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REVIEW

# Epidemiology of ovarian cancer: a review

Brett M. Reid, Jennifer B. Permuth, Thomas A. Sellers
Department of Cancer Epidemiology, Division of Population Sciences, Moffitt Cancer Center, Tampa 33612, FL, USA

**ABSTRACT** Ovarian cancer (OC) is the seventh most commonly diagnosed cancer among women in the world and the tenth most common in China. Epithelial OC is the most predominant pathologic subtype, with five major histotypes that differ in origination, pathogenesis, molecular alterations, risk factors, and prognosis. Genetic susceptibility is manifested by rare inherited mutations with high to moderate penetrance. Genome-wide association studies have additionally identified 29 common susceptibility alleles for OC, including 14 subtype-specific alleles. Several reproductive and hormonal factors may lower risk, including parity, oral contraceptive use, and lactation, while others such as older age at menopause and hormone replacement therapy confer increased risks. These associations differ by histotype, especially for mucinous OC, likely reflecting differences in etiology. Endometrioid and clear cell OC share a similar, unique pattern of associations with increased risks among women with endometriosis and decreased risks associated with tubal ligation. OC risks associated with other gynecological conditions and procedures, such as hysterectomy, pelvic inflammatory disease, and polycystic ovarian syndrome, are less clear. Other possible risk factors include environmental and lifestyle factors such as asbestos and talc powder exposures, and cigarette smoking. The epidemiology provides clues on etiology, primary prevention, early detection, and possibly even therapeutic strategies.

**KEYWORDS** Ovarian cancer; epidemiology; risk factors; histology; reproductive history

## Introduction

Ovarian cancer (OC) accounts for an estimated 239,000 new cases and 152,000 deaths worldwide annually[1]. The highest rates (11.4 per 100,000 and 6.0 per 100,000, respectively) are seen in Eastern and Central Europe. Although China has a relatively low incidence rate (4.1 per 100,000), the large population translates to an estimated 52,100 new cases and 22,500 related deaths in 2015[2]. In comparison, 21,290 cases and 14,180 related deaths are estimated to occur in the USA during the same year[3].

A woman's lifetime risk of developing OC is 1 in 75, and her chance of dying of the disease is 1 in 100[4]. The disease typically presents at late stage when the 5-year relative survival rate is only 29%. Few cases (15%) are diagnosed with localized tumor (stage 1) when the 5-year survival rate is 92%[4]. Strikingly, the overall 5-year relative survival rate generally ranges between 30%–40% across the globe and has seen only very modest increases (2%–4%) since 1995[5].

Despite the public health significance, the etiology of this lethal disease is not completely understood. This review is divided into five sections: pathologic classification, descriptive epidemiology, genetic epidemiology, risk and preventive factors, and summary and conclusions.

Correspondence to: Thomas A. Sellers
E-mail: Thomas.Sellers@moffitt.org
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## Pathologic classification of OC

Nearly all benign and malignant ovarian tumors originate from one of three cell types: epithelial cells, stromal cells, and germ cells. In developed countries, more than 90% of malignant ovarian tumors are epithelial in origin, 5%–6% of tumors constitute sex cord-stromal tumors (e.g., granulosa cell tumors, thecomas, etc.), and 2%–3% are germ cell tumors (e.g., teratomas, dysgerminomas, etc.)[6]. The pathology and classification of ovarian tumors are described in detail by Chen et al.[7]. Most epidemiologic research, including the present review, focuses on epithelial OC.

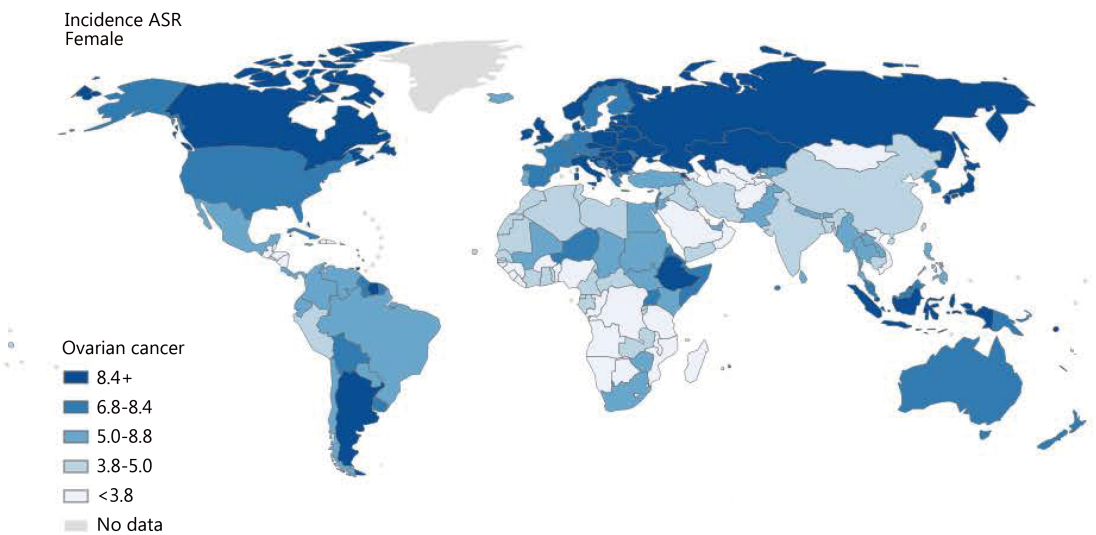
Epithelial OC reflects a heterogeneous disease with histologic subtypes (histotypes) that differ in their cellular origin, pathogenesis, molecular alterations, gene expression, and prognosis[8-11]. Malignant OC, also known as carcinomas, are comprised of five main histotypes: high-grade serous (HGSOC; 70%), endometrioid (ENOC; 10%), clear cell (CCOC; 10%), mucinous (MOC; 3%), and low-grade serous (LGSOC; <5%)[8,9]. Within each of these categories, although most often among serous and mucinous, are tumors of

uncertain malignant behavior known as borderline or low malignant potential (LMP) tumors that contain microscopic features of malignancy without frank invasion into surrounding stroma[12].

The cellular origin and pathogenesis of OC is not well understood and, interestingly, most tumors appear to originate from other gynecological tissues and involve the ovary secondarily. Morphological and genetic studies have given rise to several hypothesis of origination, particularly for high-grade serous tumors that lack a clear progression model[13,14]. Compelling data suggest high and low grade serous neoplasms originate from fallopian tube epithelium, CCOC and ENOC from endometriotic cysts associated with endometriosis, and MOC from transitional cell nests at the tubal-mesothelial junction[15,16]. HGSOC and LGSOC are both thought to arise from tubal epithelium although through separate pathways. Atypical lesions within the fimbriated end of the fallopian tube (serous tubal intraepithelial carcinomas) display similar morphology and TP53 signatures as HGSOC tumors suggesting the neoplastic process may originate at these tubal lesions and shed onto the ovary where they aggressively progress[17-19]. LGSOC tumors present along a continuum that delineates a clear progression from benign serous cystadenoma to borderline serous tumor and then low-grade carcinoma. The epithelial inclusion glands presumed to derive the cystadenoma, although located in the ovary, are phenotypically tubal suggesting they formed from transplanted tubal epithelium[20]. Similar to low-grade serous tumors, mucinous, endometrioid, and clear cell carcinomas are thought to progress from borderline tumors in a stepwise manner and are designated as Type I tumors[21]. HGSOC has an aggressive phenotype and lacks a clear precursor and is considered Type II. Type I and Type II tumors display different, often mutually exclusive mutational profiles. Type I tumors are associated with mutations in *BRAF* and *KRAS* oncogenes in serous and mucinous tumors, and *PTEN* in endometroid tumors, all of which are not characteristic of HGSOC tumors which predominantly (~50%–80%) have p53 mutations[21]. Moreover, some risk and preventive factors vary by the major histotypes. Epidemiological studies of OC are increasingly investigating etiologic factors by histopathologic and molecular subtypes[22-30], an integrative approach termed "molecular pathological epidemiology"[31]. These studies have shown that many risk factors associate differentially with the main histotypes and we present these results throughout this review.

