**Risk Factors for Epithelial Ovarian Cancer**

Although in Australia the lifetime risk of ovarian cancer is only one in 107, it is the fifth most common cause of cancer death in Australian women. Over 90% of ovarian malignancies are thought to arise from the ovarian epithelium, while the remaining 10% include germ cell tumours, sex cord tumours and malignant teratomas. Most epidemiological research to date has focussed on the more common epithelial ovarian cancers and the following discussion is restricted to these tumours.

Much remains unknown about the pathogenesis of epithelial ovarian cancer but the two main theories implicate either incessant ovulation or high levels of circulating gonadotrophins. The strongest risk factors are increasing age and a family history of ovarian cancer, but other reproductive, medical and lifestyle factors also appear to have a significant impact on risk. In this review we summarise the current state of knowledge and uncertainty regarding non-genetic risk factors for epithelial ovarian cancer (EOC).

**Hormonal and reproductive factors**

**Oral contraceptive use**

Women who have ever taken the oral contraceptive pill (OCP) have an approximately 40% lower risk of EOC than women who have never taken the OCP. Increasing duration of use is associated with a reduction in risk of about 8% per year of use and the decrease in risk may persist for more than 20 years after cessation of OCP use. The different histological subtypes of ovarian cancer have been shown to differ with respect to some risk factors but it remains unclear whether this is the case for the effect of the contraceptive pill. Some have found a similar risk reduction for all histological subtypes but one group reported an increased risk of mucinous EOC associated with ever-use of the OCP. Whether the oral contraceptive pill decreases the risk of EOC in women with BRCA mutations also remains unclear. One case-control study has reported that OCP use was associated with a decreased risk of EOC in non-carriers but not in carriers, while a second study found significant reductions in risk with both ever use and increasing duration of use among women with BRCA1 and BRCA2 mutations. Further studies are required to clarify this important issue.

**Pregnancy**

Women who have ever been pregnant have a lower risk of ovarian cancer than women who have never been pregnant.

Moreover, the risk is reduced with increasing numbers of pregnancies such that women who have had six or more children have less than half the risk of developing ovarian cancer compared to women who have had no children. This reduction in risk is likely to be a consequence of both the suppression of ovulation and the altered hormonal milieu during pregnancy. The protective effect appears to be even greater for multiple births than for singleton pregnancies, possibly because of the higher progesterone levels associated with multiple pregnancies. A pooled analysis and a recent case-control study have both suggested that failed pregnancies (spontaneous miscarriage or induced abortion) also reduce the risk of ovarian cancer but other studies have not confirmed these results.

There is now increasing evidence that the protective effects of pregnancy are greater for women who had their last pregnancy more recently (OR 0.45, 95% CI 0.30-0.65, for pregnancy in the last year compared to pregnancy 10-14 yrs ago) or at an older age (OR=0.50, 95% CI 0.32-0.77 for >35 vs <25 years). It has been suggested that pregnancy may have the effect of clearing cells with genetic damage from the ovary. There is some suggestion that younger age at first pregnancy may increase risk of ovarian cancer but these data are less consistent.

The apparent protective effects of both pregnancy and OCP use have been attributed to the fact that both suppress ovulation. A number of studies have observed that an increase in the number of calculated lifetime ovulations is associated with an increased risk of epithelial ovarian cancer with an approximately 6% (95% CI 4-8%) increase in risk for each year of ovulation. Ovulations in the 20-29 years age group were found to be associated with a greater risk (20% increase in risk per year of ovulation, 95% CI 13-26%) suggesting that ovulations at this time in a woman’s life may be more important in the carcinogenic process than those either earlier or later in life. The effects of both pregnancy and OCP use on EOC risk are, however, greater than would be expected solely on the basis of their inhibition of ovulation.

**Breast feeding**

There is fairly consistent evidence that women who breast feed their children have a lower risk of ovarian cancer than parous women who do not breast feed, although the effects are modest with about a 1% reduction in risk for each month of breast feeding. This association may also be a consequence of the fact that breast feeding suppresses ovulation.

**Age at menarche and age at menopause**

As described above, increasing numbers of ovarian cancers are associated with higher risks of ovarian cancer. On this basis, it has been hypothesised that women with an earlier age at menarche or a later age at menopause, and therefore more potential years of ovulation, would be at increased risk of ovarian cancer. The data are, however, highly inconsistent with some studies reporting positive associations, some inverse associations and some no effect at all. It is possible that this inconsistency is a consequence of the effect described above where ovulations early and late in a woman’s reproductive life may be less relevant in terms of influencing risk of ovarian cancer.

**Hormone replacement therapy**

The use of hormone replacement therapy (HRT) has been associated with a small but significant increase in risk of EOC.
and this risk appears to increase with increasing duration of use\textsuperscript{34}. Few studies have considered the different types or regimes of HRT but a recent case-control study found that women who took oestrogen alone or oestrogen with sequential progesterone were at increased risk of EOC (OR 1.43, 95% CI 1.02-2.00 and OR 1.54, 95% CI 1.15-2.05 respectively), while those who used oestrogen with continuous progesterone were not at increased risk\textsuperscript{35}. Clarification of this issue in future studies may provide important insights into the role of reproductive hormones in the pathogenesis of this cancer.

