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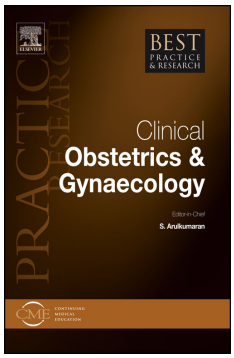


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# EPIDEMIOLOGY OF EPITHELIAL OVARIAN CANCER

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**ABSTRACT**

Globally, ovarian cancer is the seventh most common cancer in women and the eighth most common cause of cancer death, with five-year survival rates below 45%. Although age-standardised rates are stable or falling in most high-income countries, they are rising in many low and middle income countries. Furthermore, with increasing life-expectancy, the number of cases diagnosed each year is increasing. To control ovarian cancer we need to understand the causes. This will allow better prediction of those at greatest risk for whom screening might be appropriate, while identification of potentially modifable causes provides an opportunity for intervention to reduce rates. In this paper we will summarise the current state of knowledge regarding the known and possible causes of epithelial ovarian cancer and discuss some of the main theories of ovarian carcinogenesis. We will also briefly review the relationship between lifestyle and survival after a diagnosis of ovarian cancer.

[Words=148]

**KEY WORDS**

Ovarian neoplasms; epidemiology; incidence; risk factors; survival

**<A>INTRODUCTION**

Globally, 240,000 women are diagnosed with ovarian cancer every year and, with five-year survival below 45%, it is responsible for 150,00 deaths making it the 7th most common cancer and 8th most common cause of cancer death among women [1]. Figure 1A shows that age-standardised incidence rates are highest in northern and central/eastern Europe, intermediate in north America, Australia and western Europe and lowest in Asia and Africa. Rates have been decreasing in most high incidence countries but increasing in many low incidence countries (Figure 1B) thus the differences today are less marked than 30 years ago [2]. Rates also vary by ethnicity within countries such that in the United States, rates in non-Hispanic white women are approximately 30% higher than African-American and Asian women and 12% higher than Hispanic women [3].

**<FIGURE 1 NEAR HERE>**

Ovarian cancer is rare in women under 40 years of age and most cancers in this age group are germ cell tumours. Above age 40, more than 90% are epithelial tumours and the risk increases with age, peaking in the late 70s. Despite being classified as ovarian, a high proportion of high-grade serous cancers are now thought to originate from the fallopian tube. In the following discussion the term 'ovarian cancer' refers to epithelial cancers that arise in the ovary or fallopian tube as well as the histologically similar primary peritoneal cancers.

**<A>RISK FACTORS**

It is well established that women with a family history of ovarian cancer are themselves at higher risk of the disease. The risk for women with one affected first-degree relative is about three times that for women with no affected relatives [4], and even higher for those whose

relative was diagnosed below the age of 50 [5]. A high proportion of hereditary cancers are due to mutations in the BRCA genes, however BRCA mutations are also common among women with ovarian cancer who do not have a family history of either breast or ovarian cancer [6]. BRCA1 mutation carriers have an estimated 40-50% risk of developing ovarian cancer by age 70, compared to 10-20% for BRCA2 [7]. Most cancers associated with BRCA mutations are high-grade serous tumors. Lynch syndrome or hereditary nonpolyposis colon cancer (HNPCC) caused by mutations in genes involved in DNA mismatch repair also increases risk of ovarian cancer, particularly non-serous cancer [8]. Mutations in other genes including BRIP1 [9] and RAD51 [10] confer a moderately increased risk of ovarian cancer and genomewide association studies have now identified more than 20 low-risk susceptibility loci including CHEK2, WNT4, TERT, and ABO which are also associated with cancers at other sites.

The following sections review non-genetic factors known or suspected to affect a woman's risk of developing epithelial ovarian cancer, with most weight given to recent meta-analyses and pooled analyses, particularly those using data from prospective studies.

**<B>Reproductive history**

**<C>Age at menarche and menopause**

The relationship between age at menarche and ovarian cancer risk remains unclear. Although one meta-analysis [11] reported a significantly reduced risk in those with an older age at menarche, a recent pooled cohort analysis did not confirm this finding except in relation to clear cell ovarian cancer [12]. The evidence is more consistent for age at menopause. The pooled analysis found that each five-year increase in age at menopause was associated with a

6% increase in ovarian cancer risk overall, with stronger effects for endometrioid and clear cell cancers (19% and 37%, respectively) but no association for mucinous cancers.

**<C>Pregnancy**

Women who have ever given birth have a reduced risk of ovarian cancer [12] and each addtional birth is associated with a further 10-20% risk reduction [12,13]. The effect appears to hold for all the main histotypes of epithelial ovarian cancer but may be strongest for clear cell and endometrioid cancers [12]. Higher parity is also associated with reduced risk in BRCA1 mutation carriers, but perhaps not BRCA2 carriers [14], although this observation is based on small numbers.

Some have suggested the risk reduction is greater for women who were older at the time of their first [15] or last birth [16]; others have suggested that the strength of the association wanes with age [17]; and some have found that a twin pregnancy reduces risk more than a singleton pregnancy [18], but additional studies are required to confirm these findings. In contrast, most studies suggest that incomplete pregnancies (miscarriages, abortions, ectopic pregnancies) do not reduce ovarian cancer risk [19] and some have even linked multiple miscarriages with an increase in risk [20].

**<C>Breastfeeding**

Several meta-analyses have concluded that parous women who breastfeed their children have a 20-25% lower risk of ovarian cancer than parous women who have not breastfed [21,22] and that longer durations of breastfeeding are associated with greater risk reductions. However, a recent pooled analysis of cohort studies did not find a statistically significant risk reduction [12]. This inconsistency may relate to the degree of ovulation suppression induced

by breastfeeding which is greatest in the early postnatal period, reducing thereafter. In keeping with this, one study [23] found the risk reduction appeared to plateau after about six months for indiviudal episodes of breastfeeding, Further work is required to clarify the association between breastfeeding and ovarian cancer.

