Epithelial ovarian cancer cells proliferation via down-regulating expression and activating phosphorylation of PTEN, *Arch Biochem Biophys* 743: 109662. https://doi.org/10.1016/J.ABB.2023.109662
37. Syed V, Ho SM (2003) Progesterone-induced apoptosis in immortalized normal and malignant human ovarian surface epithelial cells involves enhanced expression of FasL, *Oncogene 2003* 22: 6883–6890. https://doi.org/10.1038/sj.onc.1206828
38. Syed V, Ulinski G, Mok SC, et al. (2002) Reproductive hormone-induced, STAT3-mediated interleukin 6 action in normal and malignant human ovarian surface epithelial cells, *JNCI: J Natl Cancer I* 94: 617–629. https://doi.org/10.1093/JNCI/94.8.617
39. Sarwar S, Alamro A, Huq F, et al. (2022) Insights into the role of epigenetic factors determining the estrogen response in estrogen-positive ovarian cancer and prospects of combining epi-drugs with endocrine therapy, *Front Genet* 13: 812077. https://doi.org/10.3389/FGENE.2022.812077
40. Zhou B, Sun Q, Cong R, et al. (2008) Hormone replacement therapy and ovarian cancer risk: A meta-analysis, *Gynecol Oncol* 108: 641–651. https://doi.org/10.1016/j.ygyno.2007.12.003
41. Mungenast F, Thalhammer T (2014) Estrogen biosynthesis and action in ovarian cancer, *Front Endocrinol* 5: 192. https://doi.org/10.3389/FENDO.2014.00192
42. Choi JH, Wong AST, Huang HF, et al. (2007) Gonadotropins and ovarian cancer, *Endocr Rev* 28: 440–461. https://doi.org/10.1210/ER.2006-0036
43 Yang H, Dai H, Li L, et al. (2019) Age at menarche and epithelial ovarian cancer risk: A meta-analysis and Mendelian randomization study, *Cancer Med* 8: 4012-4022. https://doi.org/10.1002/CAM4.2315
44. Nowak-Markwitz E, Spaczyński M (2012) Ovarian cancer–modern approach to its origin and histogenesis, *Ginekol Pol* 83: 454–457.
45. Kujawa KA, Lisowska KM (2015) Rak jajnika–od biologii do kliniki, *Postepy Hig Med Dosw* 69: 1275–1290.
46. Ochman K (2006) Utrata heterozygotyczności loci sprzężonych z genami BRCA1 i BRCA2 w rakach jajnika.

47. Moorman PG, Havrilesky LJ, Gierisch JM, et al. (2013) Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: A systematic review and meta-analysis, *J Clin Oncol* 31: 4188–4198. https://doi.org/10.1200/JCO.2013.48.9021
48. Merritt MA, Riboli E, Murphy N, et al. (2015) Reproductive factors and risk of mortality in the European prospective investigation into cancer and nutrition; a cohort study, *BMC Med* 13: 252. https://doi.org/10.1186/s12916-015-0484-3
49. Syed V, Ulinski G, Mok SC, et al. (2001) Expression of gonadotropin receptor and growth responses to key reproductive hormones in normal and malignant human ovarian surface epithelial cells, *Cancer Res* 61: 6768-6776.
