Genetic Epidemiology of Ovarian Cancer and Prospects for Polygenic Risk Prediction

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Summary: Epithelial ovarian cancer (EOC) is a heterogeneous disease with a major heritable component. The different histotypes of invasive disease – high grade serous, clear cell, endometrioid and mucinous – are associated with different underlying genetic susceptibility and epidemiological and lifestyle risk factors, all of which contribute to the different biology and clinical characteristics of each histotype. A combination of familial and population based sequencing studies, and genome wide association studies (GWAS) have identified a range of genetic susceptibility alleles for EOC comprising rare but highly pentrant genes (e.g. *BRCA1*, *BRCA2*) that are responsible familial clustering of ovarian cancer cases; more moderate penetrance susceptibility genes (e.g. *BRIP1*, *RAD51C/D*, *MSH6*); and multiple common but low pentrance susceptibility alleles identified by GWAS. Identifying genetic risk alleles for ovarian cancer has had a significant impact on disease prevention strategies; for example it is now routine clinical practice for individuals with germline *BRCA1* and *BRCA2* mutations to undergo risk reducing salpingo-oophorectomy. Because ovarian cancers are commonly diagnosed at a late clinical stage when the prognosis is poor, the continued development of genetic risk prediction and prevention strategies will represent an important approach to reduce

mortality due to ovarian cancer. Advances in genomics technologies that enable more high-throughout genetic testing, combined with research studies that identify additional EOC risk alleles will likely provide further opportunities to establish polygenic risk prediction approaches, based on combinations of rare high/moderate penetrance susceptibility genes and common, low penetrance susceptibility alleles. This article reviews the current literature describing the genetic and epidemiological components of ovarian cancer risk, and discusses both the opportunities and challenges in using this information for clinical risk prediction and prevention.

Epithelial Ovarian Cancer: The Clinical and Public Health Challenge:

Epithelial ovarian cancer (EOC) causes around 125,000 deaths globally per year. Over the last 40 years, long term survival rates have changed very little. About 70% of women with ovarian cancer are diagnosed with advanced stage disease (stages III/IV), of whom only ~30% will survive more than 5 years. By contrast, women diagnosed with earlier stage (stage 1) disease have a 5-year survival rate >90%. Our understanding of the biology if EOC is limited, and complicated by disease heterogeneity. Invasive EOC represents 90% of all malignant ovarian tumors and comprises four major histological subtypes; high-grade serous, endometrioid, clear cell and mucinous which have different clinical courses and survival rates. The most common histotype is high-grade serous ovarian cancer (HGSOC) and these cases represent the major clinical problem. The different histotypes probably have distinct cells of origin and can be characterized by different germline and somatic genetic changes that result in the perturbation of different molecular pathways. Even within the different histotypes there is likely to be substantial clinical and molecular heterogeneity [1, 2]. The standard treatment for EOC consists of maximal cytoreductive surgery followed by administration of platinum and taxane-based chemotherapy. Most patients with advanced stage (III/IV) HGSOC initially respond well to primary treatment with surgery and chemotherapy; but cancer usually recurs with a drug-resistant phenotype.

Given the greatly improved survival rates associated with early stage ovarian cancer, clinical intervention strategies that either detect EOC at the earliest most treatable stages, or prevention strategies for women at greatest risk may be effective approaches to reduce the burden of EOC. Unfortunately, signs and symptoms of ovarian cancer are usually absent in early stage disease. Even when they are present, symptoms are often subtle and may vary by EOC histotype [3]. There are currently no effective screening approaches for detecting early stage EOC. Serum CA-125 testing is useful for differential disease diagnosis, but has not been shown to be an effective early-stage screening approach due to its low sensitivity and specificity [4, 5]. HE4 is another candidate ovarian cancer screening marker, although it has not been extensively tested in clinical trials [6]. Vaginal ultrasonography can also be used to detect adnexal masses consistent with ovarian cancer, but once again this does not ppear to be effective for detecting early stage EOC [7]. Using a combinations of genetic, epidemiology and lifestyle risk

factors to identify women at greatest risk of EOC in the population, followed by effective clinical intervention strategies could represent a powerful population based strategy to reduce mortality associated with the disease