**<C>Infertility and fertility drugs**

While a diagnosis of endometriosis (see Medical conditions and treatment) has consistently been associated with increased risk of ovarian cancer, it is unclear whether other causes of infertility increase the risk of ovarian cancer beyond the effect of reduced parity. It is also unclear whether use of fertility drugs increases ovarian cancer risk because, despite the fact that numerous studies have investigated the association [24], most have only included small numbers of exposed women or have been limited by relatively short follow-up times or changes in treatment regimens over time. Studies that have followed cohorts of women treated for infertility have mostly revealed no excess risk among women treated with ovarian stimulation [25,26]; however, there may be an increase in risk of borderline ovarian tumours [27]. More data are required to understand whether women who have had prolonged use or remain nulliparous are at higher risk, or whether risk will become apparent only after longer periods of follow-up [13,28,29]. As the use of these treatments has increased substantially over the past 20 years, ongoing investigation is warranted.

**<B>Exogenous hormone use**

**<C>Oral contraceptives**

It is clear that use of the combined oral contraceptive (OC) pill is inversely associated with ovarian cancer risk. An analysis that pooled data from 45 studies from 21 countries showed that the risk of ovarian cancer was almost 30% lower in ever-users of oral contraceptives

compared to never-users [30]. Risk was further reduced with increasing duration of use (~20% per five years), and although the effect may attenuate over time, the benefit appeared to persist for at least 30 years after cessation, [30]. OC use has also been associated with lower risk among BRCA mutation carriers in most studies that have evaluated this [31]. The extent of risk reduction probably varies by histotype with two pooled analyses showing risk reduction for serous, endometrioid and clear cell cancers, but not mucinous cancers [12,30].

OC preparations have changed considerably over time with the amount of oestrogen halving between the 1960s and 1980s and this change might affect risk relationships with ovarian cancer. The pooled study above [30] investigated this possibility by assessing the association by calendar year of use, finding no variation across time-periods. Few studies have assessed the relationship between use of progestin-only contraceptives and risk of ovarian cancer but inverse associations have been reported with the use of oral [32] and injectable progestin-only contraceptives [33,34], as well as with progestin-releasing intra-uterine devices [35] although further studies are required to confirm these relationships.

**<C>Menopausal hormones**

Evidence from a large pooled analysis (52 studies) indicates that current use of menopausal hormone therapy (MHT) increases risk of ovarian cancer by about 40% and that even after stopping, the risk remains elevated for at least five years in women who had used MHT for five or more years [36]. In this analysis the risk did not vary according to the preparation used (oestrogen-only versus combined), however a meta-analysis of 14 population-based studies found a stronger association for oestrogen-only than combined MHT [37]. This latter analysis and another pooled analysis of prospective studies also reported that risk increased with increasing duration of use (~20% per 5 years) [12]. The current data are insufficient to

determine whether risk differs for sequential and continuous preparations of combined MHT but the risk associated with continous combined MHT may be lower than that for sequential preparations.

It is likely the risk associated with MHT varies by histotype with the two large pooled analyses reporting that MHT was associated with an increased risk of serous and endometrioid cancers, a significant 25% reduction in risk of clear cell cancers and no association with mucinous cancers [12,36].

**<B>Medical history**

**<C>Tubal ligation and hysterectomy**

The majority of epidemiologic studies have found an inverse relation between tubal ligation and ovarian cancer with pooled analyses of case-control [38] and cohort [12] studies suggesting overall risk reductions of 20-30%. Stronger effects are evident for endometrioid and clear cell cancers compared to invasive serous cancers. The effect may persist for up to 30 years after surgery but does not appear to vary by the age at which the procedure was undertaken [38]. Tubal ligation has also been associated with risk reductions amongst women carrying a BRCA mutation [39].

The association with hysterectomy (without oophorectomy) is less clear. Although earlier studies mostly reported inverse association between hysterectomy and ovarian cancer risk, studies including women diagnosed more recently have not [40]. The recent pooled analysis of cohort studies [12] also showed no overall inverse association with hysterectomy, but did report a 40% reduction in clear cell cancers. The reason for the heterogeneous results is not

clear, but may reflect different surgical approaches, indications or ages of women at surgery. This relationship requires further clarification.

**<C>Endometriosis, polycystic ovarian syndrome and other benign gynaecological conditions**

A history of endometriosis has been associated with a consistent two- to three-fold increase in risk of endometrioid and clear cell ovarian cancers in both case-control [41] and cohort studies [12]. Associations with polycystic ovarian syndrome (PCOS) are less clear. Most studies have not found a significant association [42,43], although one found a 2.5-fold increase in risk of borderline serous cancers among women who reported PCOS [44]. No clear relationships have been observed with conditions such as fibroids or ovarian cysts.

The potential for chronic local inflammation to contribute to the pathogenesis of ovarian cancer [45] has prompted investigation of associations between pelvic inflammatory disease (PID) and ovarian cancer. Results of individual studies have been inconsistent but overall there is little evidence of an association with invasive cancer but possibly a modest (~30%) increase in risk of borderline tumours, that may be greater (~2-fold risk) among those with multiple episodes of PID [46].

**<C>Diabetes Mellitus**

A 2013 meta-analysis reported a statistically significant 17% increase in risk of ovarian cancer among women with a diagnosis of diabetes (type not specified) compared to those without [47]. However, there was moderate heterogeneity between the results of the studies and newer studies have not supported an association [48]. Some of this heterogeneity may relate to differences in diabetes treatments as it has been suggested that use of metformin may

reduce ovarian cancer risk, while insulin and possibly sulfonylureas have been associated with increased risks [49]. The potential chemoprotective benefit of metformin warrants further investigation.

**<C>Non-steroidal anti-inflammatory drugs**

The potential chemopreventive effect of medications with anti-inflammatory actions is of substantial interest for a number of cancers including ovarian. Acetaminophen use was associated with risk reductions in the order of 30-50% in a meta-analysis [50] and a large Danish data-linkage study [51], although a pooled analysis of 12 case-control studies did not observe an association [52]. The pooled analysis did, however, show that regular aspirin use was associated with a significant 20% reduction in ovarian cancer risk with a similar, but non-significant, reduction for use of other non-steroidal anti-inflammatory drugs (NSAIDs). Aspirin use, particularly low-dose, was also associated with reduced ovarian cancer risk in the data linkage study [53]. Given the frequent use of these medications, including for the prevention of other conditions, further evaluation is required to confirm these associations.

