

# Epidemiology of Ovarian Cancer: Risk Factors and Prevention



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## Abstract

Ovarian cancer is one of the most aggressive reproductive cancers among women. The purpose of this review is to summarize epidemiological factors that contribute to the ovarian cancer risk. This review discusses relevant primary research articles, reviews, cohort studies, population-based studies, pooled data and meta-analysis on ovarian cancer epidemiology and summarizes the positive and negative risk factors for ovarian cancer development. Several search engines including PubMed have been utilized. Epidemiologic factors were discussed under five subheadings including hereditary factors, cancer stem cells, hormonal influences, environmental factors, and lifestyle choices. Hereditary factors such as mutations in BRCA and KRAS genes, hormone levels such as androgens and gonadotrophins, and cytokines have been shown to increase ovarian cancer risk. Ovarian cancer stem cells that reside within the tumor play a role in cancer recurrence and progression. While progesterone shows protective effects, exposure to excessive levels of estrogen may increase the risk for ovarian cancer.

Though the association is somewhat weak, exposure to environmental toxicants could be associated with ovarian carcinogenesis. Cigarette smoking is reported to be associated with subtype specific ovarian cancer. Although the association between general obesity or body mass index and the ovarian cancer risk is inconclusive, central obesity could be a risk factor for ovarian cancer. Consumption of a diet rich in glutathione and other antioxidants, maintaining a healthy weight, and regular exercise may provide protective measures against ovarian cancer. Some of the risk factors for ovarian cancer are sub-type specific and further studies are required to completely understand its complex etiology. Although some reviews are available on this topic, this review is comprehensive and provides novelty as it includes the role of cancer stem cells in ovarian cancer development in addition to other risk factors.

**Abbreviations:** OC: Ovarian Cancer; HRT: Hormone Replacement Therapy; AHR: Aryl Hydrocarbon Receptor; BRCA: Breast Cancer Gene; NFκβ: Nuclear Factor Kappa Beta; KRAS: Kirsten Ras Oncogene, PAH: Poly Cyclic Aromatic Hydrocarbons; TCDD: 2,3,7,8-Tetrachlorodibenzodioxin; FOXO1: Fork Head Family Transcription Factor; BAX: BCL-2 Associated X Protein; CAV-1: Caveolin 1; HCG: Human Chorionic Gonadotropin; FSH: Follicle Stimulating Hormone; LH: Luteinizing Hormone; HNPCC: Non-Polyposis Colorectal Cancer; BCL-2: B Cell Lymphoma 2; SHBG: Sex Hormone Binding Globulin; ER: Estrogen Receptor; AR: Androgen Receptor; PR: Progesterone Receptor; IGF: Insulin like Growth Factor; IGFR: Insulin like Growth Factor Receptor; BMI: Body Mass Index; CAG: Cytosine-Adenine-Guanine; IL: Interleukin; CXCR4: Chemokine Receptor; OCSC: Ovarian Cancer Stem Cells; CAFs: Cancer Associated Fibroblasts; FGF: Fibroblast Growth Factor; TGF-β: Transforming Growth Factor Beta; PPARγ: Peroxisome Proliferator Activated Receptor Gamma; VEGF: Vascular Endothelial Growth Factor

## Introduction

Ovarian Cancer (OC) is a global health crisis and one of the deadly gynecological cancers among women worldwide [1]. Despite OC being only 3% of all cancer incidents, the mortality rate of the OC is extremely high making it the fifth leading cause of cancer-related death in women [2-4]. According to 2008-2012 U.S. cancer statistics, 12.7 per 100,000 women were newly diagnosed with ovarian cancer. During that same time period, the death rate was 7.7 per 100,000 women [4,5]. In 2013, the incidence of OC was highest in Caucasian women and lowest in American Indian/Alaska Native women [6,7]. Most recently, in 2018 there were about 14,000 of ovarian

cancer-related deaths, accounting for 5% of female cancer deaths have been reported in US [8]. A study analyzing the rate of OC among many ethnic groups residing in the U.S. indicated that the Asian/Pacific Islanders population had a much lower risk of developing OC [9]. Globally, developed countries have a higher incidence of OC and, by continent; the highest rate is seen in Europe while Africa has the lowest rate [7]. There are three forms of ovarian tumors, each originating from a different cell type; epithelial tumors (90% of cases), germ cell tumors (5% of cases), and stromal tumors (5% of cases) [4,10].

