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The inherited genetics of ovarian and endometrial cancer

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Abstract

Endometrial and epithelial ovarian cancers are the fourth and fifth most common cancers in women in developed countries, after breast, lung, and colorectal cancer. In the United States alone, in 2008 there were about 40 000 new diagnoses of endometrial cancer and 7500 disease-related deaths. For ovarian cancer, there were about 22 000 new diagnoses and 15 000 deaths over the same period. The purpose of this article is to review the recent developments in the inherited genetics of ovarian and endometrial cancer, with particular attention to recent progress in identifying common low-penetrance susceptibility genes and their clinical implications.

Genetic predisposition

A family history of ovarian cancer confers a three to fourfold increased risk of the disease for women with a single first-degree relative affected with ovarian cancer [1]. There have been few studies of the familial risk for endometrial cancer. These have all found the endometrial cancer risk associated with having a first-degree relative affected with the disease to be elevated, with estimates of the relative risk between 1.3 and 2.8 [2-4]. In principle, familial aggregation of cancer may be caused by genetic or non-genetic factors shared within families; but twin studies suggest that genetic factors are more important [5].

Both ovarian and endometrial cancer occur as part of the same autosomal dominantly inherited syndrome, Lynch syndrome or hereditary non-polyposis colorectal cancer. Lynch syndrome is caused by germline mutation in one of several genes that function in the DNA mismatch repair (MMR) pathway, including *MLH1*, *MSH2*, *MSH6* and *PMS2* (reviewed in [6]) that predispose carriers to multiple malignancies including colorectal, endometrial, ovarian, renal, stomach, pancreas, small bowel and brain cancers. Colorectal cancer is generally regarded as the primary cancer in Lynch syndrome; but for women in Lynch syndrome families the incidence of endometrial cancer is equal to, or exceeds, that of colorectal cancer, and in more than 50% of cases, these women present with a gynaecological cancer (endometrial or ovarian cancer) as their first malignancy (Table 1) [7-9].

The *MMR* genes are the major high-penetrance susceptibility genes for endometrial cancer. For women with documented *hMLH1* and *hMSH2* germline mutations, the lifetime endometrial cancer risks are estimated to be 40–60%. In a study evaluating cancer risk in women with *hMSH6* mutations, the cumulative lifetime risk for endometrial cancer was 71% by age 70 (Table 1). The risks of ovarian cancer in *MMR* gene carriers are much lower

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than they are for endometrial cancer. A Finnish study of Lynch syndrome families estimated the cumulative lifetime risk of ovarian cancer in women with *hMLH1* or *hMSH2* mutations to be 12% [7] whilst an analysis of pooled data from four large hereditary cancer registries in Europe and the United States estimated the lifetime ovarian cancer risks in women with 'proven' or 'probable' germline MMR mutations to be 6.7% [10]. Finally, Vasen *et al.* reported a cumulative lifetime ovarian cancer risk of about 10% by age 70 in *hMLH1* or *hMSH2* mutation carriers [11].

The prevalence of Lynch syndrome in the population varies from 0.3 to 5.8%, and the population incidence is estimated to be between 1 in 660 and 1 in 2000 [12]. Recent population-based data for colorectal, endometrial and ovarian cancer cases unselected for family history suggest that *MMR* gene mutations are present in 2.2% of colorectal cancer cases [13], 2% of ovarian cancer cases unselected for age [14,15] and in 9% of endometrial cancer cases aged under 50 years [16•, 17]. Women with endometrial cancer under 50 years who also have a first-degree relative diagnosed with another Lynch syndrome related cancer have a 43% chance of carrying a *MMR* gene mutation [16•], and there is a 9% chance of carrying an *MMR* gene mutation in women from families containing two or more first-degree relatives with endometrial cancer [18].

It has been suggested that germline mutations in the *PTEN* tumour suppressor may also be associated with an increased risk of endometrial cancer; there are several case reports of women diagnosed with endometrial cancer who have germline, inactivating mutations of *PTEN* [19].