## Descriptive epidemiology

OC incidence exhibits wide geographic variation (**Figure 1**)[32]. The highest age-adjusted incidence rates are observed in developed parts of the world, including North America and Central and Eastern Europe, with rates generally exceeding 8 per 100,000. Rates are intermediate in South America (5.8 per 100,000), and lowest in Asia and Africa (≤3 per 100,000). Migration from countries with low rates to those with high rates results in greater risk[33,34] underscoring the importance of non-genetic risk factors. Within the United States, racial




Source: GLOBOCAN 2012 (IARC)

**Figure 1** Ovarian cancer incidence exhibits wide geographic variation.

differences in incidence and mortality mimic the observed international variation with rates highest among Whites, intermediate for Hispanics, and lowest among Blacks, and Asians[4]. Variation within large countries such as China also mimics international variation with incidence and mortality higher within developed, urban regions versus less developed, rural regions[35].

In most developed countries, largely including North America and Europe, OC incidence and mortality has gradually declined since the 1990s[4,36-40]. Conversely, historically less developed countries with recent economic growth and lifestyle changes have seen increases in incidence and mortality rates. In China, the increase is apparent only among rural women rather than those in more developed, urban regions[2,41].

# Genetic epidemiology

One of the most significant risk factors for OC is a family history of the disease[42]. First-degree relatives of probands have a 3- to 7-fold increased risk, especially if multiple relatives are affected, and at an early age of onset[43-47]. Rare high penetrant mutations in the *BRCA1* and *BRCA2* genes greatly increase lifetime risk[48] and account for the majority of hereditary cases and 10%–15% of all cases[49-57]. Data from the Breast Cancer Linkage Consortium suggest the risk of OC through age 70 years is up to 44% in *BRCA1* families[58] and approaches 27% in *BRCA2* families[59]. Hereditary non-polyposis colorectal cancer syndrome (HNPCC)[60] may account for at least 2% of cases and confer up to a 20% lifetime risk[48,61-64]. Women with mutations in DNA repair genes, such as *BRIP1*, *RAD51C*, and *RAD51D* have estimated lifetime risks of 5.8%, 5.2%, and 12%, respectively[65,66]. Deleterious mutations in BRCA1/2 and other double-strand DNA break repair genes are more strongly associated with HGSOC susceptibility although they do occur in other tumor subtypes[65-67]. HNPCC associated OC typically presents as endometrioid or clear cell tumors rather than the common serous subtype[68,69].

Collectively, known syndromes account for 36% of OC familial relative risk[70]. Genome-wide association studies[71-80] have discovered 22 susceptibility alleles for invasive OC with weak to moderate effects in European populations (**Table 1**). Eighteen of these risk loci are associated with all and/or serous OC, five are associated with MOC risk, one is associated with ENOC, and one is associated with CCOC, exemplifying the genetic heterogeneity by histotype. In addition, a large-scale pooled analysis of genome-wide association studies of ovarian, breast, and prostate cancers identified five novel loci[81]. The identified common risk alleles account for approximately 4% of the polygenic risk in the European population and, taken together with high risk alleles, explain 40% of the heritability[82]. Chen et al.[83] conducted a genome-wide association study of 4,464 Han Chinese women that identified two novel loci (9q22.33 and 10p11.21) and evidence that four loci previously reported in European populations (3q25, 17q12, 17q21, and 19p13.11) may also influence risk.

# Risk factors and preventive factors

## Hormonal and reproductive risk factors

Epidemiological research has clearly implicated hormonal and reproductive factors in the pathogenesis of OC. Two predominant hypotheses have emerged to fit the data[84]. The 'incessant ovulation' hypothesis posits that the number of ovulatory cycles increases the rate of cellular division associated with the repair of the surface epithelium after each ovulation, thereby increasing spontaneous mutations[85]. The correlation between increasing numbers of lifetime ovulations and higher risk[86-89] are consistent with this hypothesis. The 'gonadotropin hypothesis' attributes the impact to gonadotropins, such as luteinizing hormone and follicle-stimulating hormone[90]. Both of these proposed mechanisms provide a framework to interpret the epidemiologic data on both endogenous correlates of reproductive hormone exposure and exogenous sources of hormones. A more detailed review is available by Riman et al.[91].

### *Age at menarche and age at menopause*

According to the incessant ovulation hypothesis, early age at menarche and late age at menopause increases risk by increasing the number of ovulatory cycles. Conversely, according to the gonadotropin hypothesis, a late age at menopause delays the surge of post-menopausal gonadotropin hormones, possibly reducing risk. Results of studies that have examined the age at onset of menses are not terribly consistent[92-102]. One study among Chinese women reported lower risk with late age at menarche (after age 18)[103], while another study observed a slight increased risk with late age at menarche[104]. Additional research has failed to clarify the literature[85,93,105-112] although a meta-analysis yielded an overall inverse association with age at menarche (RR=0.85, 95% CI: 0.75–0.97)[113]. Data on age at natural menopause and OC risk are also inconsistent. Case-control studies have reported odds ratios ranging from 1.4 to 4.6 in the highest category of age at menopause[92,93,95,99,103,104,108]. In the