**Infertility and infertility treatment**

There is conflicting evidence regarding the effect of infertility treatment on the risk of EOC but a recent pooled analysis of eight population-based case-control studies found no evidence of an association (OR 0.97, 95% CI 0.76-1.25)\textsuperscript{36}. Women treated with infertility drugs who do not have a subsequent pregnancy may have a small increased risk but the independent effects of different causes of infertility and the different fertility treatments are yet to be resolved.

**Medical procedures, medications and medical conditions**

**Hysterectomy and tubal ligation**

Hysterectomy and tubal ligation have been consistently associated with a 20%-50% decrease in risk of EOC\textsuperscript{37} suggesting that both of these procedures confer a protective effect against this cancer. It has been suggested that the apparent protection provided by these surgical procedures might be due to the fact that they block passage of potential carcinogens, such as talc, to the ovary.

**Medications**

Paracetamol, aspirin and NSAIDs have been associated with decreased risk in EOC in some studies\textsuperscript{26}, but the effects have been inconsistent and no significant trends of decreasing risk with increasing use have been reported. At this stage it is not possible to draw firm conclusions about the effects of these simple analgesics on the risk of EOC. It also has been suggested that some psychotropics may influence the risk of EOC by altering the release of gonadotrophins\textsuperscript{38}. Evidence for this is limited and inconsistent so it is not possible to evaluate the effect of these medications on ovarian cancer risk.

**Medical conditions**

Accumulating evidence suggests that endometriosis of the ovary may progress to EOC, particularly the endometrioid and clear cell subtypes\textsuperscript{27}. Endometriosis is a difficult exposure to assess in case-control studies but a pooled analysis of eight such studies of ovarian cancer found a self-reported history of endometriosis was associated with a 70% increased risk of ovarian cancer (OR 1.73, 95% CI 1.10-2.71)\textsuperscript{39}. The significance of this association needs further clarification with follow-up studies of women with visually diagnosed endometriosis.

Polycystic ovary syndrome (PCOS) is associated with increased production of androgens and it has been proposed that androgens may be implicated in the pathogenesis of EOC\textsuperscript{40}. This association has rarely been studied directly but one study found women with a self-reported physician diagnosis of PCOS had a significant 2.5-fold increase in risk of ovarian cancer compared to women without such a diagnosis\textsuperscript{41}. It has also been suggested that inflammatory conditions on or around the ovary may contribute to the development of EOC\textsuperscript{42}. Some evidence suggests that pelvic infection may be associated with a modest increase in risk of EOC\textsuperscript{43} but further data are required to confirm this association.

Potential effects of diabetes mellitus on steroid hormone production as well as immune function have prompted investigation of the relationship between diabetes mellitus and EOC. Current evidence suggests that such an association is unlikely\textsuperscript{44}.

**Lifestyle and diet**

**Obesity**

Obesity has been associated with changes in circulating hormone levels, particularly oestrogen and testosterone, and elevated levels of these have been implicated in the pathogenesis of ovarian cancer\textsuperscript{45}. There is consistent evidence of a small but significant effect of high body-mass index on risk of EOC (RR 1.4, 95% CI 1.2-1.6)\textsuperscript{46}. Some studies suggest this association is strongest in women diagnosed with EOC pre-menopausally\textsuperscript{47}, but further assessment is required to confirm this finding.

**Physical activity**

The effects of physical activity on risk of EOC have been investigated infrequently and the results that have been reported are inconsistent. Some have reported an increase in risk of ovarian cancer with increased levels of physical activity\textsuperscript{48} but others have found either no association or a decrease in risk\textsuperscript{49}. Current evidence suggests it does not impact significantly on ovarian cancer risk.

**Talc use**

Talc use has long been considered a potential risk for EOC because of its structural similarity to asbestos (a known human carcinogen) and the biological possibility that retrograde movement through the genital tract may allow talc to initiate inflammatory changes near or on the epithelial surface. A recent meta-analysis reported a pooled odds ratio of 1.38 (95% CI, 1.25-1.52) for use of perineal talc versus non-use but the authors found no clear evidence of an increase in risk with increasing duration of use\textsuperscript{50}. Despite the lack of dose-response, the consistency of the findings across the population-based studies suggests that use of perineal talc is associated with a small increase in risk of EOC.

**Tobacco smoking, alcohol and caffeine**

Overall, no consistent association has been observed between cigarette smoking and EOC\textsuperscript{51} but subtype-specific analyses provide fairly consistent evidence that the risk of mucinous ovarian cancer is increased by cigarette smoking (OR ~3.0 for ≥25 pack-years)\textsuperscript{52}. There is some evidence that moderate alcohol intake may decrease the risk of ovarian cancer. An American cohort study which followed post-menopausal women for 10 years, reported a significant trend of decreasing risk of EOC with increasing consumption of alcohol up to about one standard drink per day (p=0.01)\textsuperscript{53} but this finding was not replicated by a subsequent population-based case-control study\textsuperscript{54}. More recently, another American case-control study found that current alcohol drinkers had a decreased risk of ovarian cancer compared to non-drinkers (OR 0.61, 95% CI 0.39-0.94)\textsuperscript{55}. A significant trend of decreasing risk with increasing consumption (up to 14 drinks per week) was also observed (p=0.009). The effect was strongest for wine consumption. Further studies considering types of alcohol and examining effects according to histological findings are required to confirm the effects of alcohol on risk of EOC.