**<B>Body size**

As for most other cancer types, height has been fairly consistently associated with ovarian cancer risk with prospective studies showing an 8% increase in risk per 5 cm height [54].

Obesity is associated with low-grade chronic inflammation and fat cells produce inflammatory cytokines as well as converting androstenedione to oestrone [55]. It is also associated with lower levels of sex hormone-binding globulin and thus higher levels of free oestradiol. Obesity increases risk of a number of cancers, including endometrial and post-menopausal breast cancer but, until recently, data for ovarian cancer were inconsistent. Two

large pooled analyses have now shown a positive association between body-mass index and ovarian cancer risk with a 5-29% increase in risk of ovarian cancer per 5 kg/m$^2$, although this association appears to be restricted to borderline tumours and invasive endometrioid, clear cell and mucinous cancers, and not the more common invasive serous cancers [56,57]. The same pattern was seen in a recent Mendelian randomisation analysis using genetic markers of obesity to reduce the potential for confounding [58].

In post-menopausal women, adipocytes are the primary source of endogenous oestrogen. It is therefore possible the effects of obesity might differ by menopausal status and/or MHT use as any effects of endogenous oestrogen may be masked by the higher levels of exogenous oestrogens from MHT. However, while one of the pooled analyses concluded the association with body-mass index was restricted to women who had not used MHT [56], the second did not confirm this [57].

**<B>Physical activity and sedentary behaviour**

Vigorous physical activity can lead to anovulation and amenorrhoea and it may also reduce inflammatory biomarkers and enhance immune function, all of which would potentially reduce risk of ovarian cancer. In support of this, several case-control studies have reported an inverse association with recreational physical activity [59], and a recent pooled analysis found a 34% increase in risk among women who were sedentary [60]. Results from prospective studies have, however, been mixed with little suggestion of an association with leisure-time physical activity [61] and, while some have reported increased risk among those who are sedentary [62], others have not [59]. Given the differing measures of activity and sedentary behaviour across studies, and varying timing of activity measurement relative to

cancer diagnosis, it is hard to draw clear conclusions regarding the relation between activity and/or sedentary behaviour and ovarian cancer risk at this time.

**<B>Alcohol**

High alcohol intake is associated with menstrual abnormalities and reproductive problems while more moderate consumption has been associated with elevated levels of hormones including oestradiol among post-menopausal women [63]. Alcohol is also a well-established risk factor for breast cancer [64]. Despite this, there is little evidence to suggest that alcohol increases ovarian cancer risk with large-scale pooled analyses [65,66] showing no association between total alcohol intake and ovarian cancer risk, and no clear associations for different types of alcohol.

**<B>Tobacco**

There is consistent evidence that smoking increases risk of ovarian cancer, but only the mucinous subtype. Two large-scale pooled analyses [67,68], reported significant 30-50% increases in risk of invasive mucinous cancer and 80-130% increases for borderline mucinous tumours among current smokers. The risks increased with increasing duration of smoking and declined with time after smoking cessation. In contrast, smoking was not associated with risk of serous cancers and current smokers had a 20% lower risk of developing endometrioid and clear cell cancers. This latter observation is consistent with observations that smokers also have a reduced risk of endometrial cancer [69] and may be explained by the fact that cigarette smokers have been shown to have lower levels of urinary oestradiol than non-smokers [70].

**<B>Diet**

Positive correlations between national ovarian cancer rates and per capita intake of fat, particularly animal fat, milk and meats, and inverse correlations for vegetables [71,72] suggested a potential role of diet in the aetiology of ovarian cancer. However, while subsequent case-control studies have reported associations with various dietary components, these are susceptible to selection and recall biases. Overall, a comprehensive 2014 review of the results from prospective studies found no convincing evidence for an association between diet and ovarian cancer risk but concluded the data were too limited to draw any firm conclusions [54]. Some key dietary components are discussed below.

Despite the strong international correlations, there is little evidence for an association between fruit and vegetable consumption or intake of individual micronutrients including vitamins A, C, E, folate and the major carotenoids and ovarian cancer [73]. Similarly, there is little evidence for an overall association with dietary fat intake, although a modest association with animal and saturated fats is possible [73,74]. The fact that lactose is hydrolysed to glucose and galactose and galactose is toxic to oocytes, led to the hypothesis that high lactose intake might increase risk of ovarian cancer. Data to support this hypothesis are, however, limited. The largest pooled analysis reported only a non-significant 4% increase in risk per 10g lactose [75] and, although a subsequent Swedish linkage study reported a reduced risk of ovarian cancer among women with lactose intolerance [76], another cohort study saw no association with lactose intake [77]. Early reports of increased risks of ovarian cancer among women who consumed more eggs have not been confirmed in recent studies [73].

Observations that ovarian cancer rates are higher in countries at lower latitudes suggested a possible protective role for vitamin D. Studies of dietary [75] and serum vitamin D [73] have not confirmed this but are subject to potential confounding. A randomised controlled trial of

calcium plus vitamin D supplements also found no difference in ovarian cancer incidence between the intervention and placebo groups, although the dose of vitamin D (400 IU/day) was fairly low [78]. In contrast, a recent Mendelian randomisation analysis using genetic markers of circulating 25-hydroxy-vitamin D (25(OH)D) reported a significant 54% increase in risk of high-grade serous ovarian cancer for every 20 nmol/L decrease in genetically-predicted 25(OH)D [79].

Although coffee drinking has been asociated with a reduced risk of endometrial cancer [80], there is no evidence for an association with ovarian cancer [73]. Both black and green tea contain polyphenols that inhibit carcinogenesis *in vitro*[81] but, although tea drinking, particularly green tea, was associated with a significant 70% reduction in risk of ovarian cancer in a Chinese case-control study [82], most cohort studies in non-Asian populations where black tea is more common have not reported any association [73].

