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Epidemiology of Ovarian Cancer

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Introduction

Primary carcinoma of the ovary is the fourth most common cancer among women in developed countries. In 1999, almost 7,000 new cases were reported in the United Kingdom, which equates to a lifetime risk for women of 2%. Ovarian cancer is also the most common cause of death from a gynaecological malignancy – there are about 4,500 deaths from the disease in the UK every year [1]. Worldwide, ovarian cancer incidence rates vary widely between different geographic regions and ethnic groups. The highest incidence is in Northern Europe; the lowest incidence is in Japan (Fig. 1.1). As with other cancers, there are notable increases in risk in populations that migrate from a country with low risk to a country of higher risk, indicating a possible role for dietary and environmental factors. The purpose of this article is to review the epidemiological, lifestyle and genetic factors that may be responsible for the variations in ovarian cancer risks.

Genetic Epidemiology

Familial Risks

The most significant risk factor for ovarian cancer is a family history of the disease. A meta-analysis of data from 15 case-control and cohort studies estimated that the relative risk of developing ovarian cancer for women with a single first-degree relative affected with ovarian cancer is 3.1 (95% CI = 2.6–3.7) [2]. Based on ovarian cancer incidence rates typical in northern Europe and North America,

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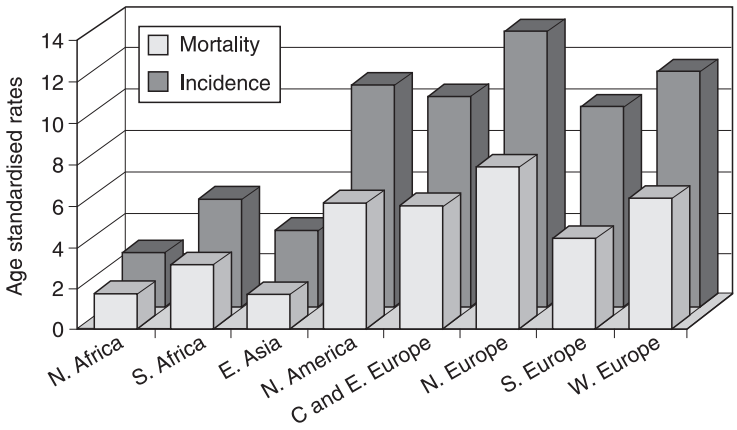

Figure 1.1 Geographical variation in incidence and mortality rates for epithelial ovarian cancer: data from the GLOBOCAN 2002 database project hosted by the Descriptive Epidemiology Group at the International Agency for Research on Cancer, Lyon, France http://www-dep.iarc.fr/.

this risk equates to a cumulative risk of 4% by age 70. This risk estimate represents an average across all ages. However, the familial risk may decline with the age at which the relative was affected and with the age of the at risk woman. In one study, the relative risk of ovarian cancer in sisters of a woman diagnosed with ovarian cancer before age 55 was 5.2 compared with 3.6 for sisters of women diagnosed after the age of 55, though this difference was not statistically significant [3].

There are varying estimates of the risks of ovarian cancer in women with two or more affected relatives. Using data from a population-based cohort study of women with two first-degree relatives with confirmed ovarian cancer, Easton *et al.* found the relative risk of death from ovarian cancer to be 24 (95% CI = 6.6–62) [4]. By contrast, Schildkraut and Thompson [5] found the relative risk of developing ovarian cancer to be 2.1 (0.20–13) for women with two affected relatives in a population-based case-control study [5]. A combined analysis of data from these studies estimated the relative risk of developing ovarian cancer to be 12 (5.3–26) for these women [2].

In another study based on women from 316 families with at least two first-degree relatives with ovarian cancer, the average relative risk of ovarian cancer was found to be 7.2 (95% CI 3.8–12). This risk declined from 16 (6.4–33) in women under 50 to 4.4 (1.6–9.5) in women 50 years of age and older, which corresponds to an absolute risk of ovarian cancer by age 70 of 11% [6].

Genetic Susceptibility to Ovarian Cancer

The two most plausible explanations for the observed association between family history and an increased risk of ovarian cancer are: (i) genetic susceptibility and (ii) environmental exposure. Despite this, family studies are not able to distinguish between genetic and non-genetic causes of familial aggregation. However, twin studies can compare the concordance of cancer between monozygotic and dizygotic twins, and have provided some information on the relative importance of genes and non-genetic factors to ovarian cancer.