Epithelial tumors are the most usually diagnosed OC in women [4,10]. Different subtypes of epithelial tumors include benign tumors such as serous and mucinous adenomas and cancerous serous, mucinous, clear cell, and endometrioid adenocarcinomas [11]. Germ cell tumors originate from germ cells that can occur at any age but are most prevalent in women in their 20s [4,10]. The three primary types of germ cell tumors include teratomas, dysgerminomas, and endodermal sinus tumors. Stromal tumors include both granulosa cell tumors and sertoli / leydig cell tumors and originate from the connective tissues of the ovaries [4,10]. While there are many hypotheses behind the disease, the etiology of ovarian cancer is still unclear [12]. This comprehensive review summarizes recent studies to address the roles of environmental toxicants, lifestyle factors, hereditary factors, and hormones in causing OC risk among women. In addition, the review discusses negative risk factors / OC preventive measures. Although there are reviews available discussing etiologies of OC, many reviews are only focused on areas such as hormonal influences and the hereditary factors.

This unique review includes the role of cancer stem cells in ovarian cancer development. In addition, this review discusses the importance of environmental toxicants and cigarette smoking as causative factors for OC. There are several epidemiological factors that may contribute to the development of ovarian cancer. They include hereditary factors such as family history, presence of breast cancer associated gene (BRCA) 1 and 2 mutations, age, estrogen influences such as early menarche, menopause after 52 years of age as well as environmental risk factors and life style choices such as exposure to PAH, cigarette smoking, and obesity [12]. All these factors have an association with fluctuations in reproductive hormones. Chemo preventive measures/negative risk factors include progesterone, dietary measures and healthy life styles. Ovarian cancer stem cells play a major role in ovarian cancer recurrence.

### Contribution of Genetic / Hereditary Factors to Ovarian Carcinogenesis

Genetic mutations are the greatest risk factor for the development of OC, with 10-15% of women diagnosed having a hereditary link. A mutation in the breast cancer genes BRCA1 or BRCA2 accounts for 5-10% of all OC cases [4]. For BRCA1 mutation carriers, the average cumulative risk by age 70 is estimated to be 59%. For BRCA2 carriers, the risk is estimated to be 16.5% [13]. KRAS gene mutations have also been associated with well-differentiated mucinous ovarian carcinomas [14], and 11% of epithelial ovarian cancers had KRAS mutations [14]. Other genetic risk factors for the development of OC include a 12% increased risk for patients with Hereditary Non-Polyposis Colorectal Cancer (HNPCC or Lynch Syndrome), a 1.4% increased risk for women with a first-degree relative diagnosed with OC, and a previous history of breast, uterine, colon or rectal cancer [4,10].

### Contribution of Ovarian Cancer Stem Cells (OCSCs) to Ovarian Carcinogenesis

Small populations of cells located inside the ovarian tumor with self-renewal and differentiation capabilities are called ovarian can-

cer stem cells (OCSCs) [2,15]. This OCSC niche could be originated from fallopian tubes [16, 17] as this was the site where ovarian cancer reported to be originated [18]. These OCSCs play a major role in cancer pathogenesis [16-20], and drug resistance [19,21,22] leading to cancer recurrence following treatment [15,23,24]. OCSCs contributes to ovarian cancer progression via interacting with several other cell types including cancer associated fibroblasts (CAFs) and carcinoma associated mesenchymal stem cells (CA-MSCs) in the tumor microenvironment [2]. CAFs aid OCSC self-renewal via activation of the fibroblast growth factor (FGF) signaling [25,26] through FGF receptors (FGFR2) that are expressed in the OCSCs [26]. FGF induces vascular endothelial growth factor (VEGF) secretion causing angiogenesis, the new blood vessel formation in tumors [27]. VEGF-A, a member of the VEGF family, activates OCSCs leading to ovarian cancer progression [28].

CA-MSCs can differentiate into other types of tumor microenvironment cells such as fibroblasts and adipocytes [29]. They induce OCSC proliferation via upregulation of tumor growth factor  $\beta$  (TGF- $\beta$ ) / BMP signaling [30]. In addition, OCSCs aid differentiation of monocytes to tumor associated macrophages termed M2 macrophages, another cell type present in the tumor microenvironment [31,32]. These M2 macrophages can secrete many factors including VEGF, cytokines, peroxisome proliferator activated receptor  $\gamma$ , and TGF- $\beta$  [31-36]. OCSCs influence tumor growth and metastasis via activation of cytokines including IL-17 [37] and IL-10 [31,32]. IL-17 receptors are reported to be present in OCSCs [37]. Upregulation of these cytokines and other factors such as VEGF, PPAR  $\gamma$ , and TGF- $\beta$  lead to OCSC self-renewal, which is partially mediated by NF $\kappa$ B, PPAR  $\gamma$ , and P-38 MAPK signaling [32,37].