**<B>Talcum powder**

Talc is a natural mineral fiber similar to asbestos, a known carcinogen, and talc fibres have been detected in ovarian tissue. Case-control studies have consistently shown a 20-25% increased risk of ovarian cancer among women who used talc in the genital region [83]. This would equate to a 1.6% lifetime risk of ovarian cancer for a talc-user compared to 1.3% for a non-user. However it is still uncertain whether the association is causal because there is little evidence that risk increases with increasing frequency and/or duration of talc use and the association does not appear to be weaker among women who have undergone procedures such as tubal ligation that would prevent talc from reaching the ovaries [83]. Prospective studies have not reported significant associations overall [84,85], although one did report an

association for serous cancers [84], but they had limited power to detect an effect of this magnitude.

**<B>Other**

Studies of the atomic bomb survivors suggest high doses of ionising radiation may modestly increase risk of ovarian cancer [86] but there is no consistent evidence that therapeutic or diagnostic radiation increases risk. Others have suggested associations with various occupational exposures including shift-work or sleep duration but overall the data are limited and inconclusive.

**<A>THEORIES OF CARCINOGENESIS**

The relationships described above have led to a number of theories about the mechanisms by which ovarian cancer develops. While the ovarian surface epithelium was thought to be the origin of epithelial ovarian cancers when these theories were developed, most of the processes they invoke also apply to the fallopian tube epithelium and so remain relevant.

Most commonly cited is the incessant ovulation theory which suggests that recurrent ovulation with repeated breakdown and repair of the ovarian surface epithelium (or recurrent exposure to hormone and cytokine-rich follicular fluid) increases the likehood of DNA damage and carcinogenesis [87]. Thus, the more ovulations a woman experiences in her lifetime, the greater her risk of developing ovarian cancer. Others have suggested that elevated levels of gonadotrophins stimulate proliferation of epithelium within inclusion cysts (potentially from fallopian tube epithelium) either directly or via induction of steroidogenesis resulting in greater potential for neoplastic transformation [88]. Strong inverse relationships with OC use and full-term pregnancy as well as observed pro-aptotic actions of progestins

have led others to suggest that the relative influences of reproductive hormones are the key to ovarian carcinogenesis with progestins reducing the risk of neoplastic transformation, and oestrogen (and possibly androgens) promoting malignancy [89]. It has also been suggested that chronic inflammation plays a role, with proponents of this theory pointing to the pro-inflammatroy effects of recurrent ovulation and the likely inflammatory effects of retrograde menstruation or contaminants such as talc [45]. However, None of these theories account fully for the associations documented here and this may, at least in part, relate to the histological and molecular heterogeneity of epithelial ovarian cancers with the relevance of the various processes described above varying by histological subtype.

**<TABLE 1 NEAR HERE>**

**<A>OPPORTUNITIES FOR PREVENTION**

Unfortunately, many of the factors known to influence a woman's risk of ovarian cancer (Table 1) are not amenable to modification or, like pregnancy and OC use, cannot be promoted for cancer prevention. Furthermore, the factors that can be modified such as smoking, obesity and use of MHT have a small effect and/or only influence risk of some histotypes. Accordingly, an Australian study found that only 7% of ovarian cancers could be attributed to modifiable factors and thus potentially preventable; if breastfeeding were added to the list of protective behaviours this proportion increased to 10-11% [90]. Although a British study estimated a higher proportion of ovarian cancers (21%) were potentially preventable, this used an older and much stronger estimate of the potential protective effect of breastfeeding and so may be an overestimate [91].

**<A>SURVIVAL**

We know much less about the influence of environmental factors on survival after a diagnosis of ovarian cancer. Obese women may have poorer survival than their normal weight counterparts, perhaps, in part, due to the practice of dose-capping whereby obese women are not given the full chemotherapy dose for their body-size because of toxicity concerns [92]. A recent pooled analysis suggested women who were sedentary prior to diagnosis had worse outcomes [93] and others have reported benefits for those with a more healthy diet [94]. However, these and most other studies are based on what women did prior to their diagnosis. Aside from the likely benefits of physical activity based on evidence from other cancer types [95], there is currently a lack of evidence to inform lifestyle advice for women after they are diagnosed with ovarian cancer.

[3869 words]

**SUMMARY**

Ovarian cancer remains a significant cause of morbidity and mortality globally with rising rates in many low and middle income countries and increasing case numbers in high income countries because of population aging. Five-year relative survival is below 45% and, unlike other common cancer types, the proportion of women who die from their disease has not improved substantially over time. There are several well-established risk and protective factors for epithelial ovarian cancer; most relate to reproductive and hormonal factors. Higher parity, oral contraceptive use and tubal ligation all significantly reduce risk, while family history of ovarian or breast cancer, older menopausal age, obesity, menopausal hormone therapy use, a history of endometriosis and smoking increase risk. The strength of some associations varies by histotype: endometriosis only increases risk of endometrioid and clear cell cancers while smoking only increases risk of mucinous cancers. Risk reductions may also be associated with prolonged breastfeeding, aspirin use and higher vitamin D levels but these relations require confirmation. Existing evidence does not suggest a strong role for diet or physical activity. While much is known about ovarian cancer aetiology, only a small proportion of cases can be attributed to readily modifiable factors thus avenues for prevention are currently limited. Very little is known about the relation between lifestyle and survival after a diagnosis of ovarian cancer. Additional efforts are required to better understand the causes of this cancer to facilitate risk stratification for screening and identify opportunities for preventive interventions.

## RESEARCH AGENDA

- What is the nature of the relationship between breastfeeding and risk of ovarian cancer?
- Does use of continuous-combined menopausal hormone therapy (MHT) increase risk to the same extent as sequential MHT and do the relationships differ for the different histotypes of ovarian cancer?
- Does the relationship between obesity and non-serous ovarian cancer vary by menopausal status and use of menopausal hormone therapy?
- The potential chemoprotective benefits of metformin, aspirin and vitamin D warrant further investigation.
- Does lifestyle influence the risk of ovarian cancer recurrence and/or death?