The largest twin study of ovarian cancer included data on nearly 10,000 pairs of twins [7]. The ovarian cancer risk to a monozygotic twin of an affected woman was 6-fold greater, which is twice the sibling risk. This would be expected if most of the excess familial risk were due to genetic, rather than shared environmental factors.

Genetic models of familial cancer can be formally tested using segregation analysis (statistical assessment of patterns of transmission of disease within families). Such studies in ovarian cancer have provided evidence for different types of genetic effect. In one study, Houlston *et al.* analysed 462 pedigrees ascertained through an unaffected relative. They found the observed pattern of ovarian cancer was compatible with an autosomal dominant gene. The gene frequency of the abnormal allele was predicted to be 0.0015–0.0026 [8]. In contrast, an analysis of ovarian cancer families ascertained from a population-based series of ovarian cancer cases found evidence for a recessive gene [9].

High Penetrance Ovarian Cancer Susceptibility Genes

Ovarian cancer is part of the phenotype of two distinct familial cancer syndromes: hereditary breast/ovarian cancer syndrome and Lynch syndrome (hereditary non-polyposis colorectal cancer). No gene that confers increased susceptibility to ovarian cancer alone has yet been isolated, and so site-specific familial ovarian cancer and the hereditary breast ovarian cancer syndrome are considered to be part of the same spectrum.

Two genes have been identified that are responsible for most multiple case hereditary breast/ovarian cancer families: the *BRCA1* gene on chromosome 17q12–21 and the *BRCA2* gene on chromosomes 13q12–13 [10–12]. There have been many studies that have examined the contribution of *BRCA1* and *BRCA2* to hereditary breast and ovarian cancer families; but only two studies have analysed families ascertained primarily on the basis of a family history of ovarian cancer [13,14]. The largest of these was based on 112 families from the UK and suggested

that the proportion of families that were found to have a mutation varied according to the extent of the family history [13]. Mutations were present in the majority of families containing multiple cases ovarian cancer (≥3 cases) or ovarian and breast cancer (≥2 cases of both cancers), but in only 20% of families with two cases of ovarian cancer only.

There have been several studies reporting the prevalence of *BRCA1* mutations in ovarian cancer cases unselected for family history [14–18]; each study provides different estimates of mutation prevalence. In the first published study of 374 ovarian cancer cases from Southern England, 12 truncating mutations were identified (3%) [19]. A further, larger study reported a higher prevalence (8%) in 515 patients from Canada [18]. However, a substantial proportion of these mutations were in cases from the Ashkenazi Jewish or French-Canadian ethnic groups, in whom common founder mutations are known to be prevalent. In the 316 cases of British origin, only 8 (2.5%) were *BRCA1* mutation carriers. Less data are available for *BRCA2*, but the Canadian study reported 21 truncating mutations out of the total of 515 cases (4%) of which 7 occurred in the 316 cases of British origin (2.2% prevalence). The study reported by Rubin *et al.* found only one *BRCA2* mutation carrier in 116 cases [23].

The risks of developing ovarian cancer in *BRCA1/2* mutation carriers have been estimated from both familial studies and from the analysis of ovarian cancer cases unselected for a family history. For *BRCA1* carriers the lifetime risks are 16–44% and for *BRCA2* carriers 27% [19–22].

Clinical Features of BRCA1- *and* BRCA2-*Associated Ovarian Cancers*

The data looking at the association between patient outcome and *BRCA1/2* mutations status are conflicting. One study reported improved survival of *BRCA1*-associated ovarian cancer patients compared to sporadic controls [23] but was subsequently criticised for possible selection bias. Another study also reported improved survival for *BRCA1/2*-associated ovarian cancer patients presenting with stage III disease, though the result was no longer significant when early stage cases were included in a multivariate analysis that also adjusted for age at diagnosis [24]. Other studies have found no difference in survival of *BRCA1*-associated ovarian cancer in breast cancer families compared with population controls [25], and no survival difference in ovarian cancer patients from *BRCA1* and *BRCA2* ovarian cancer families compared to patients from families in which no mutation could be found [26].