### Contribution of Reproductive Factors & Other Hormones to Ovarian Carcinogenesis

**Hormonal Risk Factors and Hormone Replacement Therapy (HRT):** Epidemiological studies have identified a number of hormone-related risk factors [12] for OC including early age of menarche [38,39], late age of menopause, null parity, never taking oral contraceptives [38-41], and having received hormone replacement therapy (HRT) [39,41-43]. Several studies have shown that post-menopausal estrogen replacement therapy, regardless of the presence of progestin, increases the risk of developing OC [44-48]. This risk is higher with estrogen-only HRT [49]. A recent study from Morch et al. concluded that HRT-related OC risk is dependent on type of the tumor [50]. Ovarian endometriosis has also been associated with increased risk for OC [51-53].

On the other hand, women with unilateral ovariectomy [39,54], longer duration use of oral contraceptives [39,54,55] and a higher number of full-term pregnancies [39] had a lower risk of developing OC. The relationship between breast feeding and ovarian cancer development is inconclusive. Some cohort studies and population-based studies suggest that women who breast fed for a period of 6-12 months shows decreased incidents of ovarian cancer [42,56]. Other cohort studies that investigated reproductive factors and ovarian cancer occurrence concluded that breast feeding is not associated with ovarian cancer development [54,57]. There is in-

conclusive evidence on polycystic ovarian syndrome (POS) as a risk factor for the ovarian cancer. Some studies suggest that POS is a risk factor for ovarian cancer [58,59] and the involvement of POS in ovarian cancer development could be specific to ovarian cancer subtype [58]. The association between POS and ovarian cancer can be mitigated by factors such as women's leanness and LH hormone levels [59]. Few other studies suggest no association between POS and ovarian cancer [60,61]. However, POS is significantly associated with endometrial cancer [60-62].

**Role of Progesterone:** Progesterone shows a protective effect against ovarian carcinogenesis [12,63]. High levels of progesterone during pregnancy and progestin-containing oral contraceptives are associated with a decreased risk for OC [54,64]. Progesterone has been shown to suppress cellular growth in ovarian cancer cells by activating apoptosis [65-70] and decreasing cyclin dependent kinase activity resulting in a reduced number of transformed cells [71]. The tumor suppressive effects of progesterone occur via activation of the tumor suppressor / pro-apoptotic genes including P-53, Cav-1, BAX [70,72] and down regulation of anti-apoptotic genes such as BCL-2 [70,72]. Further, progesterone inhibits cell migration by activating expression of nm 23-H2, a suppressor protein that inhibits cell motility [72-74] and inhibits metastasis in OC [73,74].

More recently, it was shown that progesterone can upregulate FOXO1 transcription, a fork head transcription factor that in turn, increases the rate of senescence [75]. These studies provide accumulative evidence that progesterone may be important in controlling cellular growth, and that dysregulation of progesterone could greatly reduce these activities resulting in increased cancer growth and metastasis. In fact, several studies have shown that progesterone receptor expression is down regulated in many ovarian tumors [76,77], while PR expression is associated with improved disease-specific survival [78].

**Role of Estrogen:** Estrogen receptors  $\alpha$  and  $\beta$  are expressed in normal ovarian cells [76], and though it is possible that estrogens stimulate ovarian carcinogenesis through its proliferation promoting effects [49,79], estrogen's involvement in ovarian cancer is inconclusive. However, at high concentrations estrogens are reported to be involved in the early steps of malignant transformation [63]. Estrogen has been shown to increase cell motility and metastasis via down regulating nm23-H2 expression and upregulating PI3 kinase / AKT phosphorylation pathway [73] and to induce early onset of ovarian tumors and decrease survival in a mice model [79]. In another study using fluorescent ER negative and ER positive human epithelial OC cells, it was observed that estrogen significantly increased the size of tumors and promoted lymph node metastasis [80]. Women who are at high risk for developing OC may choose to have a hysterectomy or tubal ligation in order to reduce their risk [81-85]. The treatment of OC cells with estrogen caused attenuation of chemo protective effects of progesterone via decreasing expression of progesterone receptors at the transcriptional level [86].