Coffee and tea are chemically complex beverages containing both potential carcinogens as well as chemoprotective agents\textsuperscript{56,57}. The weight of evidence suggest there may be a small
positive association between coffee drinking and the risk of EOC, however many of the associations have been weak and without clear evidence of a dose response. One study has suggested that the effect of coffee may be moderated by menopausal status but this has yet to be confirmed. Tea has been examined less frequently in relation to EOC and most studies have found no effect although one Chinese study reported a strong inverse association between tea consumption and EOC. It is thus possible that any effect of tea may depend on the type of tea (green or black) that is consumed.

**Diet**

Dietary factors that have been examined in relation to ovarian cancer risk include fruit and vegetables, eggs and dairy products as well as a range of macronutrients, such as dietary fat, and micronutrients. Limited data suggest an inverse relationship between fresh fruit and/or vegetables and ovarian cancer risk and all have found an increased risk associated with eating two or more eggs per week. The basis for this association remains speculative but one study has suggested that contamination of eggs by pesticides may possibly moderate the effect of coffee may be moderated by menopausal status but this has yet to be confirmed. Tea has been examined less frequently in relation to EOC and most studies have found no effect although one Chinese study reported a strong inverse association between tea consumption and EOC. It is thus possible that any effect of tea may depend on the type of tea (green or black) that is consumed.

**Summary and conclusions**

A summary of the main risk and protective factors for epithelial ovarian cancer is presented in table one. Aside from increasing age and a family history of breast or ovarian cancer, the most significant risk factors for epithelial ovarian cancer are those related to reproductive history. High parity and long-term use of the oral contraceptive pill confer significant decreases in risk of EOC and it is likely that this is also the case for breastfeeding. Tubal ligation, hysterectomy and possibly a diet high in fruit and vegetables also appear to reduce risk. Factors that may increase the risk of epithelial ovarian cancer include use of hormone replacement therapy, obesity, cigarette smoke (mucinous tumours only), application of talc to the perineal region, regular consumption of eggs, endometriosis and pelvic inflammatory disease.

Much, however, remains unknown about the aetiology of this disease. Many studies to date have treated epithelial ovarian cancer as a single disease and it is now clear that the different histological subtypes may differ with respect to key risk factors. Larger studies are needed in order to evaluate the risk factors for the specific subtypes. Further research is required to clarify the potential role of modifiable exposures such as diet and physical activity in the prevention of this commonly fatal disease. Additional work is also required to clarify the association between factors such as oral contraceptive use, hysterectomy and tubal ligation and ovarian cancer risk among women who carry BRCA mutations and so are at high risk of developing ovarian cancer before we can recommend these measures as preventive interventions in this group.

**REFERENCES**


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

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Association</th>
<th>Approximate relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral contraceptives</td>
<td>↓↓</td>
<td>0.4-0.6 for ≥ 5 years use</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>↓↓</td>
<td>0.5-0.7 for ever vs never pregnant</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>↓</td>
<td>0.8 for ever having breastfed</td>
</tr>
<tr>
<td>Age at menarche / menopause</td>
<td>–</td>
<td>0.8 for ever having breastfed</td>
</tr>
<tr>
<td>HRT</td>
<td>(↑) for oestrogen +/- sequential progesterone</td>
<td>0.5 – 0.8</td>
</tr>
<tr>
<td>Infertility</td>
<td>?</td>
<td>1.7-1.9</td>
</tr>
<tr>
<td>Hysterectomy / Tubal ligation</td>
<td>↓↓</td>
<td>1.2 – 1.5</td>
</tr>
<tr>
<td>Analgesics</td>
<td>?</td>
<td>1.3</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>↑</td>
<td>1.3</td>
</tr>
<tr>
<td>Polycystic ovary syndrome</td>
<td>↑</td>
<td>1.3</td>
</tr>
<tr>
<td>Obesity</td>
<td>↑</td>
<td>1.3</td>
</tr>
<tr>
<td>Smoking</td>
<td>↑ for mucinous tumours only ~3.0 for ≥ 25 pack-years</td>
<td>-</td>
</tr>
<tr>
<td>Alcohol</td>
<td>(↓)</td>
<td>-</td>
</tr>
<tr>
<td>Coffee/Tea</td>
<td>?</td>
<td>-</td>
</tr>
<tr>
<td>Diet</td>
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<tr>
<td>Fat</td>
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</tr>
<tr>
<td>Eggs</td>
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<td>2-3 for 2+ eggs per week</td>
</tr>
<tr>
<td>Vegetables</td>
<td>(↓)</td>
<td>-</td>
</tr>
</tbody>
</table>

1 Direction and approximate strength of likely and (possible) associations.