Hereditary Non-Polyposis Colorectal Cancer

Hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome is characterised by marked susceptibility to malignancies of the large bowel but cancers in other organs, including the ovary, also occur frequently [27]. Cancer susceptibility in HNPCC families is the result of mutation in one of several genes that function in DNA mismatch repair pathway (*MSH2*; *MSH3*; *MLH1*; *PMS1*; *PMS2*). Mutations in *MSH2* and *MLH1* account for 70% of reported HNPCC cases with *PMS1*, *PMS2* and *MSH3* accounting for some of the rest [28]. The cumulative risk of colorectal cancer in *MMR* gene mutation carriers from *HNPCC* families is over 80%, and that of ovarian cancer 12% [29].

Low Penetrance Ovarian Cancer Susceptibility

The known ovarian cancer susceptibility genes explain approximately 10% of all ovarian cancer cases and <40% of the excess familial risks (Fig. 1.2). Thus, it is likely that other ovarian cancer susceptibility genes exist. Several genetic models may explain residual familial clustering but other highly penetrant genes are likely to be rare, because *BRCA1* and *2* are responsible for most families containing ≥3 ovarian cancer cases. Alternatively, several moderate risk genes with a combined frequency of 5% could account for the remaining excess familial risk, and for the remaining multiple case families. Finally, there may be multiple low risk (low penetrance) genes that confer relative risks of less than three.

The most widely used study design in the search for common, low-penetrance alleles is the genetic association study. The aim is to identify polymorphic genetic variants that have a direct causal effect on cancer susceptibility. There are several types of polymorphism in the human genome that may alter protein function in one of several ways; these include: (1) single nucleotide polymorphisms (SNPs) in the coding sequence of genes that lead to amino acid substitution in the protein

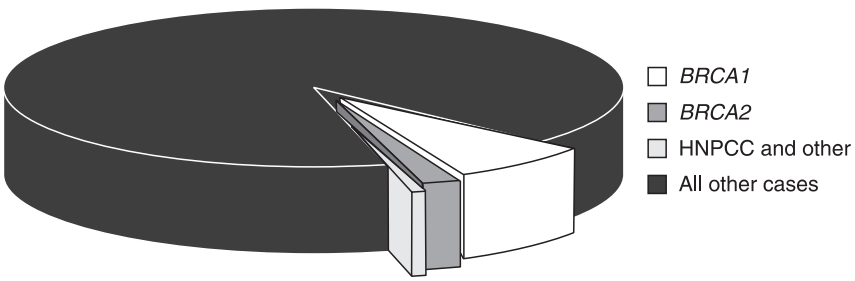

Figure 1.2 The contribution of high-risk susceptibility genes to epithelial ovarian cancer.

product and (2) polymorphisms in non-coding or regulatory sequences that may affect mRNA, expression, stability and translation.

Many candidate SNP/gene association studies for ovarian cancer have been published over the past few years; these include polymorphisms in the progesterone receptor gene (*PGR*) [30–34], the androgen receptor (*AR*) [35,36], *CYP17* [37,38], *TP53* [38–40], prohibitin [41], epoxide hydrolase [42,43], *GSTM1* *GSTP1* and *GSTT1* [44–46] and *HRAS1* [47]. Few of the published studies report results that are statistically significant; but few had sufficient statistical power to detect moderate risks even for common genetic variants. Furthermore, very few studies have used comprehensive tagging approaches to capture all the common variation in a gene. Where positive associations have been found, the case for a susceptibility allele remains unproven, due either to conflicting results from follow-up studies or because a positive result awaits confirmation in other ovarian cancer population studies. So far, positive associations include: an increased ovarian cancer risk reported for 2 *PROGINS* haplotypes [33]; a protective effect for the PGR promoter +331A allele in endometrioid ovarian tumours [34]; and an increased risk of borderline ovarian cancer associated with the pro72arg polymorphism in the *TP53* gene [41].

Reproductive and Hormonal Factors

Early Menarche and Late Menopause

There have been several epidemiological studies that have looked at age at menarche as a risk factor for ovarian cancer. In general, these have found no association [48–52].

Although no association has been found between age at menopause and ovarian cancer risk in most studies [50,53], a small number of studies have suggested that late menopause may increase risk with estimates ranging from a 1.5 to 2.9-fold increased risk in the oldest menopause groups compared with younger referents [49,52,54].

Parity

Epidemiological studies have continually shown that parity is protective against ovarian cancer. Whittemore *et al.* [50] reviewed 12 case-control studies and showed that parity had a significantly protective effect against ovarian cancer; there was an

approximately 40% reduction in risk with first birth and a further reduction of 10% with each subsequent birth.