**Role of Androgen:** Like progesterone, elevated androgens may increase the risk of ovarian cancer [12,63]. Epidemiologic data

implicate that abnormal androgen homeostasis could promote aggressive epithelial ovarian cancer biology, especially with elevated androgenicity [12,63]. Obesity may induce elevated androgenicity since previous studies have shown that increased adipose tissue can stimulate increased circulating levels of free testosterone and decreased sex hormone binding globulin levels (SHBG) [87]. One of the pathologic prognostic factors for ovarian cancer development is represented by the length of the cytosine-adenine-guanine (CAG) repeat sequence on exon 1 of the androgen receptor (AR) [87]. According to several studies, obesity and a short AR allele type ( $\leq 19$  CAG repeats) were identified as being associated with poor survival or a poor prognostic factor in advanced stages of the disease [87]. Based on a retrospective review performed on 81 patients with papillary serous epithelial ovarian cancer, the combination of short AR allele type and obesity (BMI  $>25$ ) correlated with decreased overall survival [87], which further supports that an abnormal androgen environment may contribute to aggressive epithelial ovarian tumor biology [12,87]. Future studies should be directed to explore the potential use of anti-androgen and weight management in the treatment of ovarian cancer.

**Role of Gonadotrophins:** According to the gonadotropin hypothesis, ovarian cancer develops from excess stimulation of ovarian tissue by the pituitary gonadotropins, follicle stimulating hormone (FSH), and luteinizing hormone (LH) [12,88]. Most ovarian cancer patients are diagnosed during the postmenopausal stage when circulating FSH and LH levels remain high due to the lack of negative feedback by ovarian steroids [88]. Gonadotropins (LH and FSH) are involved in the elevated serum beta human chorionic gonadotropin (b-hCG), activation of oncogenic pathways, inhibition of cellular apoptosis, and aberrant p53 tissue expression [12], all which lead to advanced stage, grade, and poor prognosis of ovarian cancer. It is also well established that pregnancies and oral contraceptives have protective effects by suppressing gonadotropin secretion by the pituitary gland [88]. The secretion of these hormones is controlled by gonadotropin releasing hormone (GnRH). Ovarian cancer risk could be associated with variation in gonadotropin signaling pathway genes including GnRH [88]. However, further evaluation is required to conclude the genetic association with the ovarian cancer risk.

**Role of Insulin and Insulin-like Growth Factor-1 (IGF-1):** Both insulin [89-91] and IGF-1 [91,92] are shown to exert proliferative and anti-apoptotic effects that could lead to several cancers [93-95]. Insulin and IGF-1 mediated downstream signaling via binding to IGF-1 receptor, leads to synthesis of other hormones including androgens, which may also induce ovarian cancer development [63,93]. At this time, however, there is not enough direct evidence to include insulin or IGF-1 as risk factors for OC development [63].

### Role of Inflammatory Cytokines

Inflammatory cytokines / chemokines and the chemokine receptor CXCR are known to be involved in ovarian carcinogenesis [96]. Increased expression of interleukin 8 (IL-8) / CXCL-8 and IL-8 receptors are expressed in serous ovarian carcinomas [96]. IL-1 $\beta$ , which is secreted by ovarian cancer cells, is reported to cause

ovarian tumorigenesis via suppressing the p53 protein [97]. IL-6 also significantly contributes to the progression of ovarian carcinogenesis [98,99]. Antibodies raised against these interleukins can be used as a therapeutic tool to treat OC [96-98]. These cytokines have been shown to induce Nuclear Factor Kappa beta (NFK $\beta$ ) mediated signaling, which may serve as a link between inflammation and the development of ovarian cancer [12]. NFK $\beta$  serves many functions such as mediating the effects of sex steroid hormones, tumor invasion, adhesion, and metastasis [12].

### Contribution of Environmental Risk Factors to Ovarian Carcinogenesis

**Polycyclic Aromatic Hydrocarbons (PAHs):** Polycyclic aromatic hydrocarbons (PAHs) are a class of chemicals known to be environmental pollutants, with some being classified as carcinogens [100-103]. Exposure to PAHs can occur through diet, the environment, or through occupational sources [100,102,104]. Environmental toxicity depends on the size of the particulates in the environment [105] and can occur by differing degrees since PAHs are produced through the burning of natural compounds such as wood, coal, gasoline, diesel and tobacco smoke [100,104]. Smaller sized particulates less than 10  $\mu\text{M}$  (PM10) to 2.5  $\mu\text{M}$  (PM2.5) have a higher probability of containing PAHs. These are more likely to be absorbed through the alveoli of the lungs, increasing risk for not only localized toxicity but systemic toxicity as well [105]. PAHs can also be absorbed through the skin [106,107] and GI tract [108,109]. Urban areas have higher concentrations of PAHs because of increased traffic congestion leading to greater exposure of motor vehicle exhaust [110,111].