**Table 1** Common, low penetrance alleles associated with epithelial OC susceptibility

| Cytoband | SNP | BP (gene) | MAF | Histotype | OR (95% CI) | *P* | Consortia/study [a] | Reference [b] |
|---|---|---|---|---|---|---|---|---|
| 1p36 | rs56318008 | 22470407 (WNT4) | 0.15 | All | 1.11 (1.07–1.16) | 7.6E-09 | OCAC + CIMBA | Kuchenbaecker, 2015 [f] |
| 1p34.3 | rs58722170 | 38096421 (RSPO1) | 0.23 | Serous | 1.12 (1.08–1.18) | 2.7E-12 | OCAC + CIMBA | Kuchenbaecker, 2015 [f] |
| 2q13 | rs17041869 | 111896243 (BCL2L11) | 0.88 | All [d] | 0.94 (0.93–0.96) | 5.1E-09 | OCAC + BCAC + PRACTICAL | Kar, 2016 |
| | rs752590 | 113972945 | 0.21 | Mucinous | 1.34 (1.21–1.49) | 3.3E-08 | OCAC | Kelemen, 2015 |
| 2q31.1 | rs711830 | 177037311 (HOXD3) | 0.32 | Mucinous | 1.30 (1.20–1.40) | 7.5E-12 | OCAC | Kelemen, 2015 |
| | rs2072590 | 177042633 (HAGLR) | 0.32 | Serous | 1.20 (1.14–1.25) | 3.8E-14 | OCAC | Goode, 2010 |
| 3q25 | rs7651446 | 156406997 (TIPARP) | 0.05 | All | 1.44 (1.35–1.53) | 1.5E-28 | OCAC | Pharoah, 2013 |
| 4q26 | rs17329882 | 119949960 (SYNPO2) | 0.24 | All | 1.09 (1.06–1.13) | 1.4E-08 | OCAC + CIMBA | Kuchenbaecker, 2015 [f] |
| 4q32.3 | rs4691139 | 165908721 | 0.48 | All | 1.20 (1.17–1.38) | 3.4E-08 | CIMBA | Couch, 2013 |
| 5p15.33 | rs10069690 | 1279790 (TERT) | 0.26 | Serous | 1.15 (1.11–1.20) | 1.3E-11 | OCAC | Bojesen, 2013 |
| 6p22.1 | rs6456822 | 28480635 (GPX6) | 0.31 | Serous | 0.91 (0.87–0.94) | 3.0E-08 | OCAC + CIMBA | Kuchenbaecker, 2015 [f] |
| 8q21.13 | rs11782652 | 82653644 (CHMP4C) | 0.07 | Serous | 1.24 (1.16–1.33) | 7.0E-10 | OCAC | Pharoah, 2013 |
| 8q24.21 | rs10088218 | 129543949 (LINC00824) | 0.13 | Serous | 0.76 (0.70–0.81) | 8.0E-15 | OCAC | Goode, 2010 |
| 9p22 | rs3814113 | 16915874 | 0.27 [c] | Serous | 0.77 (0.73–0.81) | 4.1E-21 | OCAC | Song, 2009 |
| 9q22.33 | rs1413299 | 101761241 (COL15A1) | 0.48 [c] | All | 1.53 (1.25–1.86) | 1.88E-08 | Chinese GWAS | Chen, 2014 [g] |
| 9q31 | rs200182588 | 106856690 (SMC2-AS1) | 0.56 | All [e] | 0.95 (0.94–0.97) | 8.9E-09 | OCAC + BCAC | Kar, 2016 |
| 9q34.2 | rs635634 | 136155000 | 0.85 | All | 1.11 (1.07–1.16) | 4.4E-09 | OCAC + CIMBA | Kuchenbaecker, 2015 [f] |
| 10p11.21 | rs1192691 | 37169295 | 0.38 [c] | All | 0.71 (0.60–0.83) | 2.62E-08 | Chinese GWAS | Chen, 2014 [g] |
| 10p12 | rs1243180 | 21915619 (MLLT10) | 0.31 | All | 1.10 (1.06–1.13) | 1.8E-08 | OCAC | Pharoah, 2013 |
| 11q12 | rs7937840 | 61893972 (INCENP) | 0.26 | All [d] | 1.05(1.03–1.06) | 5.0E-09 | OCAC + BCAC + PRACTICAL | Kar, 2016 |
| 15q26 | rs8037137 | 91506637 (RCCD1) | 0.86 | All [e] | 1.07 (1.05–1.10) | 9.1E-10 | BCAC + OCAC | Kar, 2016 |
| 17q11.2 | rs143663961 | 29181220 (ATAD5) | 0.95 | All | 0.91 (0.88–0.94) | 2.6E-09 | OCAC + CIMBA | Kuchenbaecker, 2015 [f] |
| 17q12 | rs7405776 | 36093022 (HNF1B) | 0.38 | Serous | 1.13 (1.09–1.17) | 3.1E-10 | OCAC | Shen, 2013 |
| | rs11651755 | 36099840 (HNF1B) | 0.49 | Clear cell | 0.77 (0.70–0.84) | 1.6E-08 | OCAC | Shen, 2013 |
| 17q21.31 | rs2960000 | 43534353 (PLEKHM1) | 0.18 | Serous | 1.16 (1.12–1.20) | 3.3E-10 | OCAC | Permuth-Wey, 2013 |
| 17q21.32 | rs9303542 | 46411500 (SKAP1) | 0.27 | All | 1.12 (1.08–1.16) | 6.0E-11 | OCAC | Pharoah, 2013 |
| 19p13.11 | rs2363956 | 17394124 (ANKLE1) | 0.51 [c] | Serous | 1.16 (1.11–1.21) | 3.8E-11 | OCAC | Bolton, 2011 |
| | rs1469713 | 19528806 (GATAD2A) | 0.64 | All [d] | 0.96 (0.95–0.97) | 3.4E-10 | OCAC + BCAC + PRACTICAL | Kar, 2016 |
| 19q13.2 | rs688187 | 39732752 | 0.32 | Mucinous | 0.67 (0.60–0.75) | 6.8E-13 | OCAC | Kelemen, 2015 |

All=all histotypes; Serous=high and low grade serous histotypes; Mucinous=borderline/LMP and invasive mucinous histotypes; Low-grade serous=borderline/LMP serous histotypes.

[a] Ovarian Cancer Association Consortium (OCAC) of case-control studies in European women; Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) European population; Breast Cancer Association Consortium (BCAC) European population; Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL) European population; Chinese GWAS of six studies: Tianjin Ovarian Cancer Study (TOCS), Chinese Academy of Medical Sciences Cancer Hospital (CAMSCH), Beijing University of Chemical Technology (BUCT), Nanjing Ovarian Cancer Study (NOCS), Shanghai Ovarian Cancer Study (SOCS), and Guangzhou Ovarian Cancer Study (GOCS).

[b] First genome-wide significant SNP results reported and referenced. Loci may have been identified or replicated in other GWAS.

[c] MAF in affected subjects reported.

[d] Pleiotropic variant associated with ovarian, breast, and prostate cancers.

[e] Pleiotropic variant associated with ovarian and breast cancers.

[f] OR are reported from OCAC (not CIMBA) study since no meta-analysis OR were reported.

[g] OR and MAFs are reported from Stage 1 OC cases while *P*-values are from meta-analysis of all stages, all phases.

European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, age at menopause (>52 *vs.* ≤45 years) was associated with an increased risk (HR=1.57, 95% CI: 1.16–2.13); however after women diagnosed with OC within the first two years of follow-up were excluded the risk was slightly attenuated and marginally statistically significant (HR=1.40, 95% CI: 0.98–2.00)[109]. The authors speculated that older women in the sub-clinical stage of OC may mistake bleeding for menses. Other case-control studies[98,100,106,107,114-116] and several cohort studies[101,105] found no association. The inconsistent findings with ages at menarche and menopause may reflect differences in definitions, recall and misclassification bias, or differences in analysis[117]. The etiologic heterogeneity of tumor subtypes may also contribute to differential findings. A report from the Nurses' Health Study (NHS) and NHS II found that age at natural menopause was associated with an increased risk of endometrioid tumors (RR=1.13, 95% CI: 1.04–1.22), but not serous invasive or mucinous tumors[29]. Studies conducted among populations with different distributions of age at menarche[99,111,118] and age at menopause[119] indicate differences in the genetic heritability of these factors across ancestral groups[120-122]. Regardless, the available evidence suggests that any magnitude of effect is likely small.