There may also be an association with the age at first birth, although this is less clear. Some hospital-based studies suggest that an older rather than younger age at first birth is more protective [50,53,54]; but case-control studies with population-based controls indicate that the reverse is true [49,55,56].

Whilst the impact of full-term pregnancies on the ovarian cancer risk is clear, the effect of miscarriages, terminations and ectopics is not. A case-control study from Denmark found no relationship between ovarian cancer and pregnancies that fail to go to term [57]. However, other studies suggest that incomplete pregnancies confer some risk reduction, albeit a weaker protective effect than for full-term pregnancies [51,52,55].

Lactation

Most studies that have separated the effects of breast-feeding from pregnancy have demonstrated a small protective effect from lactation. Risk estimates range from between 0.6 and 0.9 in parous women who have breastfed their children compared with those who have never breastfed [50,55,57,58].

Oral Contraceptive Pill

Based on a large body of epidemiological studies, it is now accepted that the oral contraceptive pill (OC) protects against ovarian cancer. The cause of this protective effect has been put down to the cessation of ovulation and/or the decrease in gonadotrophin levels in mid-cycle. In case-control and prospective studies, 'ever' users of OCs have been shown to have a lower risk compared to never users [49–51,54,57,60,62]. The protective effect increases with duration of OC use; there is a 10–12% decrease in risk associated with a one-year OC use [62] and an approximate 50% decrease after 5 years of use [63]. The risk reduction associated with OC use continues for a long time after cessation of the OC; several studies showed a 40–70% risk reduction even 10 years after cessation of OC use [49,50,54,62]. One recent study even suggested a risk reduction after 25 years of OC use [61].

OCs confer a protective effect regardless of other known risk factors such as parity or age [60–62]. However, there does appear to be an additive effect for parity and OC use combined; Franceschi *et al.* found that women who have two children

and have taken the oral contraceptive pill for ≥5 years had a 70% risk reduction for ovarian cancer [63].

The risk reduction for OC use may also be associated with a different histological sub-type of ovarian cancer. In a case-control study that examined the effect of OC use on the risk of mucinous and non-mucinous ovarian cancer, Risch *et al.* found that the risk of mucinous ovarian cancer was not reduced in women on the combined oral contraceptive pill [64].

There is a wide variety of oral contraceptives with differing contents of oestrogens and progestins. The initial OCs of the 1960s were high-dose monophasic formulations. Hormonal doses were then reduced in the 1970s, and in the 1980s biphasic and triphasic formulations were introduced. The majority of studies showing the protective role of OCs were based on women using the early monophasic formulations. The protective effect appears to be present in newer formulations as well; use of one of two types of low-dose OC formulations (≤35 μg of ethinyl oestradiol) compared to never users was associated with a reduced relative risk of ovarian cancer of 0.7 and 0.4, respectively, and there was a risk reduction with multiphasic OCs as well [59]. In another study, in which both high and low-dose OCs reduced the risk of ovarian cancer, the high-dose regimen appeared slightly more effective [65].

A few studies that have evaluated the effect of progesterone-only contraceptives on ovarian cancer suggest a slight protective effect. In a study of 5,000 women receiving medroxyprogesterone injections with a follow-up of 4–13 years, there was an insignificant decrease in ovarian cancer risk (RR 0.8, 95% CI 0.1–4.6) [66].

The association between oral contraceptive use and ovarian cancer risk in women who are *BRCA* carriers has also been studied. In a population-based study, no association was observed between oral contraceptive use and risk reduction in high-risk women [67]. However, in a family-based study, a 60% risk reduction was observed in women with *BRCA* mutations who had been on the pill for 6 or more years [68]. More recently, in a study of 451 *BRCA1/2* mutation carriers, the odds-ratio for ovarian cancer associated with the use of oral contraceptives for 6 or more years was 0.62 (95% CI 0.35–1.09) after adjusting for parity [69].