Areas with higher concentrations of smaller particulates (PM2.5) have been shown to result in an increased risk of mortality from OC [110,112]. A study that investigated OC mortality in women who live near Spanish industries revealed that OC-related mortality was significantly higher in women residing near industries that release PAHs, and metals [112]. Cigarette smoke contains several known carcinogens including PAHs [113-115]. PAHs form DNA adducts that directly cause cellular mutations, which could result in tumor formation [116]. PAH-DNA adducts are indicators to assess the degree of carcinogen exposure [116,117]. Adduct concentrations are higher in smokers compared to non-smokers [116,117]. Cervical tissue collected from smokers and non-smokers revealed a greater number of PAH (benzo(a)pyrene diol-epoxide)-DNA adducts in tissue from smokers indicating the involvement of PAH-induced genotoxicity in the female reproductive tract [118] that eventually led to carcinogenesis. PAH exposure is a known risk factor for breast cancer development [119-121].

Studies based on ovarian cells exposed to varying levels of PAHs have resulted in ovarian tumor growth and primary ovarian insufficiency [104]. Benzo (a) pyrene is reported to cause ovarian tumorigenesis in mice that are deficient in glutathione [104], a critical component for the detoxification of PAH metabolites. TCDD 2,3,7,8-Tetrachlorodibenzo-p-dioxin, also known as TCDD or dioxin, is an environmental contaminant best known for its use in the Vietnam War as the herbicide agent orange [122-124]. TCDD per-

sists in the environment and bio accumulates [122]. Exposure to TCDD primarily occurs through the diet [123] and is classified by the International Agency for Research on Cancer (IARC) as a carcinogen in animal models [125]. TCDD induces hepatic carcinogenesis in rats [126]. TCDD may be a human carcinogen although its ability to induce human cancers is still inconclusive [127]. In humans, TCDD has been shown to cause hyperkeratosis of skin [128,129], wasting syndrome [130-132], and reproductive, developmental, and immune related complications [125].

Chronic exposure to TCDD has been shown to induce ovarian tumor growth in female Sprague Dawley rats [133]. In a Caov-3 OC cell line, TCDD exposure resulted in increased expression of TCDD and ER-linked genes [134]. It has also been shown to reduce the number of ovarian follicles, which could result in infertility [135]. TCDD has been shown to exert its effects via binding to the aryl hydrocarbon receptor and modulating downstream PI3Kinase and MAPK (ERK) signaling [128,136]. In mouse epithelial OC cells, TCDD activates Protein kinase C delta, which is involved in cell proliferation, leading to OC progression [132]. In addition, TCDD has been shown to induce human breast cancer cell growth via inhibiting apoptosis in human mammary epithelial cells [137]. However, some studies show negative association between TCDD and ovarian cancer progression. TCDD shows anti-proliferative effects in OVCAR-3 ovarian cancer cell line [138]. Therefore, more evidence is needed to conclude TCDD's association with ovarian cancer.

### Contribution of Lifestyle Factors to Ovarian Carcinogenesis

**Cigarette smoking:** The correlation between cigarette smoking and the development of OC has been inconclusive. According to the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO), there is insufficient evidence to conclude any effect of smoking on OC risk [10]. A number of population based studies utilizing OC patients has assessed the risk of cigarette smoking on different OC types including invasive and borderline cancer, mucinous, epithelial, and serous tumors. While some studies have suggested that an association exists between smoking and OC, others showed no relationship. It has been suggested that the association of smoking and OC risk may be based on the histological type of the ovarian cancer [56]. In a study using 558 epithelial (border line and invasive) OC patients, active smokers showed an increased risk for borderline serous cystadenomas but not with borderline mucinous cystadenoma and invasive ovarian cancers [139]. Long-term smokers or previous long-term smokers of 20 years or more showed a decreased risk of invasive OC development [139]. In agreement with Goodman et al. several other studies have concluded that there is no significant correlation between active cigarette smoking and development of epithelial tumors [56,140].

In contrary to the study by Goodman et al. other population based, case controlled studies concluded that both active and long-term cigarette smoking increases ovarian epithelial tumors including mucinous tumors and borderline OC [141]. Women who started smoking at a younger age (less than 20), and smoked more than

20 years showed a higher risk of developing epithelial OC [141]. Borderline tumor risk increased for those who had smoked or were previous smokers within the past 15 years and those with a longer history of total pack-years of smoking [142]. The number of mucinous and serous tumor cases were also found to be greater in women who had a longer history of smoking, greater pack-year history, and if they were active smokers within 15 years of diagnosis [142]. There were no increases in endometrial, clear cell, or other histologic subtypes of OC associated with smoking [142]. According to a recent meta-analysis based on 51 epidemiological studies, however, smoking is only associated with mucinous ovarian cancers, mainly tumors of borderline malignancy [143]. According to this meta-analysis, there was no positive correlation between cigarette smoking and occurrence of serous or any other form of tumorigenesis / carcinogenesis [143].