50. Ye Q, Cai W, Zheng Y, et al. (2014) ERK and AKT signaling cooperate to translationally regulate survivin expression for metastatic progression of colorectal cancer, *Oncogene* 33: 1828–1839. https://doi.org/10.1038/ONC.2013.122
51. Modugno F (2004) Ovarian cancer and polymorphisms in the androgen and progesterone receptor genes: A HuGE review, *Am J Epidemiol* 159: 319–335. https://doi.org/10.1093/AJE/KWH046
52. Pearce CL, Wu AH, Gayther SA, et al. (2008) Progesterone receptor variation and risk of ovarian cancer is limited to the invasive endometrioid subtype: results from the ovarian cancer association consortium pooled analysis, *Br J Cancer* 98: 282–288. https://doi.org/10.1038/SJ.BJC.6604170
53. Terry KL, De Vivo I, Titus-Ernstoff L, et al. (2005) Genetic variation in the progesterone receptor gene and ovarian cancer risk, *Am J Epidemiol* 161: 442–451. https://doi.org/10.1093/AJE/KWI064
54. Leite DB, Junqueira MG, de Carvalho CV, et al. (2008) Progesterone receptor (PROGINS) polymorphism and the risk of ovarian cancer, *Steroids* 73: 676–680. https://doi.org/10.1016/J.STEROIDS.2008.02.005
55. Runnebaum IB, Wang-Gohrke S, Vesprini D, et al. (2001) Progesterone receptor variant increases ovarian cancer risk in BRCA1 and BRCA2 mutation carriers who were never exposed to oral contraceptives, *Pharmacogenetics* 11: 635–638. https://doi.org/10.1097/00008571-200110000-00010
56. Throwba P.K H, Unnikrishnan L, Pangath M, et al. (2022) The epigenetic correlation among ovarian cancer, endometriosis and PCOS: A review, *Crit Rev Oncol Hematol* 180: 103852. https://doi.org/10.1016/J.CRITREVONC.2022.103852
57. Reid BM, Permuth JB, Sellers TA (2017) Epidemiology of ovarian cancer: A review, *Cancer Biol Med* 14: 9–32. https://doi.org/10.20892/J.ISSN.2095-3941.2016.0084
58. Troisi R, Bjørge T, Grotmol T, et al. (2018) The role of pregnancy, perinatal factors, and hormones in maternal cancer risk: A review of the evidence, *J Intern Med* 283: 430–445. https://doi.org/10.1111/JOIM.12747
59. Tsilidis KK, Allen NE, Key TJ, et al. (2011) Oral contraceptive use and reproductive factors and risk of ovarian cancer in the European Prospective Investigation into Cancer and Nutrition, *Br J Cancer* 105: 1436–1442. https://doi.org/10.1038/bjc.2011.371
60 Toufakis V, Katuwal S, Pukkala E, et al. (2021) Impact of parity on the incidence of ovarian cancer subtypes: a population-based case-control study, *Acta Oncol* 60: 850–855. https://doi.org/10.1080/0284186X.2021.1919754
61. Ramírez-de-Arellano A, Villegas-Pineda JC, Hernández-Silva CD, et al. (2021) The relevant participation of prolactin in the genesis and progression of gynecological cancers, *Front Endocrinol* 12: 747810. https://doi.org/10.3389/FENDO.2021.747810

62. Lurie G, Wilkens LR, Thompson PJ, et al. (2008) Combined oral contraceptive use and epithelial ovarian cancer risk: Time-related effects, *Epidemiology* 19: 237–243. https://doi.org/10.1097/EDE.0B013E31816334C5
63. Samkari AA, Alsulami M, Bataweel L, et al. (2022) Body microbiota and its relationship with benign and malignant breast tumors: A systematic review, *Cureus* 14: e25473. https://doi.org/10.7759/CUREUS.25473
64. Reitano E, de'Angelis N, Gavriilidis P, et al. (2021) Oral bacterial microbiota in digestive cancer patients: A systematic review *Microorganisms* 9: 2585. https://doi.org/10.3390/microorganisms9122585
65. Yu X, Shi Y, Yuan R, et al. (2023) Microbial dysbiosis in oral squamous cell carcinoma: A systematic review and meta-analysis, *Heliyon* 9: e13198. https://doi.org/10.1016/J.HELIYON.2023.E13198
66. Mun LS, Lum SW, Sze GKY, et al. (2021) Association of microbiome with oral squamous cell carcinoma: A systematic review of the metagenomic studies, *Int J Environ Res Public Health* 18: 7224. https://doi.org/10.3390/IJERPH18147224
67. Banerjee S, Tian T, Wei Z, et al. (2017) The ovarian cancer oncobiome. *Oncotarget* 8: 36225–36245. https://doi.org/10.18632/ONCOTARGET.16717