PTEN functions as a negative regulator of the phosphoinositide 3-kinase/AKT pathway for cell growth and is responsible for Cowden syndrome, a rare autosomal dominant disorder characterised by multiple hamartomas and an increased risk for breast and thyroid cancers [20,21]. However, the analysis of *PTEN* in 240 patients with pathologically confirmed endometrial carcinoma failed to identify any deleterious mutations, and so if this gene does confer susceptibility to endometrial cancer, mutations are likely to be rare [22].

The strongest known genetic risk factors for ovarian cancer are the *BRCA1* and *BRCA2* genes, which cause the hereditary breast-ovarian cancer syndrome. These two genes are responsible for the majority of families containing four or more cases of breast and/or ovarian cancer [23,24,25•]. Prevalence estimates for each of these genes in families with ovarian cancer vary considerably between studies (reviewed in [26]). The most comprehensive analysis of *BRCA1/BRCA2* in familial ovarian cancer evaluated 283 families with two of more first-degree relatives with ovarian cancer [25•]. The prevalence of *BRCA1* mutations in this study was 37%, and 9% for *BRCA2*. However, mutation prevalence was strongly associated with the extent of ovarian and breast cancer family history. A *BRCA1/BRCA2* mutation was identified in 81% families containing three or more cases of ovarian cancer and at least one case of breast cancer but in only 54% and 27% of families containing three or two cases only of ovarian cancer, respectively. Several studies have now been published in which *BRCA1* and *BRCA2* have been analysed in ovarian cancer cases unselected for a family history of the disease (see [26] for overview). In non-Ashkenazi Jewish case series the frequency of *BRCA1* and *BRCA2* mutations ranged from 3 to 10% and from 0.6 to 6%, respectively. For studies that only screened for the founder mutations in the Ashkenazi Jewish population, mutation frequencies ranged from 12 to 36% for *BRCA1* and 8 to 14% for *BRCA2*.

The cumulative risk of ovarian cancer by age 70 has been estimated at 44–63% in *BRCA1* carriers and 27–31% in *BRCA2* carriers using data from multi-case families. In contrast, the ovarian cancer risks estimated from population-based studies tend to be lower with the

average cumulative risk of ovarian cancer by age 70 in *BRCA1* carriers being 39% (95% CI, 18–54) and in *BRCA2* mutation carriers 11% (95% CI, 2.4–19) [27]. The differences in risk estimates based on multi-case family data and data from population-based case series suggest that the cancer risks associated with mutations in these genes are modified by other factors that segregate in families. These factors could include lifestyle/environment as well as genetic modifiers. Evidence for genetic modifiers of *BRCA1* and *BRCA2* associated breast cancer risks is beginning to emerge [28,29], but no modifiers of ovarian cancer risk have yet been identified.

Common moderate–low-penetrance susceptibility genes

The known high-penetrance susceptibility genes explain <40% of the excess familial risk of ovarian cancer [30]. Thus, it is likely that other ovarian cancer susceptibility genes exist. Several genetic models may explain residual familial clustering but, as most multi-case families can be explained by *BRCA1* and *BRCA2*, other highly penetrant genes are probably very rare. 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. A similar range of genetic models is also likely for endometrial cancer although evidence for residual familial clustering after accounting for known high-penetrance genes is lacking.

The most widely used study design to search for common, low-moderate penetrance alleles is the genetic association study. The aim is to identify polymorphic genetic variants that have a direct causal effect on cancer susceptibility. It is estimated that there are approximately 15 million single nucleotide polymorphisms (SNPs) in the genome with a minor allele frequency of 1% or greater, of which ~7–10 millions have a frequency of 5% or greater; and so identifying a handful of SNPs that are linked to a disease phenotype is a challenge. Two major approaches have been used: first, the candidate gene approach which uses knowledge of the putative functional role of genes in disease aetiology and looks for differences in the frequency of genetic variation within candidate genes between cases and controls, and second, the genome-wide association study (GWAS), which evaluates the frequency of hundreds of thousands genetic variants distributed throughout the genome, without any prior knowledge or selection based on putative function.