**Obesity and Physical Activity:** The association between the body mass index (BMI) or general obesity and ovarian cancer occurrence is inconclusive. Obesity could be weakly associated with OC and this association is OC subtype specific [144,145]. Based on few cohort studies, a high body mass index greater than 30 among post-menopausal women has been shown to be associated with increased OC development [146,147]. According to an original research study using genetically engineered mouse model of serous ovarian cancer, the authors have concluded that the greater body mass index increases ovarian cancer specific mortality [148] likely due to the production of estrogen by the increased adipose tissue [4,145]. In addition, using a p53, BRCA1 knock-out mouse model, Makowski and colleagues concluded that obesity increases the aggressiveness of tumors [148]. However, some population based prospective cohort studies suggest there is no association between general obesity (body fat percentage) or BMI and ovarian cancer occurrence [149,150].

Based on population based prospective cohort studies, abdominal adiposity / central obesity as measured by waist to hip ratio [149] and weight gain, but not overall obesity, are risk factors for ovarian cancer development [151]. The influence of physical activity as a protective measure for ovarian cancer remains inconclusive. However, based on some case -controlled studies, meta-analysis and epidemiological reviews, increased physical activity attenuates obesity and possibly a negative risk factor / preventive measure for OC development [152-156]. In addition, lack of physical activity is reported to associate with increased risk of mortality in patients suffering from invasive epithelial ovarian cancer [157] and participating in physical activity prior to ovarian cancer diagnosis lowers the risk of mortality [158]. Lack of physical activity and obesity also worsen the quality of life in ovarian cancer survivors [159]. However, some population- based cohort studies do not suggest a protective role of physical activity for ovarian carcinogenesis [160-162].

**Dietary Factors and Chemoprevention:** Although there are no reports linking consumption of a high fat diet or grilled meat

with OC risk [163], consumption of some food items, such as diets rich in fat content [164,165], preservatives [166], and grilled meat [167] increases the risk for many other cancers in both human and animal models. In contrast, diets rich in cruciferous vegetables [168], green tea [169,170], soy products [171,172], and mushrooms [173,174] have been reported to decrease OC risk. Cruciferous vegetables are rich in glutathione, which eliminates carcinogenic metabolites from the body via Phase 2 drug biotransformation reactions [175]. They are also rich in isothiocyanates, which may induce apoptosis in certain cell lines [168]. Soy products, which are rich in phytoestrogen such as genistein [176], can inhibit carcinogenesis via many mechanisms including inducing cell death [176], inhibiting DNA damage, and inactivating carcinogens in animal models [168].

Based on many prospective cohort studies, meta-analysis and population-based case-controlled studies; there is no association between alcohol consumption and OC risk [177-181]. However, a few studies show weak association between alcohol consumption and ovarian cancer risk, which is dependent upon several other factors such as alcohol type, tumor invasiveness, and, the type of the cancer [182,183]. There is some evidence to suggest that caffeine is inversely associated with OC risk [140,184]. Caffeine also has anti-proliferative effects in A2780 human OC cells [185,186]. However, additional studies have shown no association between caffeine consumption and OC risk [187-189]. Therefore, the association between caffeine consumption and the ovarian cancer risk is inconclusive.

