Editorial Commentary

Identifying modifiable and non-modifiable risk factors of epithelial ovarian cancer—can we get it better?

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Ovarian cancer is the fifth most common cancer in women worldwide, with an estimated lifetime risk of one in 54–75, and one in 100 of ovarian cancer-related mortality (1). The role of irreversible and reversible risk factors in development of epithelial ovarian cancer (EOC) has been researched extensively, with a heavy focus on genetic factors and family history of breast/ovarian cancer. Ovarian cancer is one of the most heritable cancers with a three-fold increase in risk of developing ovarian cancer in women with a first degree relative (FDR) diagnosed with ovarian cancer; the relative risk (RR) is twofold higher for FDRs diagnosed younger than 50 years of age compared with those diagnosed older (4.72 *vs.* 2.53, P=0.0052), and higher for serous EOC compared to non-serous (RR 3.64 *vs.* 2.25, P=0.023) (2). The study by Kim *et al.* (3) considers the interaction between genetic [28 common single nucleotide variants (SNVs)] and environmental [oral contraceptive pill (OCP) use, parity, tubal ligation, breastfeeding, hormone replacement therapy (HRT), body BMI and endometriosis] risk factors, in 9,971 cases and 15,566 controls from 17 case-control studies included in the international Ovarian Cancer Association Consortium (OCAC).

Of non-genetic factors, hormonal factors in particular are known to play a significant role. A greater number of menstrual cycles throughout life confers a higher risk of EOC, suggesting that ovulation is involved in ovarian carcinogenesis. Ovulation-reducing factors including OCP use, pregnancy and breastfeeding are protective and ovulation-increasing factors such as early age at menarche, nulliparity, and later menopause are associated with higher risk (4). These factors have varying and interdependent effects. Pregnancies and OCP use have been found to reduce ovarian cancer risk of by 8–10% for each avoided year of ovulation, and age at menarche and menopause reduce risk for each avoided year of ovulation by 2.5% (5). The protective effect of pregnancy differs by age at first pregnancy, risk decreasing by approximately 10% for each progressive 5-year age at first childbirth, and having more than one child has been shown to significantly reduce risk of EOC, with an odds ratio (OR) of 0.6 for having 3 children and 0.5 for 4 or more (6). The risk associated with nulliparity differs depending on menopausal status, with lifetime ovulatory years being significantly associated with premenopausal women (OR =2.49) but not postmenopausal women (OR =0.88) (7).

Taking the OCP for five or more years reduces risk of EOC, with an OR of 0.56 (95% CI, 0.40–0.78) in one study for ever users (8). This effect has been observed to persist over time, and women who have taken it for more than 15 years have a 0.5% reduced cumulative incidence up to 75 years of age and 0.3% reduced mortality (4). The use of HRT has been found to have a modest effect on EOC risk. A meta-analysis of 12,110 women found the RR with <5 years of HRT to be 1.43 (95% CI, 1.31–1.56) and

1.53 (95% CI, 1.40–1.66) for serous ovarian cancer (9). They found that risk reduced the longer HRT had been stopped, but there was still a small increased risk 10 years after cessation of HRT (RR 1.25, 95% CI, 1.07–1.46, P=0.005). Meta-analysis has found tubal ligation to reduce risk for endometrioid cancers (RR =0.4) and serous cancers (RR =0.72) (10). The findings by Kim *et al.* are comparable with these figures.

The exact relationship between ovarian cancer and increased weight is unclear, with some evidence for increased risk of EOC but mixed findings regarding prognosis for those with the disease. Meta-analyses have shown obesity to be associated with increased risk of EOC (pooled effect OR =1.3, 95% CI, 1.1–1.5) and smaller effects for being overweight (OR =1.2, 95% CI, 1.0–1.3) (11). Obesity is a complex issue relating to many other variables. For example there has been shown to be significant heterogeneity (P<0.001) in the risk relating to BMI between women who have ever used HRT and those who have not (RR for never-users per 5 kg/m^2 increase in BMI =1.10, 95% CI, 1.07–1.13; P<0.001; RR for ever-users =0.95, 95% CI, 0.92–0.99; P=0.02) (12).

The link between endometriosis and ovarian cancer has been known since 1925. Conferring an up to a 3-fold increased risk, 15–20% of clear cell and endometrioid ovarian cancers are associated with endometriosis (13). A significant association has also been found with diabetes mellitus, controlling for related factors age, BMI, smoking and alcohol intake (RR 1.55, 95% CI, 1.11–2.19) (14). While alcohol is not a significant risk factor in any EOC subtypes, tobacco smoking has been found to be associated with risk of mucinous ovarian cancer alone (15).

As expected for a cancer with significant heritability, several genes have been identified as associated with increased ovarian cancer risk; most notably *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1*, *PALB2*, and *BARD1* involved in homologous recombination and *MSH2*, *MSH6*, *MLH1* and *PMS2* involved in mismatch repair as summarised previously (16). Pathogenic variants in moderate to high risk genes have been calculated to explain ovarian cancer risk in approximately 20–25% of ovarian cancers. Following identification of a pathogenic variant it is essential affected women and their families can be offered risk-reduction advice and interventions if appropriate. The use of screening for women deemed high-risk has been investigated using serum Ca-125 and transvaginal ultrasound, however impact on survival is unknown (17).