### *Parity and infertility*

The association between pregnancy and OC risk has been studied extensively. Pregnancy causes anovulation and suppresses secretion of pituitary gonadotropins and is thus consistent with both the 'incessant ovulation' and the 'gonadotropin' hypotheses. Indeed, parous women have a 30%-60% lower risk than nulliparous women[85,92,99,103-107,115,117,123-126] and each additional full-term pregnancy lowers risk by approximately 15%[98,105,127]. Studies in African American[128] and Asian[129,130] populations have yielded similar results. The protective effect associated with parity is evident across the main histotypes although perhaps slightly weaker for serous carcinomas, with roughly 20% lower risk in parous women, versus other subtypes, particularly clear cell and endometrioid that show 50%–70% reductions in risk[28-30,131,132]. Comparable to the breast cancer literature, case-control studies with hospital controls have reported elevated risk with late age at first birth (>30 years of age)[92,97,98,106,108,123,133-136], but not among studies with population controls[96,98,137]. Recent data also suggests that OC risk does not vary by the time interval between the first and last birth[138].

It is unclear whether spontaneous or induced abortions impact OC risk. About half of the published studies found that an increased number of incomplete pregnancies may slightly decrease risk[85,92,97,98,104,105,139-141] while others have reported risk to be increased[107,126], or not affected[96,99,100,102,106,115,123,125,142]. Induced abortions have been associated with lower risk in several studies[105,140,141], but not others[96,108,139]. With regard to spontaneous abortions, positive[100,123,139], inverse[102], and null associations[103,125,140] with risk have been reported. Interpretation of this literature is difficult because of the recognized potential for recall bias Should be 'abortions' here not pregnancies but better to end at recall bias.[143].

Infertility is a term that is used to describe a heterogeneous group of biologically distinct conditions ranging from genital tract infections and tubal disturbances to medical conditions such as endometriosis and polycystic ovarian syndrome (PCOS)[144,145]. Infertility appears to be a risk factor in most studies[92,98,102,106,115,123,125,126,136,144], but not all[105,146]. The inconsistent results may reflect the failure to examine the various types of infertility separately. It is yet to be determined whether nulliparity and low parity *per se*, rather than difficulty becoming pregnant due to female infertility, is the relevant factor. Infertility seems to pose the greatest risk among women who remain nulliparous, while periods of temporary infertility among parous women are of little concern[92,98,102,106,125]. For example, in a large Canadian case-control study in which most nulliparous women were so by choice, infertility was not associated with risk among parous women but there was a trend towards elevated risk among a small group of infertile nulliparous women (OR=2.5, 95% CI: 0.6–4.1)[102]. A particular challenge is trying to distinguish an influence of infertility from an adverse effect of fertility drug exposure. Although some studies report that women with a prior history of fertility drug use who remain nulliparous are at an elevated risk for ovarian tumors, particularly tumors of LMP[98,147], the results are not consistent[144-146,148-150]. Early detection bias may explain the discrepant findings, as early-stage cancers may be over-diagnosed in infertile women due to the close medical surveillance[151]. Further muddying of the water is caused by factors that may influence both infertility and OC risk such as a personal history of endometriosis[152-154], PCOS[155], and BRCA1 mutations[156].

### *Lactation*

Lactation suppresses secretion of pituitary gonadotropins and leads to anovulation, particularly in the initial months after delivery[157]. Both the incessant ovulation and gonadotropin hypotheses would predict lactation reduces the risk of OC. In fact, most studies indicate a slight protective effect from breastfeeding, with odds ratios approximating

0.6–0.7[98,99,102,124-126,158-161], although some have not[96,100,115]. Few studies have explored the association by tumor subtype, with one report of the greatest risk reduction for endometrioid tumors[162] while another observed the strongest reduction among mucinous cancers[30]. A recent meta-analysis indicates a significant protective effect (summary RR=0.68, 95% CI: 0.61–0.76) for breastfeeding that increased with longer duration (summary RR=0.85, 0.73, and 0.64 for <6 months, 6–12 months, and >12 months of total breast-feeding duration)[163]. Thus, lactation protects against epithelial OC, especially for long-term duration.

### *Benign gynecologic conditions and gynecologic surgery*

Several gynecologic conditions have been examined as risk factors for OC, including PCOS, endometriosis, and pelvic inflammatory disease (PID). PCOS is a multi-factorial disease often characterized by obesity, hirsutism, infertility, and menstrual abnormalities. Due to unopposed endogenous estrogen and/or elevated androgens, women with PCOS have an increased risk for endometrial cancer. The association between PCOS and OC risk was investigated using data from the Cancer and Steroid Hormone Study, a population-based case-control study[155]. Among 476 histologically confirmed epithelial OC cases and 4,081 controls, 7 cases (1.5%) and 24 controls (0.06%) reported a history of PCOS (OR=2.5, 95% CI: 1.1–5.9)[155]. The limited data was insufficient for a consensus statement that PCOS is a risk factor[164]. Larger studies that adjust for potential confounders are clearly needed.

Endometriosis is one of the most common gynecological disorders, affecting 10%–15% of women in reproductive years[165]. Despite being considered a benign condition, endometriosis has been linked with OC in the medical literature since 1925. Sayasneh and colleagues[165] conducted a systematic review of eight studies; seven reported an increased risk of OC, with effect sizes ranging from 1.3 to 1.9. The strongest associations with endometriosis are evident among endometrioid and clear cell histologies[30,165,166], consistent with molecular data that supports endometrial epithelium as the origin of these subtypes[8]. In addition, Pearce and colleagues[167] identified an increased risk of low-grade serous OC (OR=2.11, 95% CI: 1.39–3.20) among women with endometriosis as well as for endometrioid (OR=2.04, 95% CI: 1.67–2.48) and clear cell cancers (OR=3.05, 95% CI: 2.43–3.84). The authors speculated that the processes of endometriosis and endosalpingiosis may result from a similar underlying host susceptibility to implantation of exfoliated Müllerian epithelial cells from both the endometrium and fallopian tube. The association between endometriosis and endometrioid and clear cell ovarian carcinomas may represent shared risk factors[165], genetic susceptibility[168], and/or pathogenesis[169] rather than a causal association.

PID causes inflammation of the endometrium, fallopian tubes, and ovaries. Studies evaluating the association between PID and OC risk have yielded inconsistent results[103,170-172]. Lin and colleagues[173] evaluated this association in a large nationwide cohort from Chinese Taiwan that included 67,936 women with PID (42 of whom later developed OC) and 135,872 women without a history of PID (48 of whom developed OC). A history of PID was a significant risk factor (adjusted HR=1.92, 95% CI: 1.27–2.92), especially among subjects diagnosed with PID before the age of 35 and women who had at least 5 episodes of PID. Other studies found no association[171,172]. In the Danish MALOVA (MALignant OVArian tumor) case-control study of 2,300 women, PID history was associated with increased risk of ovarian borderline tumors but not with invasive OC[174]. Rasmussen et al.[175] further evaluated borderline ovarian tumors in a cohort of over 1.3 million Danish women and found that history of PID was associated with an 85% increased risk of serous borderline tumors but not those of the mucinous subtype. In previous studies of PID and OC risk, some only considered invasive tumors[103,108,173] whereas others included both invasive and borderline tumors[172] perhaps contributing to the inconsistent findings. There is no evidence that risk associated with PID history varies by histotype of invasive ovarian carcinomas[172,174].