## CONFLICT OF INTEREST STATEMENT

Conflicts of interest: none.

**Figure 1.** (A) Ovarian cancer incidence and mortality rates in 2012, age-standardised to the world population, by geographic region (Drawn from [1]), (B) Ovarian cancer incidence rates, age-standardised to the world population, in selected countries over time (Drawn from [2]).

**REFERENCES**


1. Ferlay J, Soerjomataram I, Ervik M et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancerbase No. 11 [internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed 14 July 2016.
2. Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9. Lyon: International Agency for Research on Cancer; 2014. Available from: http://ci5.iarc.fr, accessed 14 July 2016.
3. Surveillance Epidemiology and End Results (SEER) Program (www.seer. cancer.gov). Seer*Stat Database: Incidence-SEER 18 Regs Research Data+Hurricane Katrina impacted Louisiana Cases, Nov 2015 sub (2000-2013). National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, April 2016.
4. Stratton J, Pharoah P, Smith SK et al. A systematic review and meta-analysis of family history and risk of ovarian cancer. Br J Obstet Gynaecol 1998;105(5):493-9.
5. Jervis S, Song H, Lee A et al. Ovarian cancer familial relative risks by tumour subtypes and by known ovarian cancer genetic susceptibility variants. J Med Genet 2014;51(2):108-13.
6. Alsop K, Fereday S, Meldrum C et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: A report from the Australian Ovarian Cancer Study Group. J Clin Oncol 2012;30(21):2654-63.
7. Boyd J. Specific keynote: Hereditary ovarian cancer: What we know. Gynecol Oncol 2003;88(1 Pt 2):S8-10.
8. Lynch HT, Casey MJ, Lynch J et al. Genetics and ovarian carcinoma. Semin Oncol 1998;25(3):265-80.

9. Ramus SJ, Song H, Dicks E et al. Germline mutations in the BRIP1, BARD1, PALB2, and NBN genes in women with ovarian cancer. J Natl Cancer Inst 2015;107(11) 10.1093/jnci/djv214.

10. Song H, Dicks E, Ramus SJ et al. Contribution of germline mutations in the RAD51B, RAD51C, and RAD51D genes to ovarian cancer in the population. J Clin Oncol 2015;33(26):2901-7.

11. Gong TT, Wu QJ, Vogtmann E et al. Age at menarche and risk of ovarian cancer: A meta-analysis of epidemiological studies. Int J Cancer 2013;132(12):2894-900.

*12. Wentzensen N, Poole EM, Trabert B et al. Ovarian cancer risk factors by histologic subtype: An analysis from the Ovarian Cancer Cohort Consortium. J Clin Oncol 2016.

13. Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk: Collaborative analysis of 12 US case-control studies. ii. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group. Am J Epidemiol 1992;136(10):1184-203.

14. Kotsopoulos J, Lubinski J, Gronwald J et al. Factors influencing ovulation and the risk of ovarian cancer in BRCA1 and BRCA2 mutation carriers. Int J Cancer 2015;137(5):1136-46.

15. Mills PK, Riordan DG, Cress RD. Epithelial ovarian cancer risk by invasiveness and cell type in the central valley of california. Gynecol Oncol 2004;95(1):215-25.

16. Whiteman DC, Siskind V, Purdie DM, Green AC. Timing of pregnancy and the risk of epithelial ovarian cancer. Cancer Epidemiol Biomarkers Prev 2003;12(1):42-6.

17. McGuire V, Hartge P, Liao LM et al. Parity and oral contraceptive use in relation to ovarian cancer risk in older women. Cancer Epidemiol Biomarkers Prev 2016;25(7):1059-63.

18. Whiteman DC, Murphy MF, Cook LS et al. Multiple births and risk of epithelial ovarian cancer. J Natl Cancer Inst 2000;92(14):1172-7.

19. Dick ML, Siskind V, Purdie DM, Green AC. Incomplete pregnancy and risk of ovarian cancer: Results from two Australian case-control studies and systematic review. Cancer Causes Control 2009;20(9):1571-85.

20. Braem MG, Onland-Moret NC, Schouten LJ et al. Multiple miscarriages are associated with the risk of ovarian cancer: Results from the European Prospective Investigation into Cancer and Nutrition. PLoS One 2012;7(5):e37141.

21. Ip S, Chung M, Raman G et al. A summary of the agency for healthcare research and quality's evidence report on breastfeeding in developed countries. Breastfeed Med 2009;4 Suppl 1:S17-30.

22. Luan NN, Wu QJ, Gong TT et al. Breastfeeding and ovarian cancer risk: A meta-analysis of epidemiologic studies. Am J Clin Nutr 2013;98(4):1020-31.

23. Jordan SJ, Siskind V, A CG et al. Breastfeeding and risk of epithelial ovarian cancer. Cancer Causes Control 2010;21(1):109-16.

24. Rizzuto I, Behrens RF, Smith LA. Risk of ovarian cancer in women treated with ovarian stimulating drugs for infertility. Cochrane Database Syst Rev 2013;8:CD008215.

25. Venn A, Watson L, Bruinsma F et al. Risk of cancer after use of fertility drugs with in-vitro fertilisation. Lancet 1999;354:1586-90.

26. Jensen A, Sharif H, Frederiksen K, Kjaer SK. Use of fertility drugs and risk of ovarian cancer: Danish population based cohort study. Br Med Journal 2009;338:b249.

27. Stewart LM, Holman CD, Finn JC et al. In vitro fertilization is associated with an increased risk of borderline ovarian tumours. Gynecol Oncol 2013;129(2):372-6.

28. Ness RB, DW C, Goodman MT et al. Infertility, fertility drugs and ovarian cancer: A pooled analysis of case-control studies. Am J Epidemiol 2002;155(3):217-24.

29. Trabert B, Lamb EJ, Scoccia B et al. Ovulation-inducing drugs and ovarian cancer risk: Results from an extended follow-up of a large united states infertility cohort. Fertil Steril 2013;100(6):1660-6.

*30. Collaborative Group on Epidemiological Studies of Ovarian Cancer, Beral V, Doll R et al. Ovarian cancer and oral contraceptives: Collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet 2008;371(9609):303-14.

