Open access • Journal Article • DOI:10.1016/J.BPOBGYN.2016.08.006

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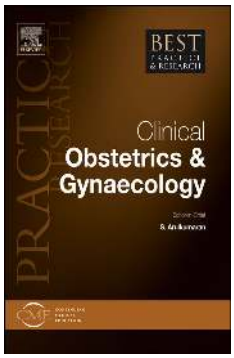
Published on: 01 May 2017 - Best Practice & Research in Clinical Obstetrics & Gynaecology (Baillière Tindall)

Topics: Epidemiology of cancer, Cancer and Ovarian cancer

Accepted Manuscript



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PII: S1521-6934(16)30091-8

DOI: 10.1016/j.bpobgyn.2016.08.006

Reference: YBEOG 1650

To appear in: *Best Practice & Research Clinical Obstetrics & Gynaecology*

Received Date: 15 August 2016

Accepted Date: 17 August 2016

Please cite this article as: Webb PM, Jordan SJ, Epidemiology of epithelial ovarian cancer, *Best Practice & Research Clinical Obstetrics & Gynaecology* (2016), doi: 10.1016/j.bpobgyn.2016.08.006.

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]).

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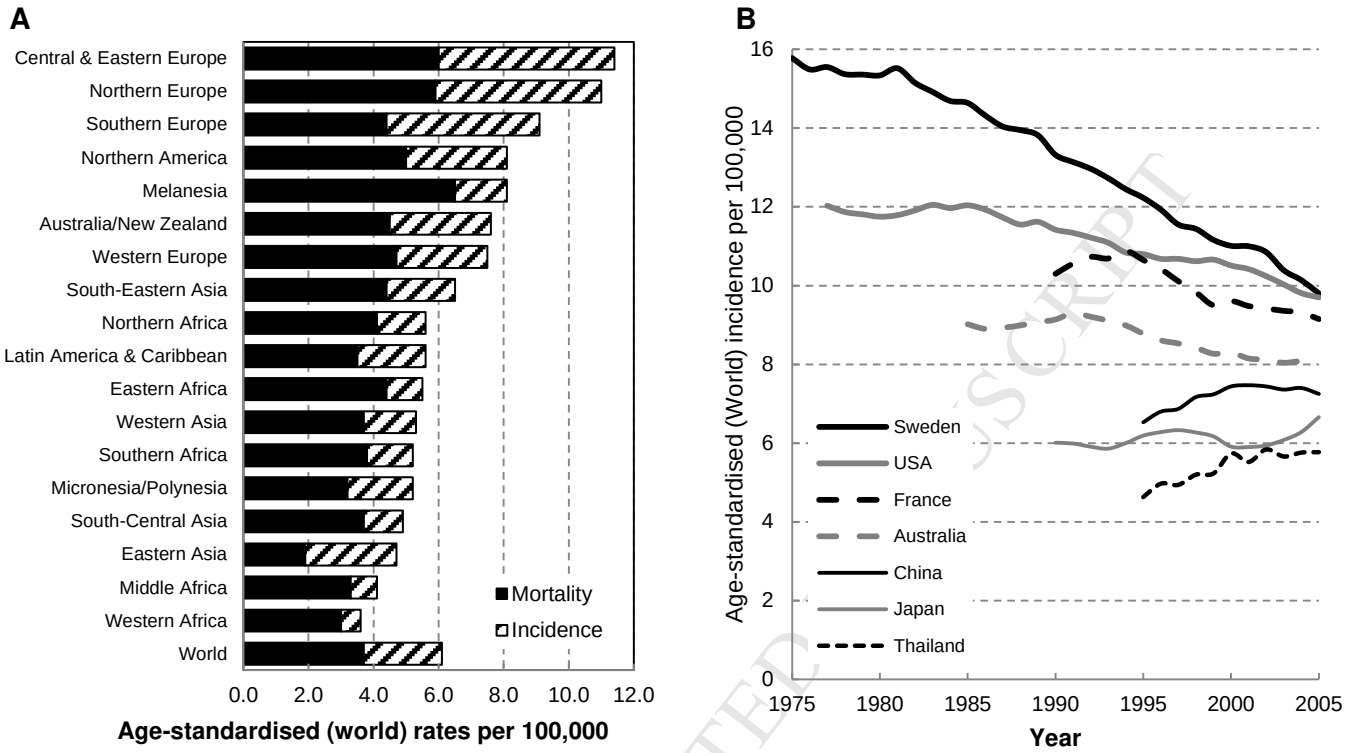
Table 1. Summary of risk and protective factors for epithelial ovarian cancer

Association	Increase Risk	Decrease Risk
Established	Family history of ovarian cancer Endometriosis (END & CCC) Smoking (MUC) Oestrogen-only MHT Greater height Obesity (non-HGSC)	Pregnancy (>6 months) Oral contraceptive use Tubal ligation
Probable	Older age at menopause	Breastfeeding
Possible	Younger age at menarche Combined MHT Pelvic inflammatory disease (borderline tumours) Diabetes mellitus Talc (genital use)	Older age at last birth Aspirin 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