Several gynecologic procedures appear to influence the risk for OC. It is well established that among high risk women, bilateral prophylactic oophorectomy decreases risk by at least 90%[176]. Numerous studies have identified a reduced risk associated with either a hysterectomy or tubal ligation ranging from 30%–40%[92,102,177-183] with the highest risk reductions observed among endometrioid and clear cell histotypes[30,181,184-187]. Furthermore, the risk reduction from these procedures appears to last for at least 10–15 years, which argues against screening bias (due to selective removal of subclinical ovarian tumors)[116,178,188,189]. Although it is unknown how these procedures reduce the risk of OC, it has been proposed that through retrograde menstruation (i.e. menstrual fluid flows backwards into the fallopian tubes instead of leaving the body through the vagina) endometrial tissue implants on peritoneal and ovarian surfaces (endometriosis) and becomes invasive, developing into endometrioid or clear cell ovarian carcinomas[13,190]. Indeed,

this hypothesis is supported by epidemiological studies that show the strongest associations with tubal ligation and endometriosis for ENOC and CCOC.

### *Oral contraceptives and other forms of contraception*

The epidemiological literature over the past several decades has consistently reported that use of oral contraceptives is inversely associated with the risk of OC. The protective effect increases with longer duration of use[98,102,191-195] with about a 20% decreased risk for each 5 years of use that persists decades after use has ceased[115,124,193,196-200]. Moreover, the risk reduction does not appear to be specific to any particular oral contraceptive formulation[195,201] or OC histotype, although oral contraceptive use appears less effective for mucinous cancers in some studies[23,27,28,30,118,131,200]. Oral contraceptive use corresponds to the prevention of approximately 30,000 OC cases every year and has already prevented an estimated 200,000 OC cases and 100,000 deaths over the last 50 years[200]. Progestin-only contraceptives have been less studied, mostly due to the low prevalence of use, but the available data suggest they may also lower risk of OC[124,193,202].

Relatively few studies have examined methods of contraception other than oral contraceptives. The use of an intrauterine device (IUD) has been associated with reduced OC risk in several studies[182,203,204] while the NHS cohort observed increased risks[205], however, there was a low prevalence of IUD use in that population which occurred prior to the newer IUD formulations. Similar to oral contraceptives, any protective effect associated with IUD use may be dependent upon duration of use. Huang and colleagues[203] evaluated IUD use and OC risk in the Shanghai Women's Health Study cohort and found long-term IUD use of at least 20 years was associated with a 38% reduction in risk. IUD use is the most common contraceptive method in China with a prevalence rate of about 50% among women of reproductive age[206]. The authors propose that the high prevalence of long-term IUD use and the associated strong protective effect may contribute to the low incidence of OC observed in China[203]. Vasectomy has been evaluated in association with OC risk and findings have been inconclusive[205], although Ness and colleagues[182] reported that vasectomy may confer a small reduction in risk (adjusted OR=0.77, 95% CI: 0.61–0.99), perhaps due to reduced exposure to sperm. Given that contraceptive methods are modifiable, further research to replicate these findings is needed. Additionally, research is needed to elucidate how different types of contraception influence OC risk, especially by histotype.

### *Hormone replacement therapy (HRT)*

Unlike oral contraceptive use that has a well-established benefit on OC risk, the association with HRT is less clear. HRT reduces the secretion of gonadotropins and should therefore decrease risk, but the reduced levels are still higher than pre-menopausal women[207]. Conversely, postmenopausal HRT may enhance estrogen-induced proliferation of ovarian cells and therefore increase risk[208]. Initial studies on the topic have focused on unopposed estrogen therapy (ET) among postmenopausal women. Several case-control[98,209,210], cohort[211] and meta-analysis[212,213] studies have found no association with duration of use, although two have observed either a significant or suggestive trend in increased risk[23,214]. More recent studies indicate that OC risk is increased in ever users of HRT[215-218] and larger increases are seen for longer durations of use[219-223]. For example, in the NHS cohort both current and past HRT users of five or more years had a significantly higher risk than never users (RR=1.41, 95% CI: 1.07–1.86 and RR=1.52, 95% CI: 1.01–2.27, respectively), but no association with risk was seen for users of less than five years for either current or past users (RR=1.01, 95% CI: 0.70–1.44 and RR=0.88, 95% CI: 0.64–1.19, respectively)[219]. The authors concluded that the elevated risk appeared to be driven largely by duration rather than by status of use. Conversely, a collaborative re-analysis of 52 epidemiological studies found OC risk was increased in current HRT users, even those with less than 5 years of use[224]. Furthermore, risk decreased over time after cessation of use, although a small excess in risk was still observed even 10 years after stopping long duration HRT.

Combined estrogen and progestin use and OC risk have only recently been evaluated in studies with sufficient statistical power. It has been hypothesized that progestin promotes apoptosis while estrogen promotes proliferation of ovarian epithelial cells[225] thus the effects of unopposed ET are thought to be more detrimental to the ovaries than estrogen plus progestin (EPT)[225]. Most studies that investigated EPT use and OC risk have found no association or a weak protective association[118,215,216,218,219,222,225-227]. A few prospective studies[215,221,228] and meta-analysis[217] have reported a small increased risk for EPT users compared to ET only users. For example, a recent meta-analysis of 14 population-based studies concluded that ET is associated with a 22% increased risk of OC per 5-year increment of use; however, the risk among women who used EPT was attenuated to only a 10% increase[216]. The authors suggest that the addition of progestin mitigates the effect of estrogen,

because the increased risk among EPT users was statistically significantly lower than the risk among ET users ($P$=0.004)[216]. However, several prospective cohort studies observed similar increased risks for both ET and EPT users[224,228]. The basis for the inconsistent literature is not readily apparent.

Some studies have indicated that any HRT-associated risk is limited to specific histologic subtypes. For example, in the NHS the increased risk was slightly stronger for endometrioid tumors and was not present for mucinous tumors, consistent with other studies[29,30,131,210,229]. Endometrioid tumors are histologically similar to endometrial tissue[230] and ET use increases the risk of endometrial cancer[208], enhancing plausibility.

The available data indicates that HRT is a risk factor for OC. The magnitude may be moderate, but women should be counseled about the potential dangers of long-term use, particularly for unopposed ET. Although large-scale reductions in hormone therapy have occurred since reports of negative health effects from the Heart and Estrogen/Progestin Replacement Study (HERS) and the Women's Health Initiative (WHI)[231], approximately 12% of women over 40 still take HRT for menopausal symptoms[232,233] totaling some 6 million women in the USA and UK alone[224]. Given the prevalence of HRT and that many women take HRT several years before the peak age-specific incidence of OC, even a small change in risk may have a significant impact on OC rates at the population level.