There are hundreds of published papers reporting studies based on the candidate gene approach to search for common moderate risk variants associated with ovarian and endometrial cancer risk. Genes have generally been selected from relevant biological pathways including those that control steroid hormone metabolism, DNA repair and cell cycle control, as well as known oncogenes and tumour suppressor genes. For ovarian cancer, these studies have revealed several possible genetic associations of borderline significance (e.g. for polymorphisms in *PGR* [31], *TP53* [32] and *CDKN2A* [33] (see [34] for overview)). However, none of these associations are definitive and the majority are likely to be false positive findings. The evidence for endometrial cancer is even less compelling (reviewed in [35•]).

The emergence of high-throughput, genotyping platforms, combined with ever increasing detail about genetic variation throughout the genome has enabled scientists to carry out empirical studies that evaluate common genetic variation across the genome for disease susceptibility using GWAS. The last two years has seen a plethora of GWAS for common diseases including several common cancers, notably breast, prostate and colorectal cancers [36]. At the time of writing, 27 loci with common susceptibility alleles had been reported for prostate cancer, 13 for breast cancer and 11 for colorectal cancer.

The success of GWAS has depended not only on the availability of new genotyping technologies, but also on the availability of case–control studies with large sample sizes. This has been made possible by the emergence of multi-centre consortia. The Ovarian Cancer Association Consortium (OCAC) was started in 2005 [37] and laid the foundation for a GWAS in ovarian cancer that has recently published its first results [38••]. A similar consortium has also been established for endometrial cancer with a GWAS currently in progress, but no results have yet been published. The ovarian cancer GWAS employed a standard, multi-stage design in which the SNPs genotyped in cases and controls at each stage are subjected to a process of increasingly stringent statistical sieving of putative genetic associations in order to identify SNPs that reach genome-wide levels of statistical significance ($p < 10^{-7}$) (Figure 1a). The first publication from this study reported a single common genetic susceptibility locus at chromosome 9p22.2 with the best marker being rs3814113 (Figure 1b/c). The risk allele for this SNP has a frequency of approximately 72% in European populations and confers a per-allele relative risk of 1.22. It is not known whether this SNP is the causal variant or simply a marker for the true causal variant, nor is the molecular mechanism of action known for this locus. rs3814113 lies ~44 kb upstream of *BNC2* a highly conserved, DNA-binding, zinc-finger protein that is highly expressed in the ovary and shows extensive transcriptional variability. Further analysis of the GWAS data and follow-up of the most promising loci in the OCAC has since identified an additional five susceptibility loci a 8q24, 19p13, 2q31, 3q25 and 17q21 (unpublished data) (Table 2).

Epithelial ovarian cancer exhibits substantial histopathological heterogeneity, comprising four main subtypes of invasive disease: serous, endometrioid, clear cell and mucinous. The underlying genetic basis of ovarian cancer contributes to this heterogeneity. Mutations in *BRCA1* and *BRCA2*, which are involved in double strand DNA break repair, lead to the development of serous cancers [39,40], and mutations of DNA mismatch repair genes are more frequently associated with mucinous and endometrioid ovarian cancers [41]. Ovarian tumours from patients with and without *BRCA1* or *BRCA2* mutations have also been shown to accumulate different profiles of somatic genetic alterations during their development suggesting that the germline genetic status can strongly influence the genetic make-up of cancers [42]. Disease heterogeneity is also influenced by common low-penetrance genetic variation, with rs3814113 at 9p22.2 being more strongly associated with the serous subtype than the other sub-types [38••]. For the next five common ovarian cancer susceptibility loci to be identified there is also some evidence that germline genotype influences histological subtype; four loci show stronger associations in serous cases, and one locus appears to predispose to multiple subtypes of ovarian cancer subtypes (Table 2; Figure 2).