68. X. Hu, et al. (2023) Gut microbiota dysbiosis promotes the development of epithelial ovarian cancer via regulating Hedgehog signaling pathway. *Gut Microbes* 15: 2221093. https://doi.org/10.1080/19490976.2023.2221093
69. Siddiqui R, Makhlouf Z, Alharbi AM, et al. (2022) The gut microbiome and female health. *Biology* 11: 1683. https://doi.org/10.3390/BIOLOGY11111683
70. Sipos A, Ujlaki G, Mikó E, et al. (2021) The role of the microbiome in ovarian cancer: mechanistic insights into oncobiosis and to bacterial metabolite signaling, *Mol Med* 27: 33. https://doi.org/10.1186/S10020-021-00295-2
71. Nené NR, Reisel D, Leimbach A, et al. (2019) Association between the cervicovaginal microbiome, BRCA1 mutation status, and risk of ovarian cancer: A case-control study, *Lancet Oncol* 20: 1171–1182. https://doi.org/10.1016/S1470-2045(19)30340-7
72. Łaniewski P, Ilhan ZE, Herbst-Kralovetz MM (2020) The microbiome and gynaecological cancer development, prevention and therapy, *Nat Rev Urol* 17: 232–250. https://doi.org/10.1038/S41585-020-0286-Z
73. Lu YC, Yeh WC, Ohashi PS (2008) LPS/TLR4 signal transduction pathway. *Cytokine* 42: 145–151. https://doi.org/10.1016/J.CYTO.2008.01.006
74. Bertani B, Ruiz N (2018) Function and biogenesis of lipopolysaccharides. *EcoSal Plus* 8: 1–19. https://doi.org/10.1128/ECOSALPLUS.ESP-0001-2018
75. Cazzaniga M, Cardinali M, Di Pierro F, et al. (2022) Ovarian microbiota, ovarian cancer and the underestimated role of HPV. *Int J Mol Sci* 23: 16019. https://doi.org/10.3390/IJMS232416019
76. Gulve N, Rudel T (2019) *Chlamydia trachomatis* and human herpesvirus 6 infections in ovarian cancer—Casual or causal? *PLoS Pathog* 15: e1008055. https://doi.org/10.1371/JOURNAL.PPAT.1008055
77. Pathak S, Wilczyński JR, Paradowska E (2020) Factors in oncogenesis: Viral infections in ovarian cancer. *Cancers* 12: 561. https://doi.org/10.3390/CANCERS12030561
78. Gonzalez SL, Stremlau M, He X, et al. (2001) Degradation of the retinoblastoma tumor suppressor by the human papillomavirus type 16 E7 oncoprotein is important for functional inactivation and

is separable from proteasomal degradation of E7. *J Virol* 75: 7583–7591. https://doi.org/10.1128/JVI.75.16.7583-7591.2001

79. Liu X, Clements A, Zhao K, et al. (2006) Structure of the human papillomavirus E7 oncoprotein and its mechanism for inactivation of the retinoblastoma tumor suppressor. *J Biol Chem* 281: 578–586. https://doi.org/10.1074/JBC.M508455200
80. Paradowska E, Jabłońska A, Studzińska M, et al. (2019) Detection and genotyping of CMV and HPV in tumors and fallopian tubes from epithelial ovarian cancer patients. *Sci Rep* 9: 19935. https://doi.org/10.1038/s41598-019-56448-1
81. Malisic E, Jankovic R, Jakovljevic K (2012) Detection and genotyping of human papillomaviruses and their role in the development of ovarian carcinomas. *Arch Gynecol Obstet* 286: 723–728. https://doi.org/10.1007/S00404-012-2367-6
82. Svahn MF, Faber MT, Christensen J, et al. (2014) Prevalence of human papillomavirus in epithelial ovarian cancer tissue. A meta-analysis of observational studies. *Acta Obstet Gyn Scan* 93: 6–19. https://doi.org/10.1111/AOGS.12254
83. Olsen CM, Green AC, Whiteman DC, et al. (2007) Obesity and the risk of epithelial ovarian cancer: A systematic review and meta-analysis. *Eur J Cancer* 43: 690–709. https://doi.org/10.1016/J.EJCA.2006.11.010
84. Urbute A, Frederiksen K, Kjaer SK (2022) Early adulthood overweight and obesity and risk of premenopausal ovarian cancer, and premenopausal breast cancer including receptor status: Prospective cohort study of nearly 500,000 Danish women. *Ann Epidemiol* 70: 61–67. https://doi.org/10.1016/J.ANNEPIDEM.2022.03.013
85. Liu ZY, Gao X, Zhu S, et al. (2019) Dietary inflammatory index and risk of gynecological cancers: A systematic review and meta-analysis of observational studies. *J Gynecol Oncol* 30: e32. https://doi.org/10.3802/JGO.2019.30.E23