31. Iodice S, Barile M, Rotmensz N et al. Oral contraceptive use and breast or ovarian cancer risk in brca1/2 carriers: A meta-analysis. Eur J Cancer 2010;46(12):2275-84.

32. The Cancer Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. The reduction in risk of ovarian cancer associated with oral-contraceptive use. New Engl J Med 1987;316(11):650-5.

33. Wilailak S, Vipupinyo C, Suraseranivong V et al. Depot medroxyprogesterone acetate and epithelial ovarian cancer: A multicentre case-control study. Br J Obstet Gynaecol 2012;119(6):672-7.

34. Urban M, Banks E, Egger S et al. Injectable and oral contraceptive use and cancers of the breast, cervix, ovary, and endometrium in black South African women: Case–control study. PLoS Med 2012;9(3):e1001182.

35. Soini T, Hurskainen R, Grenman S et al. Impact of levonorgestrel-releasing intrauterine system use on the cancer risk of the ovary and fallopian tube. Acta Oncol 2016;10.1080/0284186X.2016.1175660.

*36. Collaborative Group on Epidemiological Studies of Ovarian Cancer, Beral V, Gaitskell K et al. Menopausal hormone use and ovarian cancer risk: Individual participant meta-analysis of 52 epidemiological studies. Lancet 2015;385(9980):1835-42.

37. Pearce CL, Chung K, Pike MC, Wu AH. Increased ovarian cancer risk associated with menopausal estrogen therapy is reduced by adding a progestin. Cancer 2009;115(3):531-9.

38. Sieh W, Salvador S, McGuire V et al. Tubal ligation and the risk of ovarian cancer subtypes. Int J Epidemiol 2013;42:579-89.

39. Antoniou AC, Rookus M, Andrieu N et al. Reproductive and hormonal factors, and ovarian cancer risk for BRCA1 and BRCA2 mutation carriers: Results from the international BRCA1/2 carrier cohort study. Cancer Epidemiol Biomarkers Prev 2009;18(2):601-10.

40. Jordan SJ, Nagle CM, Coory MD et al. Has the association between hysterectomy and ovarian cancer changed over time? A systematic review and meta-analysis. Eur J Cancer 2013;49(17):3638-47.

*41. Pearce C, Templeman C, Rossing M et al. Association between endometriosis and risk of histological subtypes of ovarian cancer: A pooled analysis of case–control studies. Lancet Oncol 2012;13:385-94.

42. Brinton LA, Moghissi KS, Westhoff CL et al. Cancer risk among infertile women with androgen excess or menstrual disorders (including polycystic ovary syndrome). Fertil Steril 2010;94(5):1787-92.

43. Gottschau M, Kjaer SK, Jensen A et al. Risk of cancer among women with polycystic ovary syndrome: A Danish cohort study. Gynecol Oncol 2015;136(1):99-103.

44. Olsen CM, Green AC, Nagle CM et al. Epithelial ovarian cancer: Testing the 'androgens hypothesis'. Endocr Relat Cancer 2008;15(4):1061-8.

45. Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. J Natl Cancer Inst 1999;91(17):1459-67.

46. Rasmussen C, Kjaer S, Albieri V et al. Pelvic inflammatory disease and risk of ovarian cancer and borderline ovarian tumors: A pooled analysis of 13 case-control studies. Am J Epidemiol 2016;(in press).

47. Lee J-Y, Jeon I, Kim JW et al. Diabetes mellitus and ovarian cancer risk: A systematic review and meta-analysis of observational studies. Int J Gynecol Cancer 2013;23(3):402-12.

48. Chen H-F, Chang Y-H, Ko M-C, Li C-Y. A large scale population-based cohort study on the risk of ovarian neoplasm in patients with type 2 diabetes mellitus. Gynecol Oncol 2014;134(3):576-80.

49. Bodmer M, Becker C, Meier C et al. Use of metformin and the risk of ovarian cancer: A case-control analysis. Gynecol Oncol 2011;123(2):200-4.

50. Bonovas S, Filioussi K, Sitaras NM. Paracetamol use and risk of ovarian cancer: A meta-analysis. Br J Clin Pharmacol 2006;62(1):113-21.

51. Baandrup L, Friis S, Dehlendorff C et al. Prescription use of paracetamol and risk for ovarian cancer in Denmark. J Natl Cancer Inst 2014;106(6):dju111.

*52. Trabert B, Ness RB, Lo-Ciganic WH et al. Aspirin, nonaspirin nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: A pooled analysis in the Ovarian Cancer Association Consortium. J Natl Cancer Inst 2014;106(2):djt431.

53. Baandrup L, Kjaer SK, Olsen JH et al. Low-dose aspirin use and the risk of ovarian cancer in Denmark. Ann Oncol 2015;26(4):787-92.

*54. World Cancer Research Fund /American Institute for Cancer Research. Continuous update project report. Food, nutrition, physical activity, and the prevention of ovarian cancer. 2014. Available at http://www.dietandcancerreport.org/cup/cup_resources.php.

55. Calle EE, Kaaks R. Overweight, obesity and cancer: Epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004;4(8):579-91.

56. Collaborative Group on Epidemiological Studies of Ovarian Cancer. Ovarian cancer and body size: Individual participant meta-analysis including 25157 women with ovarian cancer from 47 epidemiological studies. PLoS Medicine 2012;9(4):e1001200.

*57. Olsen CM, Nagle CM, Whiteman DC et al. Obesity and risk of ovarian cancer subtypes: Evidence from the Ovrian Cancer Association Consortium. Endocr Relat Cancer 2013;20(2):251-62.

*58. Dixon SC, Nagle CM, Thrift AP et al. Adult body mass index and risk of ovarian cancer by subtype: A Mendelian randomization study. Int J Epidemiol 2016;DOI:10.1093/ije/dyw158.

59. Cannioto RA, Moysich KB. Epithelial ovarian cancer and recreational physical activity: A review of the epidemiological literature and implications for exercise prescription. Gynecol Oncol 2015;137(3):559-73.