## Obesity

In postmenopausal women the predominant source of circulating estrogens is aromatization of androgens in adipose tissue[84,234]. The compelling role of obesity in the pathogenesis of hormone-related cancers, such as endometrial and post-menopausal breast cancers[235], has prompted research on the potential association with OC[236]. One measure of great interest is body mass index (BMI), calculated as weight in kilograms divided by height in meters squared. A 2007 meta-analysis of 28 population studies reported an increased risk of OC for overweight women (BMI of 25–29.9 kg/m$^2$) and obese women (BMI $\geq$ 30 kg/m$^2$) compared with normal weight (BMI of 18.5–24.9 kg/m$^2$), pooled RR=1.2 and 1.3, respectively[237]. In a 2008 analysis of 12 prospective cohort studies, an increased risk was seen among pre-menopausal obese women compared to normal weight women (RR=1.72; 95% CI: 1.02–2.89); however, this increased risk was not apparent among post-menopausal women (RR=1.07; 95% CI: 0.87–1.33)[238]. A more recent analysis of 12 case-control studies by the Ovarian Cancer Association Consortium (OCAC) also found that the positive association with BMI was stronger among pre-menopausal women[239]. Conversely, the EPIC cohort study observed the strongest risk associations for measures of adiposity (BMI and weight) among post-menopausal women[240]. In the NHS, greater hip circumference, a measure of fat distribution, was a risk factor among post-menopausal women, but waist-to-hip ratio, waist circumference and BMI were not[241].

Several studies have evaluated obesity and OC risk stratified by HRT use[239-244]. The results for BMI did not differ by HRT use in the OCAC analysis, NHS, or EPIC study. In contrast, three studies observed an increased risk only for obese women that have never used HRT [RR 1.8 (95% CI: 1.2–2.8)[242] and RR=1.10 (95% CI: 1.07–1.13)[244]] and for never HRT users with greater weight gain since age 18 (RR=1.8; 95% CI: 1.0–3.0 for $\geq$40 lbs. *vs.* stable weight), a larger waist circumference (RR=1.8; 95% CI: 1.1.–3.0 for $\geq$35 *vs.* <35 inches) and a larger waist-to-height ratio (RR=1.8; 95% CI: 1.1.–3.1 for $\geq$35 *vs.* <35 inches)[243].

The risk associated with obesity may be specific to non-serous and low-grade serous subtypes. Two large-scale pooled analyses, one performed by OCAC[239] and another by the Collaborative Group on Epidemiological Studies of Ovarian Cancer[244], observed the strongest risk increases for borderline serous tumors (OR/RR=1.24 and 1.29 per 5 kg/m$^2$, respectively) and somewhat lower increases for clear cell (OR/RR=1.06 and 1.05 per 5 kg/m$^2$), mucinous (OR/RR=1.19 and 1.15 per 5 kg/m$^2$), and endometrioid (OR/RR=1.17 and 1.08 per 5 kg/m$^2$) tumors. Overall, serous tumors were not associated with an increased risk in either study, however, the OCAC analysis included stratification by tumor grade and found an increased risk for low-grade serous tumors only (OR=1.13 per 5 kg/m$^2$). OCAC confirmed these findings in a later Mendelian randomization study where genetically predicted BMI was associated with an increased risk for non-high-grade serous subtypes only (OR=1.29; 95% CI: 1.03–1.61 per 5 BMI units) and the strongest increase was observed for low-grade serous tumors (OR=1.93; 95% CI: 1.33–2.81)[245]. An increased risk for OC has been observed between waist-to-hip ratio and risk of mucinous tumors (HR per 0.05 unit increment=1.19; 95% CI: 1.02–1.38), but not with serous, endometrioid, or clear cell tumors[240]. The large prospective NIH-AARP Diet and Health Study reported obese women had elevated risk of endometrioid OC (RR=1.64; 95% CI: 1.00–2.70), but not for serous[131]. Similarly, in the NHS, obesity was associated with increased endometrioid risk[29]; however, in a systematic review only the pooled analysis and one case-control study

found BMI to be associated with an increased risk of endometrioid OC[237].

In summary, elevated BMI appears to increase risk of OC. Since adiposity is a modifiable risk factor for OC, other cancers and other chronic diseases, weight control is prudent.

## Diet and nutrition

Despite numerous analytical epidemiological studies, whether diet affects risk of OC is largely unresolved. The notable exception is intake of vegetables, for which the evidence that higher intakes are associated with lower risk is emerging[246] and to a certain extent also for consumption of whole grain foods and low-fat milk. Associations with specific fats and oils, fish and meats and certain milk products are inconsistent and no firm conclusions can be made. Recently, the EPIC cohort study and Netherlands Cohort Study performed a nutrient-wide association analysis evaluating 28 foods/food groups and 29 nutrients by dietary questionnaires from 430,476 women including 1,522 incident OC cases. Meta-analysis of the two cohort studies found that women with a high intake of saturated fats had elevated risks (HR=1.21, 95% CI: 1.04–1.41). Studies on meat consumption are not consistent[247-249]. A large prospective study found that women in the highest intake quartile of dietary nitrate had an increased risk of OC (HR=1.31, 95% CI: 1.01–1.68, and *P*=0.02). Similarly, the association between coffee and tea intake is inconclusive[104,108,250-256].

Although the majority of vitamin D is produced in the skin from UV-B exposure[257], it is also partly obtained from our diet or dietary supplements. Vitamin D is converted to 25-hydroxyvitamin [25(OH)D] in the liver and metabolized to the active form in the kidney. 1, 25-dihydroxyvitamin D [1, $25(OH)_2D_3$] is involved in bone metabolism, modulation of the immune response, and regulation of cell proliferation and differentiation[257,258]. Experimental studies have shown that 1, $25(OH)_2D_3$ inhibits cell proliferation in OC cell lines and induces apoptosis[259]. However, epidemiological evidence that vitamin D status influences OC risk is inconsistent. One systemic review concluded that there is no strong evidence that vitamin D decreases risk[260] and a meta-analysis of ten longitudinal studies[261] as well as other cohort studies[262] reached a similar conclusion. In the meta-analysis the protective effect was evident in seven of the ten studies and the pooled estimate was a 17% reduced risk with increasing 25(OH)D levels; however, the pooled estimate was not statistically significant (RR = 0.83, 95% CI: 0.63–1.08)[261]. To address the conflicting findings from observational studies, a recent Mendelian randomization study[263] of almost 32,000 European women was conducted and found single nucleotide polymorphisms (SNPs) associated with circulating vitamin D levels were associated with an increased risk of OC (OR=1.27; 95% CI: 1.06–1.54). The beneficial effect of vitamin D may be more pronounced among overweight or obese women[259,264] perhaps reflecting differential bioavailability of circulating 25(OH)D levels[259].