Clinical significance of identifying genetic susceptibility loci

The clinical utility of testing for deleterious mutations in *BRCA1*, *BRCA2* and the mismatch repair genes is well established. Prophylactic total abdominal hysterectomy and/or bilateral salpingo-oophorectomy in *BRCA1/2* and *MMR* gene mutation carriers is commonly used to remove the risks of endometrial and ovarian cancer, and is recommended for women carrying mutations who have completed their families. The benefits of risk reducing surgery are clear; in Lynch Syndrome families for example, up to 33% of women who did not have surgery went on to develop endometrial cancer and 5.5% of women developed ovarian cancer [43]. However, the provision of genetic testing is often limited; in populations where there are no common, founder mutations, mutation testing is generally restricted to multi-case families because of the technical difficulties and cost of searching for mutations in large genes with complex exonic structures.

Various risk prediction models have been developed to evaluate cancer risks and likely carrier status for the *BRCA1/BRCA2* and *MMR* genes, based on mutation prevalence and

disease penetrance estimates, and family history of cancer. These models vary widely with respect to the genes they cover, the thoroughness of genetic testing, the detail of family history, the epidemiological risk factor information incorporated into the model and the statistical methodologies used in their design. For example, several algorithms that predict the likelihood of carrying a *BRCA1* or *BRCA2* mutation are currently used in clinical practice to identify such individuals. A review comparing five of these models (BOADICEA, BRCAPRO, IBIS, the Manchester scoring system and Myriad tables) and their ability to predict carrier status using 1934 families from the UK has recently been published [44•]. For Lynch syndrome, the initial Leiden (Wijnen) model, which estimated the combined probability for *MLH1* and *MSH2* gene mutations using logistic regression analysis [45], has been regularly updated, and four new models (MMRpro, PREMM, Barnetson and AIFEG) have recently been developed and validated (reviewed in [46]). It is likely that these models will become more sophisticated and effective at predicting disease risk as the body of research data on which they rely both improves and starts to incorporate genetic (and possibly epigenetic) information emerging from genome-wide scans to identify new susceptibility loci. Advances in technology that enable much more rapid and accurate sequence analysis of candidate genes are likely to lead to less selective testing with the potential to identify significant numbers of women in the population that are at high risk of ovarian and endometrial cancer.

Currently, the clinical benefits of testing for common low-penetrance susceptibility alleles for ovarian and endometrial cancer are unclear. Only a handful of common susceptibility loci have so far been identified for ovarian cancer and none for endometrial cancer, and the modest increases in risk associated with these risk alleles are too small to provide clinically useful information. Recently, Pharoah *et al.* described the potential value of using multiple, low-penetrance susceptibility alleles to refine screening and early detection strategies for breast cancer [47••]. Given the likelihood that more common, low-penetrance loci will emerge over the next few years it is conceivable that a similar ‘polygenic’ approach might be applied to ovarian and endometrial cancers. However, the efficacy of screening for these cancers has not yet been established, and so any strategies for targeted screening based on genetic risk prediction will need to be developed alongside new and validated approaches to screening.

For patients with endometrial cancer, disease is often diagnosed at an early stage when it is associated with a good prognosis, and so it is not clear whether screening would improve morbidity or survival in these women. Ovarian cancer is more frequently diagnosed at the later stages, and so early detection of the disease would potentially save many lives, particularly if a genetic screening approach could be used to identify the proportion of the population that would benefit most from screening. Multi-centre clinical trials are currently underway in the UK and United States to explore the benefit of frequent screening (every three to four months) for detecting early-stage ovarian cancers in high-risk women [48]. Clinical trials are also ongoing to test the effect of screening on mortality from ovarian cancer in the general population. For example the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) is a randomised controlled trial involving more than 200 0000 post-menopausal women; in a recent interim report, the trial has demonstrated the feasibility of large scale ovarian cancer screening and suggested that using multi-model screening (using serum CA125 or trans-vaginal ultrasound) is more sensitive at detecting early-stage ovarian cancers compared to screening by ultrasound alone [49].

Finally, it is also likely that identifying common genetic susceptibility alleles will lead to a greater understanding of disease aetiology, potentially leading to the development of more effective, individualised therapies for ovarian and endometrial cancers. This has been exemplified for cancers associated with the *BRCA1* and *BRCA2* mutations genes. The

subsequent functional characterisation of *BRCA1* and *BRCA2* has led to the development of a potential novel therapy for patients deficient in *BRCA1/BRCA2* function based on the inhibition of the poly (ADP-ribose) polymerase (PARP) DNA repair pathway. In a phase 1 clinical trial, oral olaparib, that inhibits PARP, significantly reduced tumours burden in ovarian cancer *BRCA1/BRCA2* carriers [50].