60. Cannioto R, LaMonte MJ, Risch HA et al. Chronic recreational physical inactivity and epithelial ovarian cancer risk: Evidence from the Ovarian Cancer Association Consortium. Cancer Epidemiol Biomarkers Prev 2016;(in press).

61. Moore S, Lee I-M, Weiderpass E et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. JAMA Internal Medicine 2016;176(6):816-25.

62. Hildebrand JS, Gapstur SM, Gaudet MM et al. Moderate-to-vigorous physical activity and leisure-time sitting in relation to ovarian cancer risk in a large prospective us cohort. Cancer Causes Control 2015;26(11):1691-7.

63. Endogenous Hormones Breast Cancer Collaborative Group, Key TJ, Appleby PN et al. Circulating sex hormones and breast cancer risk factors in postmenopausal women: Reanalysis of 13 studies. Br J Cancer 2011;105(5):709-22.

64. Tsoref D, Panzarella T, Oza A. Aspirin in prevention of ovarian cancer: Are we at the tipping point? J Natl Cancer Inst 2014;106(2):djt453.

65. Genkinger JM, Hunter DJ, Spiegelman D et al. Alcohol intake and ovarian cancer risk: A pooled analysis of 10 cohort studies. Br J Cancer 2006;94(5):757-62.

66. Kelemen LE, Bandera EV, Terry KL et al. Recent alcohol consumption and risk of incident ovarian carcinoma: A pooled analysis of 5,342 cases and 10,358 controls from the Ovarian Cancer Association Consortium. BMC Cancer 2013;13:28.

*67. Collaborative Group on Epidemiological Studies of Ovarian Cancer, Beral V, Gaitskell K et al. Ovarian cancer and smoking: Individual participant meta-analysis including 28,114 women with ovarian cancer from 51 epidemiological studies. Lancet Oncol 2012;13(9):946-56.

68. Faber MT, Kjaer SK, Dehlendorff C et al. Cigarette smoking and risk of ovarian cancer: A pooled analysis of 21 case-control studies. Cancer Causes Control 2013;24(5):989-1004.

69. Setiawan VW, Yang HP, Pike MC et al. Type I and II endometrial cancers: Have they different risk factors? J Clin Oncol 2013;31(20):2607-18.

70. Westhoff C, Gentile G, Lee J et al. Predictors of ovarian steroid secretion in reproductive-age women. Am J Epidemiol 1996;144(4):381-8.

71. Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. Int J Cancer 1975;15(4):617-31.

72. Rose D, Boyar A, Wynder E. International comparisons of mortality rates for cancer of the breast, ovary, prostate and colon, and per capita food consumption. Cancer 1986;58:2363-71.

73. World Cancer Research Fund /American Institute for Cancer Research. Systematic literature review continuous update project report: The associations between food, nutrition and physical activity and the risk of ovarian cancer. London: 2013. Available at http://www.wcrf.org/sites/default/files/Ovarian-Cancer-SLR-2013.pdf.

74. Merritt MA, Tzoulaki I, van den Brandt PA et al. Nutrient-wide association study of 57 foods/nutrients and epithelial ovarian cancer in the European Prospective Investigation into Cancer and Nutrition Study and the Netherlands Cohort Study. Am J Clin Nutr 2015;DOI:10.3945/ajcn.115.118588.

75. Genkinger JM, Hunter DJ, Spiegelman D et al. Dairy products and ovarian cancer: A pooled analysis of 12 cohort studies. Cancer Epidemiol Biomarkers Prev 2006;15(2):364-72.

76. Ji J, Sundquist J, Sundquist K. Lactose intolerance and risk of lung, breast and ovarian cancers: Aetiological clues from a population-based study in Sweden. Br J Cancer 2015;112(1):149-52.

77. Merritt MA, Poole EM, Hankinson SE et al. Dairy food and nutrient intake in different life periods in relation to risk of ovarian cancer. Cancer Causes Control 2014;25(7):795-808.

78. Brunner RL, Wactawski-Wende J, Caan BJ et al. The effect of calcium plus vitamin D on risk for invasive cancer: Results of the Women's Health Initiative (WHI) calcium plus vitamin D randomized clinical trial. Nutr Cancer 2011;63(6):827-41.

79. Ong J, Cuellar-Partida G, Lu Y et al. Association of vitamin D levels and risk of ovarian cancer: A Mendelian randomization study. Int J Epidemiol 2016;(in press).

80. World Cancer Research Fund /American Institute for Cancer Research. Continuous update project report. Food, nutrition, physical activity and the prevention of endometrial cancer. 2013. Available at http://www.dietandcancerreport.org.

81. Yang CS, Maliakal P, Meng X. Inhibition of carcinogenesis by tea. Ann Rev Pharmacol Toxicol 2002;42:25-54.

82. Zhang M, Binns CW, Lee AH. Tea consumption and ovarian cancer risk: A case-control study in China. Cancer Epidemiol Biomarkers Prev 2002;11(8):713-8.

83. Terry KL, Karageorgi S, Shvetsov YB et al. Genital powder use and risk of ovarian cancer: A pooled analysis of 8,525 cases and 9,859 controls. Cancer Prev Res 2013;6(8):811-21.

84. Gertig DM, Hunter DJ, Cramer DW et al. Prospective study of talc use and ovarian cancer. J Natl Cancer Inst 2000;92(3):249-52.

85. Houghton SC, Reeves KW, Hankinson SE et al. Perineal powder use and risk of ovarian cancer. J Natl Cancer Inst 2014;106(9):dju208.

86. Tokuoka S, Kawai K, Shimizu Y et al. Malignant and benign ovarian neoplasms among atomic bomb survivors, hiroshima and nagasaki. J Natl Cancer Inst 1987;79(1):47-57.

87. Fathalla MF. Incessant ovulation-a factor in ovarian neoplasia? Lancet 1971;2(7716):163.

88. Cramer D, Welch WR. Determinants of ovarian cancer risk. ii. Inferences regarding pathogenesis. J Natl Cancer Inst 1983;71(4):717-21.