The most significant potential intervention is risk-reduction salpingo-oophorectomy (RRSO). This has been found by meta-analysis to reduce risk of ovarian/fallopian tube cancer by 80%, with greater risk reduction for women carrying pathogenic variants in *BRCA2* than those with *BRCA1* (18). The National Comprehensive Cancer Network (NCCN) recommends offering RRSO to pre-menopausal women with pathogenic *BRCA1/2* variants who have completed childbearing (19). The ages they recommend RRSO are 45–50 years for *RAD51C*, *RAD51D*, *BRIP1* and *BRCA2* carriers and 35–40 for *BRCA1* carriers (19). While research in salpingectomy alone is continuing, currently risk-reducing salpingectomy alone is not recommended outside of a clinical trial in international guidelines (19).

However, the increased risk of ovarian cancer in significant proportion of women with ovarian cancer and a strong family history of breast and/or ovarian cancer, who do not carry a pathogenic variant in a ovarian cancer predisposition gene, is unexplained. Of the genetic variants known to carry risk of ovarian cancer, the related confidence intervals of that risk are wide. Attention has turned to the contribution SNVs can make to ovarian cancer risk. Genome-wide association studies (GWAS) are well established and effective in identifying genetic loci associated with disease. The majority of variants are assumed not to be causal but to tag an area of linkage disequilibrium containing functional variants. Several GWAS to date have looked at variants associated with EOC risk, and GWAS-identified variants were calculated by Phelan *et al.* to account for approximately 6.4% of ovarian cancer risk (20).

It has been suggested that the information gained from GWAS of complex traits or diseases is surprisingly small despite large numbers of SNVs found to be reproducibly associated with phenotypes and traits, possibly because the pathophysiology of certain conditions is already well understood. One question is whether it would be better to focus on sequencing rather than divert resources into further GWAS. Annotating SNPs with information on expression has been found to increase ability to distinguish significant associations, and improve understanding of genes and relevant mechanisms. Increasingly variants within intronic regions are thought to be significant in regulating expression of target genes and therefore affecting susceptibility to disease. Long noncoding RNA (lncRNA) genes have been found to be significantly enriched at EOC risk regions, suggesting lncRNAs may be mechanistically involved in EOC predisposition and therefore be potential

candidates for integrative epidemiologic and functional studies (21).

While no results from multiplicative or additive models were significant with Bonferroni correction in Kim *et al.*'s study (3), the most notable finding the authors' discussed was the association of SNV rs13255292 and OCP use (ever *vs.* never) ($P=3.48\times10^{-4}$). Comparing OCP use (ever *vs.* never) in women with the TT genotype for this variant had an OR of 0.53 (95% CI, 0.46–0.60) *vs.* 0.71 (95% CI, 0.66–0.77) for women with the CC genotype. As the C genotype is the risk allele for ovarian cancer for this SNV longer use of OCP may help reduce risk for those with this genotype. As discussed, the cancer-related loci 8q24 has been described associated with ovarian cancer (20,22). The lncRNA PVT1, encoded by the human *PVT1* gene, is located in 8q24 and three mechanisms linked to tumorigenesis have been attributed to PVT1: interactions with MYC, DNA rearrangement, and encoding microRNA (23). The SNV rs6983267 at this region have been reported associated with increased ovarian cancer risk in premenopausal Han Chinese women (additive model: adjusted OR 1.62, 95% CI, 1.18–2.23, P=0.003), however there was no impact from OCP use (24).

The effect size of any single SNV even when significant is small. A more likely practical use of this data in advising women individually of risk reduction strategies is within a polygenic risk score (PRS) algorithm, combining all known significant SNVs, ideally also with non-genetic risk factor data. In women with breast cancer PRSs are shown to increase accuracy of estimating an individual's risk, and to improve accuracy estimation further when combined with other risk factors including mammographic density. A useful model to assess ovarian cancer cumulative risk in terms of risk factors is BOADICEA (https://pluto.srl.cam.ac.uk/cgi-bin/bd4/v4beta14/bd.cgi) (25). This assesses risk of ovarian and breast cancer from family history information and is being modified to include reproductive and hormonal data, more recently identified genes such as *PALB2* in addition to *BRCA1/2*, and a SNP PRS (25). Jervis *et al.* in 2014 investigated application of a polygenic score from an 11-SNP panel to ovarian cancer and no statistically significant relationship likely due to small number of SNPs used, although familial RR did increase with increasing PRS (2).

As technology in genetic analysis, and the statistical methods in analysing the 'big data' produced develop and adapt, studies such as Kim *et al.* (3) investigating different models and how we can use this combination of genetic and environmental risk factor data are important in determining the usefulness of this information and whether adjustment needs to be made for factors that affect both overall ovarian cancer risk and other risk factors that are included in models. At present only minor adjustment for one SNP appears necessary when combining a SNV PRS with known risk modifiers. By focusing on modifiable risk factors, as well as being aware of methods of risk reduction such as RRSO for women with high unmodifiable risk of EOC, scientists and physicians can help improve advice for women concerned about their risk of this life-threatening disease.

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Footnote

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