86. Ding N, Zhan J, Shi Y, et al. (2022) Obesity in children and adolescents and the risk of ovarian cancer: A systematic review and dose–response meta-analysis. *PLoS One* 17: e0278050. https://doi.org/10.1371/JOURNAL.PONE.0278050
87. Friedenreich CM, Ryder-Burbidge C, McNeil J (2021) Physical activity, obesity and sedentary behavior in cancer etiology: Epidemiologic evidence and biologic mechanisms. *Mol Oncol* 15: 790–800. https://doi.org/10.1002/1878-0261.12772
88. Baczewska M, Bojczuk K, Kołakowski A, et al. (2021) Obesity and energy substrate transporters in ovarian cancer—Review. *Molecules* 26: 1659. https://doi.org/10.3390/MOLECULES26061659
89. Khanlarkhani N, Azizi E, Amidi F, et al. (2022) Metabolic risk factors of ovarian cancer: A review. *JBRA Assist Reprod* 26: 335–347. https://doi.org/10.5935/1518-0557.20210067
90. Kolomeyevskaya N, Eng KH, Khan ANH, et al. (2015) Cytokine profiling of ascites at primary surgery identifies an interaction of tumor necrosis factor-α and interleukin-6 in predicting reduced progression-free survival in epithelial ovarian cancer. *Gynecol Oncol* 138: 352–357. https://doi.org/10.1016/J.YGYNO.2015.05.009
91. Ray A, Fornsaglio J, Dogan S, et al. (2024) Gynaecological cancers and leptin: A focus on the endometrium and ovary. *Facts Views Vis Obgyn* 10: 5–18.
92. Larsson SC, Spyrou N, Mantzoros CS (2022) Body fatness associations with cancer: Evidence from recent epidemiological studies and future directions. *Metabolism* 137: 155326. https://doi.org/10.1016/J.METABOL.2022.155326

93. Wu D, Yang H, Winham SJ, et al. (2018) Mediation analysis of alcohol consumption, DNA methylation, and epithelial ovarian cancer. *J Hum Genet* 63: 339–348. https://doi.org/10.1038/S10038-017-0385-8
94 Cvetkovic D (2003) Early events in ovarian oncogenesis. *Reprod Biol Endocrinol* 1: 68. https://doi.org/10.1186/1477-7827-1-68
95 Liu S, Feng S, Du F, et al. (2023) Association of smoking, alcohol, and coffee consumption with the risk of ovarian cancer and prognosis: a mendelian randomization study. *BMC Cancer* 23: 256. https://doi.org/10.1186/S12885-023-10737-1
96. Cook LS, Leung AC, Swenerton K, et al. (2016) Adult lifetime alcohol consumption and invasive epithelial ovarian cancer risk in a population-based case-control study. *Gynecol Oncol* 140: 277–284. https://doi.org/10.1016/j.ygyno.2015.12.005
97. Tanha K, Mottaghi A, Nojomi M, et al. (2021) Investigation on factors associated with ovarian cancer: An umbrella review of systematic review and meta-analyses. *J Ovarian Res* 14: 153. https://doi.org/10.1186/S13048-021-00911-Z
98. Pelucchi C, Bosetti C, Galeone C, et al. (2015) Dietary acrylamide and cancer risk: An updated meta-analysis. *Int J Cancer* 136: 2912–2922. https://doi.org/10.1002/IJC.29339
99. Kotsopoulos J, Vitonis AF, Terry KL, et al. (2009) Coffee intake, variants in genes involved in caffeine metabolism, and the risk of epithelial ovarian cancer. *Cancer Causes Control* 20: 335–344. https://doi.org/10.1007/S10552-008-9247-1
100. Pan JY, Haile RW, Templeton A, et al. (2018) Worldwide practice patterns in Lynch syndrome diagnosis and management, based on data from the international mismatch repair consortium. *Clin Gastroenterol H* 16: 1901–1910. https://doi.org/10.1016/j.cgh.2018.04.025
101. Harris HR, Terry KL (2016) Polycystic ovary syndrome and risk of endometrial, ovarian, and breast cancer: A systematic review. *Fertil Res Pract* 2: 14. https://doi.org/10.1186/S40738-016-0029-2
102. Rosenthal AN, Fraser LS, Philpott S, et al. (2017) Evidence of stage shift in women diagnosed with ovarian cancer during phase II of the United Kingdom familial ovarian cancer screening study. *J Clin Oncol* 35: 1411–1420. https://doi.org/10.1200/JCO.2016.69.9330

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