89. Risch H. Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone. J Natl Cancer Inst 1998;90(23):1774-86.

*90. Whiteman DC, Webb P, Green AC et al. Cancers in australia in 2010 attributable to modifiable factors: Summary and conclusions. ANZ J Publ Health 2015;39:477-84.

91. Parkin DM, Boyd L, Walker LC. 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Br J Cancer 2011;105 Suppl 2:S77-81.

92. Au-Yeung G, Webb PM, Defazio A et al. Impact of obesity on chemotherapy dosing for women with advanced stage serous ovarian cancer in the Australian Ovarian Cancer Study. Gynecol Oncol 2014;133(1):16-22.

93. Cannioto RA, LaMonte MJ, Kelemen LE et al. Recreational physical inactivity and mortality in women with invasive epithelial ovarian cancer: Evidence from the Ovarian Cancer Association Consortium. Br J Cancer 2016;115(1):95-101.

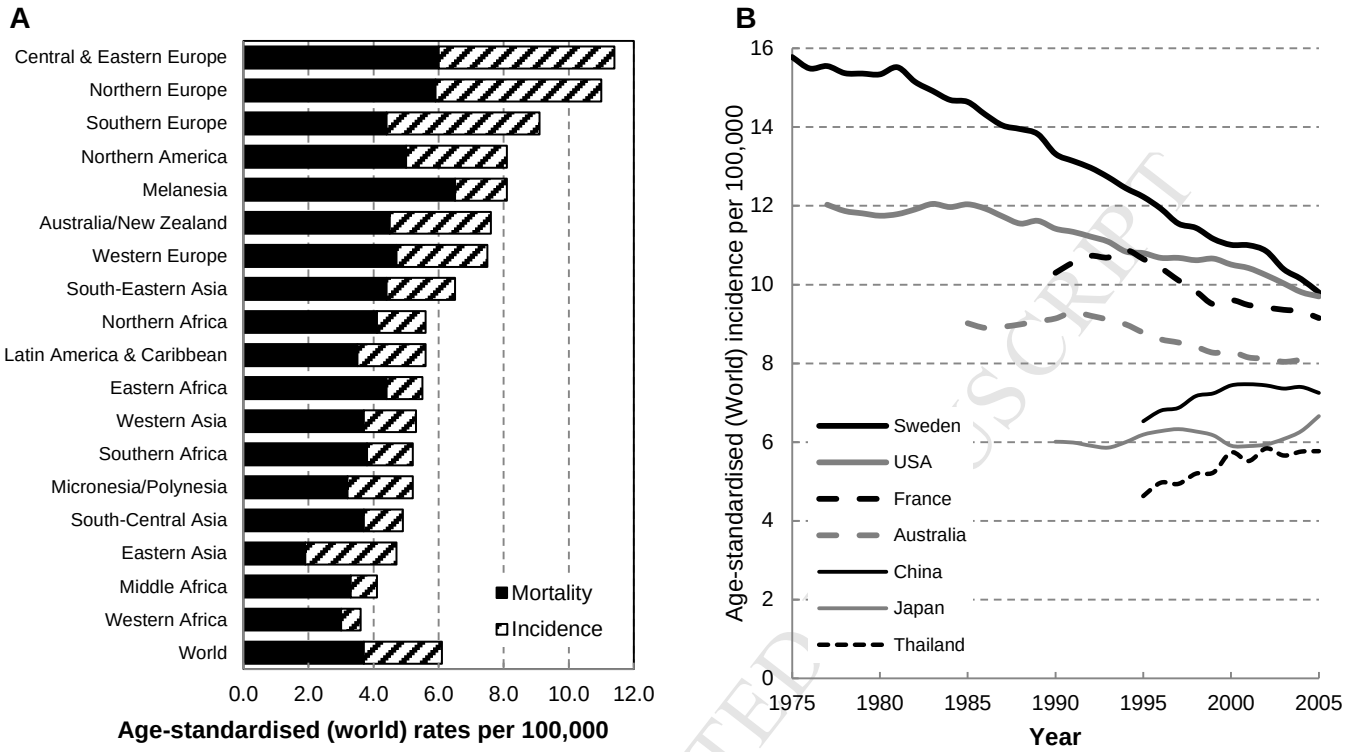
94. Poole EM, Konstantinopoulos PA, Terry KL. Prognostic implications of reproductive and lifestyle factors in ovarian cancer. Gynecol Oncol 2016;DOI:10.1016/j.ygyno.2016.05.014.

95. Bouillet T, Bigard X, Brami C et al. Role of physical activity and sport in oncology: Scientific commission of the national federation sport and cancer CAMI. Crit Rev Oncol Hematol 2015;94(1):74-86.

**Table 1.** Summary of risk and protective factors for epithelial ovarian cancer

| Association | Increase Risk | Decrease Risk |
|---|---|---|
| **Established** | Family history of ovarian cancer<br>Endometriosis (END & CCC)<br>Smoking (MUC)<br>Oestrogen-only MHT<br>Greater height<br>Obesity (non-HGSC) | Pregnancy (>6 months)<br>Oral contraceptive use<br>Tubal ligation |
| **Probable** | Older age at menopause | Breastfeeding |
| **Possible** | Younger age at menarche<br>Combined MHT<br>Pelvic inflammatory disease (borderline tumours)<br>Diabetes mellitus<br>Talc (genital use) | Older age at last birth<br>Aspirin<br>Vitamin D |
| **Unlikely or Insufficient evidence** | Infertility treatment, hysterectomy without oophorectomy, polycystic ovarian syndrome, fibroids or ovarian cysts, physical activity, alcohol intake, diet. | |

CCC: clear cell cancers; END: endometrioid cancers; HGSC: high-grade serous cancers; MHT: menopausal hormone therapy; MUC: mucinous cancers.



**Highlights**

- Ovarian cancer is a major cause of mortality and case numbers are increasing
- Five-year relative survival is below 45%
- Reproductive exposures strongly influence risk but are not readily modifiable
- Modifiable lifestyle factors have small effects or only affect risk of some histotypes
- Little is known about the relation between lifestyle and ovarian cancer survival