Conclusions

Our understanding of the molecular basis of inherited susceptibility to ovarian cancer has changed substantially in the past few years and similar changes are likely to happen for endometrial cancer in the foreseeable future. The clinical utility of these findings is yet to be clarified, but there is no doubt that they will provide clues about the molecular mechanisms of disease that may help improve treatment of these cancers.

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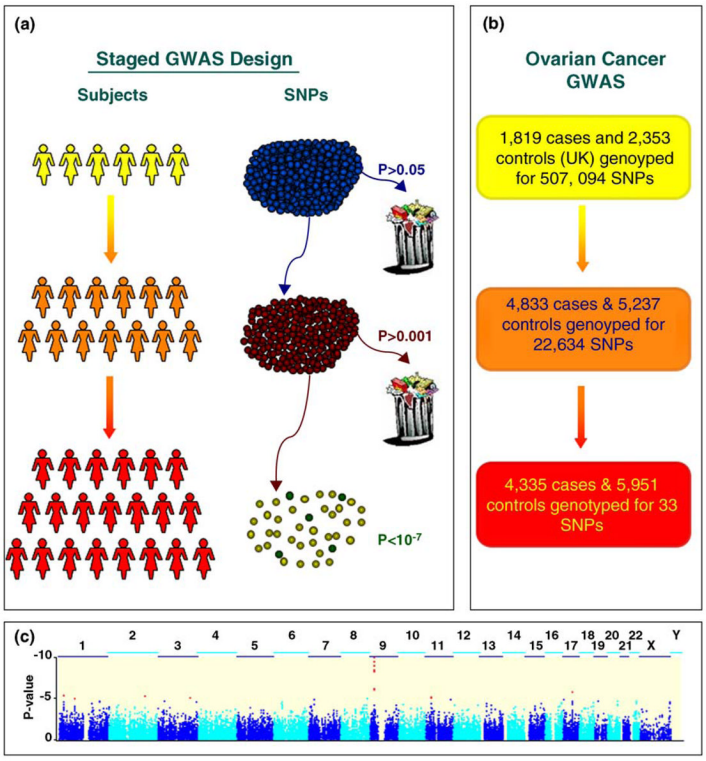

Figure 1.

Genome-wide association study (GWAS) design applied to epithelial ovarian cancer to identify common low-moderate susceptibility alleles for the disease. **(a)** As with many other genome-wide association studies, a staged study design was used in the first published GWAS for ovarian cancer [38••]. Here, a large number of SNPs are genotyped in a restricted number of subjects in a first stage, followed by statistical sieving to identify a proportion of putative associated SNPs. These SNPs then undergo validation in a larger series of subjects in stage 2 followed by more stringent statistical selection to identify a limited number of SNPs for further validation in additional cases and controls in stage 3. **(b)** Details of the ovarian cancer GWAS, which has so far included approximately 11 000 invasive epithelial ovarian cancer cases and more than 13 000 unaffected controls from 29 different ovarian cancer studies that are part of the International Ovarian Cancer Association Consortium (OCAC) ([38••] and unpublished data). **(c)** A Manhattan plot illustrating the genotyping data in a combined stage 1 and stage 2 analysis of more than 22 000 SNPs, according to statistical significance (*p*-value). Red spots indicate the most significant SNPs at $p < 10^{-5}$; note the series of correlated, statistically significant SNPs at the 9p22 locus, suggesting the location of the first common susceptibility locus identified for ovarian cancer [38••].