Infertility

In 1992, a collaborative analysis of 12 US case control studies reported that the risk of ovarian cancer in nulliparous women who received fertility treatment was increased 27-fold. However, this finding should be treated with caution for

two reasons. First, the confidence intervals for this study were wide (95%, CI 2.3–315.6) [50]. Second, the individual studies that make up the collaborative analysis differ vastly in the depth with which the relevant information was collected; only 3 of the 12 studies contained results regarding infertility therapy. Since this report, a further 2 case-control studies have failed to find an association between fertility drug use and ovarian cancer [70,71]. A number of cohort studies of women undergoing fertility treatment have also failed to show an increased ovarian cancer risk associated with infertility [72–74]. In the largest of these studies, the excess risk of ovarian cancer was observed in women with unexplained infertility that had *not* had any fertility drugs [74].

There are several difficulties in study design that make this a hard question to address, and this may be responsible for some of the disparity observed between studies. For example, it is unclear whether the risk of ovarian cancer increases as women come to an age where ovarian cancer is more common or which coincides with the timing of infertility treatment. In addition, for case-control studies, there are problems associated with defining the 'infertility type', the different types of fertility drugs used and in the selection of an appropriate control group.

Hormone Replacement Therapy

Issues relating to the use of hormone replacement therapy (HRT) and its safety continue to challenge clinicians.

HRT initially contained oestradiol or conjugated oestrogens only. It then became apparent in the 1970s that the use of oestrogen therapy (ET) was associated with an increased risk of endometrial cancer. As a result, progestins were added to the ET in women with an intact uterus. ET, however, continues to be used in women who have undergone a hysterectomy.

Studies on the effect of ET/HRT on the risk of ovarian cancer are contradictory. In a recent cohort study that followed 44,241 menopausal women for approximately 20 years, a relative risk of 1.6 (95% CI 1.2–2.0) was observed among ever users compared with never users of ET [75]. The largest risk observed in this study was for women who used ET for 20 years or more: the relative risk was 3.2 (95% CI 1.7–5.7). In another study, there was an increased risk of ovarian cancer associated with ET of 10 or more years [76].

Until recently, many of the studies that examined the effect of combined HRT on ovarian cancer risk have been too small to draw firm conclusions. One such study suggested that HRT did not increase the risk of ovarian cancer if progestin was used

for more than 15 days per month [77]. The largest trial so far on the effect of HRT on ovarian cancer risk is the Women's Health Initiative (WHI) [78]. In this double-blind control trial approximately 17,000 women were randomised to either combined HRT or placebo. After an average 5.6 years of follow-up, there was a non-statistically significant increase in ovarian cancer risk in users of HRT compared to the placebo group (hazard ratio 1.58, 95% CI 0.77–3.24).

Other Factors

Age

There is a progressive increase in ovarian cancer incidence with age. For epithelial ovarian tumours, the risk of disease in women under the age of 30 is low, even in families where there is evidence of a hereditary basis for ovarian cancer. From 30 to 50 years of age, ovarian cancer incidence rises in a linear fashion. It then continues to increase, albeit at a lower rate, reaching a maximum incidence of 60.5 per 100,000 in the 75 to 79 years age group (data from the US Surveillance, Epidemiology and End Results, see Fig. 1.3).

Talcum Powder

There is some evidence to suggest that agents that irritate and inflame the ovarian epithelium promote ovarian carcinogenesis. This theory arose from

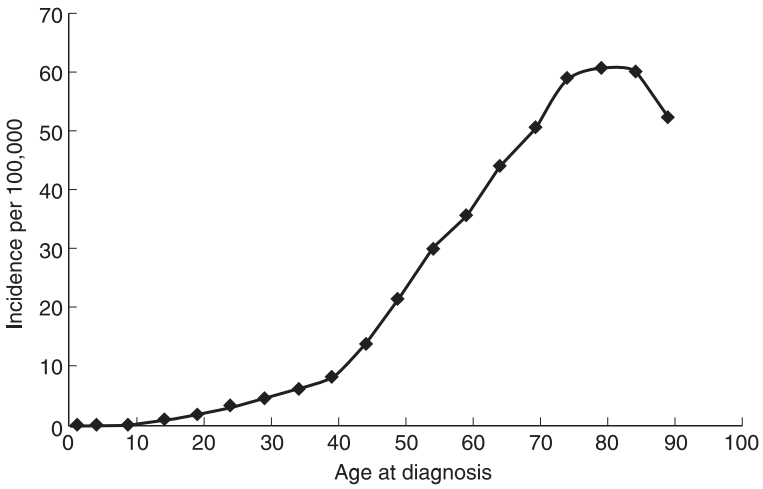

Figure 1.3 Age associated incidence of epithelial ovarian cancer.