## Discussion

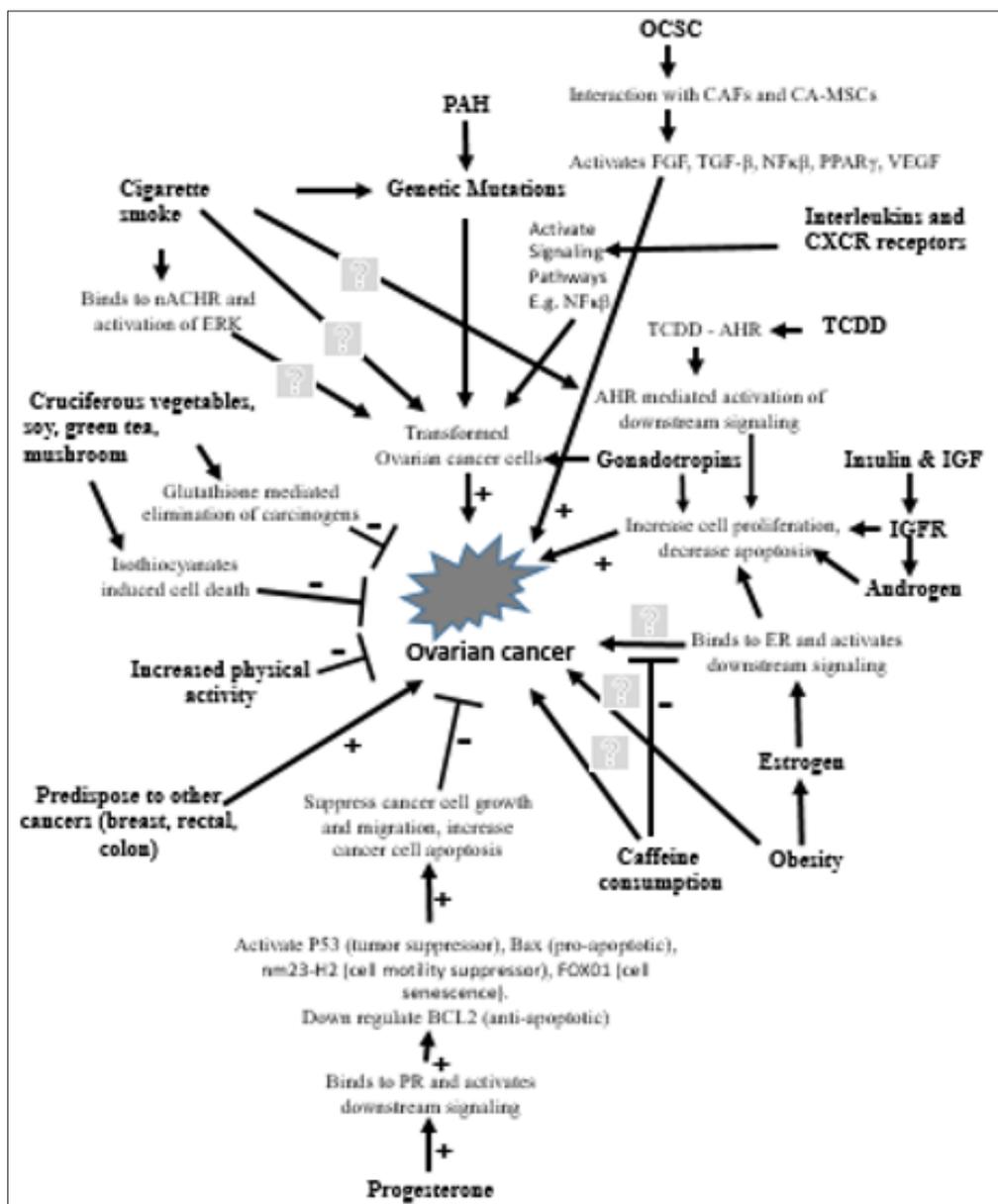
OC is one of the most aggressive reproductive cancers and it can be fatal to women if not diagnosed and treated early. Here, we have provided a comprehensive review discussing the major risk factors for the development of ovarian cancer. Please note that some of these risk factors could be specific to ovarian cancer sub-types. Based on epidemiologic studies and predicted by several hypotheses, the positive and negative risk factors (preventative measures) for ovarian cancer development were elucidated and summarized in (Table 1). While several of the risk factors show strong correlations, some risk factors remain weakly associated and some of the associations are inconclusive (Table 1). Ovarian tumorigenesis occurs via several possible mechanisms and pathways, which are summarized in (Figure 1). Hereditary factors such as genetic mutations in proto oncogenes and tumor suppressor genes play a major role in many different cancers [190,191]. BRCA1, BRCA2, and KRAS gene mutations are seen predominantly in ovarian carcinogenesis. Cancer stem cells play a crucial role in ovarian cancer pathogenesis and recurrence. Hormones such as androgens, high levels of estrogens, and gonadotrophins are positively correlated with ovarian cancer and are thought to exert their effects by activating cellular proliferation, inhibiting apoptosis, and activating oncogenic pathways.