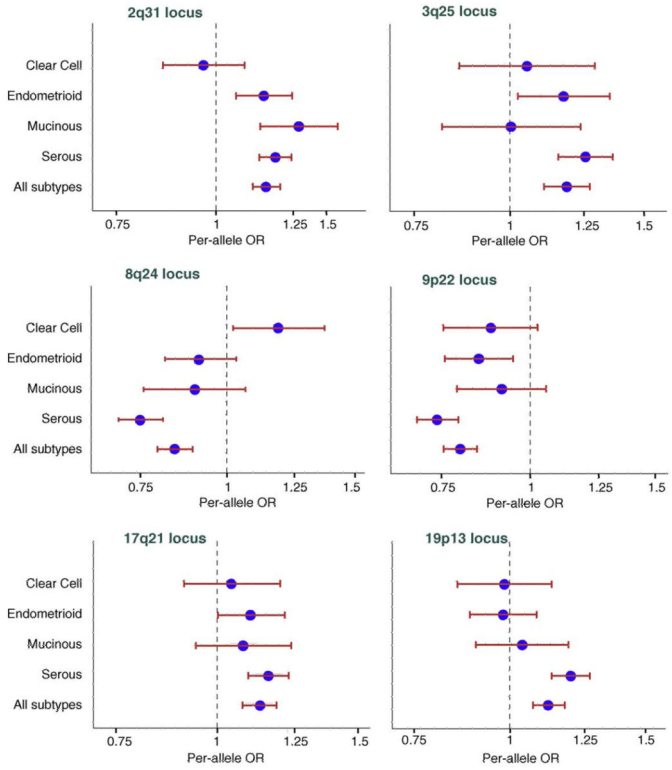

Figure 2.

Analysis of SNPs genotyped for the six most significant ovarian cancer susceptibility loci after stratifying cases according to the four main histological subtypes (serous, mucinous, endometrioid and clear cell). These data suggest substantial genetic heterogeneity. The strength of association is stronger in serous-only ovarian cancer cases compared to all other subtypes for five of the six loci. For the 8q24 and 19p13 loci, the effects appear to be specific to the serous subtype without any evidence of association for other subtypes. The only locus that shows evidence of association for additional subtypes is the 2q31 locus; the data suggest risk associations in mucinous and endometrioid ovarian cancer cases, as well as the serous subtype ([38••] and unpublished data).

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Table 1

Lifetime cumulative risks of colorectal and endometrial cancer in Lynch syndrome

Study	Gene defect	Colorectal cancer Cumulative lifetime risk	Endometrial cancer Cumulative lifetime risk
Dunlop *et al.* [51]	*hMLM* and *hMSH2*	Men 74% Women 30%	42%
Aarnio *et al.* [7]	*hMLH1* and *hMSH2*	Men 100% Women 54%	60%
Vasen *et al.* [52]	*hMLH1* and *hMSH2*	Men 92% Women 83%	42% (*hMLH1*); 61% (*hMSH2*)
Hendriks *et al.* [53]	*hMLH1*	Men 65% Women 53%	27%
	hMSH2	Men 65% Women 53%	40%
	hMSH6	Men 69% Women 30%	71%
Hampel *et al.* [54]	*hMLH1* and *hMSH2*	Men 69% Women 52%	54%
Baglietto *et al.* [55]	*hMSH6*	Men 44% Women 20%	44%
Choi *et al.* [56]	*hMLH1* and *hMSH2*	Men 67% Women 51 %	–

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Table 2

Novel common genetic susceptibility loci associated with histological heterogeneity, recently identified in a genome-wide association study of ovarian cancer ([38••] and unpublished data)

Locus	SNP	Risk allele frequency	Non-serous cases		Serous cases	
			Odds ratio	95% CI	Odds ratio	95% CI
9p22	rs3814113	0.72	1.14	1.08–1.20	1.30	1.23–1.37
2q31	rs2072590	0.32	1.10	1.05–1.16	1.19	1.14–1.25
3q25	rs2665390	0.08	1.13	1.04–1.24	1.25	1.15–1.35
8q24	rs10088218	0.88	1.06	0.98–1.14	1.30	1.23–1.41
17q21	rs9303542	0.27	1.06	1.01–1.12	1.15	1.09–1.20
19p13	rs8170	0.18	1.04	0.97–1.02	1.18	1.12–1.25