A complementary approach has been to examine SNPs in the vitamin D receptor, which mediates the biological activity of the active form of vitamin D and interacts with other cell-signaling pathways[258,265,266]. The vitamin D receptor polymorphism FokI is among the most extensively studied and several studies have observed an increased OC risk among carriers[267,268]. Associations with other common vitamin D receptor variants, BsmI, ApaI, and TaqI, and OC risk remain controversial[269]. Prescott and colleagues[270] investigated all vitamin D receptor variants genotyped as part of a GWAS stratified by predicted 25(OD)D scores (high *vs.* low) derived from known determinants of serum 25(OH)D[270]. There was evidence that OC risk was increased for minor allele carriers of rs731236 (OR=1.31) and rs7975232 (OR=1.83) among women with high predicted 25(OH)D but these findings require replication.

## Exercise and physical activity

The general health benefits of exercise are well established and a specific effect on OC might be expected, at least indirectly, through the resulting reduction of adipose tissue (and therefore estrogen levels), lower ovulation frequency, and reduced chronic inflammation[271]. To date, 29 epidemiological studies have investigated physical activity and OC risk, including fourteen prospective cohort studies[272-285], two historical cohort studies[286,287], ten population-based case-control studies[252,288-296] and three hospital-based case-control studies[297-299]. Results are not entirely consistent, but a 2007 meta-analysis estimated a nearly 20% lower risk for the most active women compared to the least active (pooled relative risk=0.81, 95% CI: 0.72–0.92)[292]. Most studies that measured physical activity across the lifespan reported consistent null findings[278,279,282,290,292] or risk reductions[252,289,291,297] in each age period. Similarly, prolonged sedentary behavior[278], high levels of total sitting duration[283,285,300], and chronic recreational physical inactivity[295] have all been noted to increase risk. The benefit of physical activity does not appear to vary by histological type[285,295] but there are insufficient data to draw firm conclusions[291,294]. Although further research can refine the picture, when considering the additional benefits of exercise on weight control, bone

density, and heart disease, the promotion of regular activity should be encouraged.

## Other lifestyle and environmental factors

### *Cigarette smoking*

The majority of early reports concluded that smoking was not a risk factor[125,253,301,302]. Results from more contemporary studies suggest this is most likely because analyses were not conducted separately for histologic subtypes. Indeed, smoking appears to increase the risk for mucinous OC in a dose-response manner, but not other subtypes[22,26,30,303]. In 2012, a meta-analysis of 51 epidemiological studies concluded that current smokers have a 50% increase in invasive mucinous OC risk and an over two-fold increase in borderline mucinous OC risk (summary RR=2.25, 95% CI: 1.64–3.08) compared to never smokers, but no increased risk of serous (0.96, 95% CI: 0.87–1.06) or clear cell (0.80, 95% CI: 0.63–1.01) cancers and lower risk of endometrioid cancers (0.82, 95% CI: 0.71–0.95)[304]. In another meta-analysis, the risk of mucinous cancer increased in a dose-response relationship with amount smoked, but returned to that of never smokers within 20–30 years of stopping smoking[305]. Histologically, mucinous ovarian tumors resemble mucinous gastrointestinal cancers, some of which (pancreatic gastric, and colorectal cancers) have also been associated with smoking[305,306]. Collectively, these findings suggest that risk of OC is one more reason to avoid cigarette smoking.

### *Alcohol consumption*

Alcohol consumption increases circulating concentrations of androgens, estrogens, and other sex hormones in serum and urine and has been linked to increased risk of breast cancer[307,308]. Studies of alcohol use and OC are inconsistent, with null associations[99,125,252,253,309-312], evidence for increased risk[104,313,314] and decreased risk[315-317]. There have been efforts to resolve the observed inconsistency by quantifying risk by the type of alcohol consumed (wine, beer, or alcohol)[314,315,318], histologic subtype of the tumor[314,315,317], or by other potential modifiers such as dietary fiber intake[319]. In a large population-based case-control study[320], consumption of beer (not liquor or wine) during early adulthood (20–30 years of age) was associated with a moderately increased risk of invasive OC, with the association limited to serous tumors (OR=1.52, 95% CI: 1.01–2.30), though results for other histological subtypes were based on sparse data. This risk was associated with regular consumption (1 or more drinks per day), and there was no evidence of a dose response relationship. Data from the Netherlands Cohort Study on Diet and Cancer found no risk association with alcohol consumption in the form of wine, beer, or liquor[321]. A pooled analysis of 10 cohort studies that included over 500,000 women and 2,001 incident OC cases also observed no risk association with total alcohol intake (pooled multivariate RR=1.12, 95% CI: 0.86–1.44 comparing > 30 to 0 g of alcohol per day) or alcohol intake from wine, beer, or spirits[322]. There was no association (OR=1.13, 95% CI: 0.92–1.38) between wine consumption and OC risk in a recent meta-analysis of 10 studies (3 cohort and 7 case-control studies) with 135,871 women, including 65,578 wine drinkers[323]. Based on these data, it seems reasonable to conclude that if alcohol intake does influence risk of OC, the magnitude is small and possibly limited to particular histologic subtypes.

### *Asbestos and talcum powder*

Both human[324,325] and animal studies[326] have found asbestos fibers in the ovaries. However, a link between asbestos exposure and OC has not been firmly established, partly due to small numbers of exposed women and disease misclassification (i.e. peritoneal mesothelioma, an asbestos-related disease, is often misdiagnosed as OC on death certificates). A systematic review and meta-analysis of fourteen cohort and two case-control studies[327] noted a statistically significant 75% excess risk of OC in women who had been exposed to asbestos (effect size=1.75, 95% CI: 1.45–2.10). However, the association was attenuated (effect size=1.29, 95% CI: 0.97–1.73) among studies that examined cancer incidence based upon pathologically confirmed cases[327]. Despite the lack of consistency, the International Agency for Research on Cancer (IARC) has declared that evidence is 'sufficient' in humans that exposure to asbestos causes OC[328].

Similar to asbestos, talcum powder is a silicate that has been studied extensively in relation to cancer risk with inconsistent results. While mechanistic, pathology, and animal studies do not support evidence for the carcinogenicity of talc on the ovarian epithelium[329], epidemiological studies have indicated an association with talc use and increased OC risk. In 2006, a meta-analysis of 21 studies[330] reported an approximately 35% increase in risk with genital exposure to talc and an earlier meta-analysis had similar findings[331]. However, more recent studies have continued to report conflicting results. In 2014, the Women's Health Initiative reported a null association among a cohort of 61,576 post-menopausal women. Cramer and colleagues[332] conducted a retrospective case-control study that observed

increased risk among talc users similar to those previously reported (OR=1.3, 95% CI: 1.16–1.52), particularly among serous and endometrioid cancers. The study also found that risk was greatest among pre-menopausal women and in post-menopausal women who used hormonal therapy, suggesting estrogen plays a role in the association. In addition, genetic studies suggest that women with certain variants in glutathionine S-transferase M1 (*GSTM1*) and/or glutathionine S-transferase T1 (*GSTT1*) may have a higher risk of OC associated with talc use[333]. Based on the available evidence, in 2006 the IARC classified genital talc use as possibly carcinogenic to humans[334].