**Table 1:** Summary of positive and negative risk factors for the ovarian cancer development.

Risk Factors	Mechanism / Details	References
Genetic mutations	Increased risk with mutations in BRCA1, BRCA2, KRAS genes Increased risk for patients diagnosed with breast, colon, rectal, and Hereditary non –polyposis colorectal (HNPCC) cancer	[1, 6, 10, 11]
Cancer stem cells	Play a role in cancer pathogenesis via activating FGF, VEGF, PPAR, TGF $\beta$ , P-38 MAPK signaling and activation of IL-17	[15-37]
Hormones Estrogen	High levels may increase risk via estrogen induced cell proliferation Inconclusive / weak association	[49, 63, 73]
*Progesterone	Protective effect through suppression of cellular growth and Inhibition of cell migration	[65-74]
HRT	Inconclusive, yet many studies support long term HRT increases risk	[39, 41-53]
Androgen	Increased risk due to androgen induced cellular proliferation	[12, 63]
Gonadotropins	FSH and LH increase risk by activating oncogenic pathways	[12, 88]
Insulin and IGF-1	Inconclusive / possible association	[63, 89-95]
Cytokines and NFK $\beta$	IL-8, IL-1 beta, IL-6, and NFK $\beta$ are linked to increased risk	[12, 96-99]
PAH	PAH-induced gene mutations leading to tumor formation Increased risk of ovarian cancer related mortality	[110, 112, 116]
TCDD	Ovarian tumor growth in animal models via TCDD –induced Modulation of AHR signaling	[128, 132-138]
Cigarette smoke	increased risk of developing mucinous epithelial ovarian cancer Weak / inconclusive association in other ovarian cancer subtypes	[10, 56, 141-143]
Obesity	Inconclusive / weak association, Increases ovarian cancer risk Possibly via production of estrogen by the adipose tissue	[5, 144-151]
Dietary factors *Glutathione	Glutathione rich food (cruciferous vegetables, green tea soy and mushroom) consumption leads to decreased risk	[168-176]
High fat diet	Inconclusive. However, high fat diet increases other risk factors Such as obesity	[164-165]
*Physical activity	Act as a negative risk factor via reducing central obesity	[152-159]
Alcohol	No association between alcohol consumption and ovarian cancer risk	[177-181]
Caffeine	Inconclusive association	[140, 184-189]

Note: \*negative risk factor

AHR = Aryl Hydrocarbon receptor, PAH = Polycyclic Aromatic Hydrocarbons, TCDD = 2,3,7,8 –Tetrachlorodibenzo-p-dioxin, HRT = Hormone Replacement Therapy, IL=Interleukin, FSH=Follicular Stimulating Hormone, LH=Luteinizing hormone, NFK $\beta$ =Nuclear Factor Kappa Beta.



**Figure 1:** Model summarizing mechanisms that lead to ovarian cancer development and preventive measures. OCSC mediated signaling, hereditary factors, hormonal influences (except progesterone), Cytokines, environmental contaminants (TCDD, PAH) are causative factors. Glutathione rich food, isothiocyanates, physical activity and progesterone inhibits ovarian carcinogenesis. The involvement of cigarette smoking, obesity, and caffeine consumption is not clear. - sign and | = inhibition / down regulation. + = activation of a pathway. ? = unknown / not clear.

Progesterone, on the other hand, has a protective effect against OC, most likely by activating tumor suppressor genes, pro-apoptotic genes, and cell senescence genes. Cytokines such as IL-1 $\beta$ , IL8, and IL6 contribute to OC development mainly via activating NFK $\beta$  mediated downstream signaling that mediates several functions including modulation of hormone levels, tumor invasion, and metastasis (Figure 1). Exposure to environmental toxicants such as TCDD contributes to ovarian carcinogenesis via AhR mediated signaling that leads to anti-apoptotic effects. Exposure to PAH increased ovarian cancer risk via PAH mediated genetic changes that led to transformation of ovarian cells. Life style choices such as cig-

arette smoking contributes to sub type specific ovarian cancer risk via many possible pathways including nAChR mediated activation of ERK signaling, genetic mutations etc. (Figure 1). Although the association between general obesity or body mass index and the ovarian cancer risk is inconclusive, central obesity could be a risk factor for ovarian cancer possibly via production of estrogen by the adipose tissue. Consumption of diets rich in glutathione provides protection against OC via glutathione mediated elimination of carcinogenic metabolites. Consumption of soy products is negatively associated with OC development via many mechanisms including inhibition of DNA damage.

## Conclusion

In conclusion, multiple factors, such as genetic/ hereditary factors, cancer stem cells, exposure to androgens, high levels of estrogens, gonadotropins, and inflammatory cytokines have been shown to increase the risk of developing OC. In addition, accumulating evidence suggests that exposure to a number of environmental toxicants can increase risk for OC. Progesterone shows protection against ovarian cancer. Choosing healthy lifestyles such as diets rich in glutathione and other antioxidants, maintaining a healthy weight, and regular exercise may provide protective measures against OC. All the risk factors that contribute to ovarian cancer are summarized in Table 1. The mechanistic pathways, which these risk factors contribute to ovarian cancer development and chemoprevention are summarized in (Figure 1).

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