### *Drug use*

Epidemiological evidence linking PID and endometriosis to increased OC risk suggests inflammation plays an important role in ovarian carcinogenesis. In addition, animal and *in vitro* studies suggest aspirin inhibits the growth of OC[335-337]. Several prospective[338,339] and case-control[340-344] studies have observed an inverse association between aspirin and nonsteroidal anti-inflammatory drugs (NSAIDS) and OC incidence, though other studies have reported no association[345,346]. Prizment and colleagues[339] investigated these drugs using data from a prospective cohort of approximately 20,000 women from the Iowa Women's Health Study. Compared to women who reported no use of aspirin, the relative risks of OC for those who used aspirin < 2, 2–5 times, and ≥ 6 times per week were 0.83, 0.77, and 0.61, respectively ($P$=0.04) but no association was observed between NSAID use and risk. Conversely, in the NHS I and II[338] regular use of NSAIDS was protective (HR=0.81, 95% CI: 0.64–1.01) but aspirin use was not (HR=1.11, 95% CI: 0.92–1.33). No dose-response relationship with increased frequency or duration of use was observed, and results did not differ when stratifying by tumor histology[338]. A recent pooled analysis of 12 case-control studies in the OCAC[340] found aspirin use was associated with a reduced risk of OC (OR=0.91, 95% CI: 0.84–0.99), especially among daily users of low-dose (<100 mg) aspirin (OR=0.66, 95% CI: 0.53–0.83). Thus, the same aspirin regimen prescribed to protect against cardiovascular events and other cancers (e.g. colorectal cancer) could reduce the risk of OC by 20%–34%[340].

A growing body of evidence supports a role for the anti-diabetic agent, metformin, in the prevention and treatment of multiple cancers[347]. A case-control study including 1,611 incident OC cases was performed using the UK-based General Practice Research Database[348]. Long-term use (≥ 30 prescriptions) of metformin (and not sulfonylureas or insulin) was associated with a trend towards reduced risk (OR=0.61, 95% CI: 0.30–1.25), but the results were not statistically significant. Additional studies have observed decreased incidence and mortality among metformin treated groups[349]. Given the absence of good screening tests, the potential for use of metformin as a chemopreventive agent merits further exploration.

## Conclusions

OC is a leading cause of cancer incidence and mortality worldwide. This review describes the magnitude of the problem and summarizes epidemiological studies that have identified genetic, environmental, and lifestyle factors that may increase and decrease risk of this lethal disease. These factors have likely impacted the diverse patterns and trends of OC incidence and mortality seen across the globe. Increased and earlier use of oral contraceptives has very likely contributed to the declining trends observed in most developed countries while reduced parity and changes in diet and physical activity could play a role in the increasing trends observed in several countries with economic growth.

Most risk factors show substantial heterogeneity across the five histologic subtypes indicating different etiologies, particularly between mucinous and non-mucinous subtypes (**Table 2**). The fact that risk factor associations support accepted models of pathogenesis for the individual histotypes give weight to causality, although such inference is limited. Mendelian randomization studies, which exclude explanations such as bias, confounding and reverse causality, have inferred a likely causal effect of BMI on risk of non-HGS OC and of vitamin D on risk of invasive and HGS OC. Additional epidemiological studies of instrumental variables and incorporating tumor histopathology are needed to refine effect estimates for histotypes and enhance causal inference.

Although many of the risk factors cannot be modified, reflecting the contribution of genetics and unavoidable exposures, a number of others can be altered. Increasing parity and oral contraceptive use lower risk of OC. The same is probably true, but to a weaker degree, of lactation, regular physical activity and avoidance of cigarettes. An individual's risk is in part a result of the cumulative effect of exposures. Several risk prediction models for OC have been developed to estimate absolute risk based on one's risk factor profile[350-353]. The EPIC study[350] modeled factors of menopausal status, hormone therapy use, oral contraceptive use, parity, oophorectomy, and BMI and estimated 5- year absolute risks of OC for women aged 68 years varied from 0.10% to 0.24% (lowest 10$^{th}$ percentile *vs*. highest 10$^{th}$

**Table 2** Summary of the five major epithelial OC histotypes

| Item | All invasive | High-grade serous [a] (HGSOC) | Low-grade serous (LGSOC) | Mucinous (MOC) | Endometrioid (ENOC) | Clear cell (CCOC) |
|---|---|---|---|---|---|---|
| Precursor lesion | NA | Serous tubal intraepithelial carcinoma (STIC) | Borderline serous tumor | Cystadenoma, borderline mucinous tumor | Atypical endometriosis | Atypical endometriosis |
| Somatic mutations | NA | BRCA1/2, TP53 | BRAF, KRAS | KRAS | PTEN, CTNNB1, ARID1A, PIK3CA | ARID1A, PIK3CA |
| Established risk factor | | | | | | |
| Age at menarche | Null-weak protection | Null | NE | Null | Null | Weak protection |
| Age at menopause | Moderate increase | Null | NE | Null | Weak risk | Moderate risk |
| Parity | Weak-moderate protection | Weak protection | NE | Weak protection | Moderate protection | Moderate-strong protection |
| Lactation | Weak-moderate protection | Weak protection | NE | Moderate protection | Moderate protection | Null-weak protection |
| Endometriosis | Moderate-strong risk | Null | Strong risk | Null | Strong risk | Strong risk |
| Tubal ligation | Moderate protection | Null-weak protection | Null | Null-weak protection | Strong protection | Strong protection |
| Oral contraceptives | Moderate protection | Moderate protection | NE | Null-weak protection | Moderate protection | Moderate protection |
| Hormone therapy | Moderate risk | Moderate-strong risk | NE | Null | Moderate-strong risk | Null-weak protection |
| Body mass index | Weak risk | Null | Weak risk | Weak risk | Weak risk | Weak risk |
| Smoking | Null | Null | NE | Moderate-strong risk | Null-weak protection | Null-weak protection |

Weak: ≤25%, Moderate: 25%–50%, Strong: ≥50%, NA=not available, NE=not estimated.
[a] Given that the majority of serous tumors are high-grade, risk associations for overall serous subtype are reported when no data is available by grade.

percentile) depending on the factors. Cumulatively, risk factors accounted for a relative risk of 1.8 for women with the average reported age at menopause (50 years old), average duration of hormone therapy use (2 years), and overweight BMI (25 kg/m$^2$). This cumulative relative risk increases to 3.5 for obese (BMI=30 kg/m$^2$) women with later age of menopause (60 years old) and longer hormone therapy use (5 years). Preventive factors accounted for a cumulative relative risk of 0.47 for women with average parity (2 full-term pregnancies) and oral contraceptive use (5 years) with stronger protection conferred with higher parity and duration of use (RR=0.33, 4 full term pregnancies and 10 years of use). Notably, modifiable factors can mitigate relative risk of unavoidable exposures such as later age of menopause. For example, reducing BMI from 30 to 24 kg/m$^2$, utilizing oral contraceptives for 5 years, and forgoing hormone therapy use, the relative risk of a woman who reaches menopause at 60 is mitigated from 3.5 to 0.99.

It is important to emphasize that the established risk factors aside from highly penetrant gene mutations confer neither large increases in risk nor account for all the variability in the incidence of this disease. Thus, additional causes of OC are yet to be identified. Additional research is needed to better understand the heterogeneous etiology of this deadly disease, with a view to better prevention and early detection strategies.

## Conflict of interest statement

No potential conflicts of interest are disclosed.

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