Genetic Epidemiology of Epithelial Ovarian Cancer

Epidemiological and lifestyle risk factors: Several epidemiologic studies have suggested that exposure to endogenous and exogenous hormones play an important role in ovarian cancer etiology [8]. Oral contraceptive (OC) use [9] and parity [10] are both protective, with decreasing risks associated with increasing duration of OC use and increasing parity. Younger age at menarche, breastfeeding and hysterectomy are associated with a reduction in EOC risk, while the use of menopausal hormone therapy (MHT) (particularly estrogen only therapy), is associated with an increase in EOC risk [9, 11-16]. In a large trial, long-term post-menopausal hormone use was associated with increased EOC risk [17], which is consistent with several cohort studies [18-21]. A meta-analysis indicated a 20% increase in ovarian cancer risk per 5 years of postmenopausal estrogen use [12]. Tubal ligation is another well-established EOC risk factor [22] which is inversely associated with EOC risk.

Some risk factors have been reported to be asociated with specific histotypes of ovairan cancer. Olsen et al. (2013) found obesity to be weakly associated with an increased risk of low-grade serous invasive tumors but there was no association with invasive high-grade serous ovarian cancer [23]. In the same study, high body mass index (BMI) was associated with increased risk of borderline serous, invasive endometrioid, and invasive mucinous ovarian cancer histotypes. It is also well established that endometriosis is risk factor for clear cell and endometrioid ovarian cancer, but not for high-grade serous or mucinous histotypes [24]. A meta-analysis has found an association between smoking and mucinous EOCs, an inverse association for risks of endometrioid and clear cell EOCs, and no association with high-grade and borderline serous histotypes [25]. Menopausal hormone therapy appears to be more associated with an increased risk of serous and possibly endometrioid histotypes compared to other subtypes [15, 18]. Finally, oral contraceptive use (ever/never) is associated

with reduced risk for the serous and endometrioid subtypes, with a suggestive, but not significant, increase in risk in mucinous and clear cell EOC [15]. Recent larger studies have reported reduced risk in all subtypes other than mucinous with oral contraceptive use, and an increase in risk of mucinous as duration of oral contraceptive use increases [26, 27].

Germline genetic risk factors: Family history remains one of the strongest EOC risk factors. A woman with a first-degree relative with ovarian cancer has a three-fold increased risk of developing the disease compared to women with no family history. Studies of twins show that the majority of this familial ovarian cancer risk is due to inherited genetic factors, rather than environmental and lifestyle factors shared within families [28]. Inheriting damaging mutations high risk ovarian cancer susceptibility genes is the strongest predictor of inherited risk for ovarian cancer. Mutations in two genes, *BRCA1* [29] and *BRCA2* [30], confer high-penetrance susceptibility to both ovarian and breast cancer [30, 31]. The risks of ovarian cancer conferred by *BRCA1* and *BRCA2* mutations have been estimated from both family and population based studies. In family studies, the cumulative risk of ovarian cancer by age 80 years are estimated to be 44% in *BRCA1* mutation carriers and 17% in *BRCA2* mutation carriers [32]. Risk estimates are generally lower in population based studies; in a combined analysis of 22 different studies average ovarian cancer risks were 39% (95% confidence interval (CI) 18%–54%) in *BRCA1*-mutation carriers and 11% (2.4%–19%) in *BRCA2*-mutation carriers [33]. The prevalence of mutations in these genes also contributes to the different risk of EOC observed in different populations. For example, *BRCA1* and *BRCA2* mutations are more prevalent in Ashkenzi Jewish populations and so average lifetime risks are high in this population (54% for *BRCA1* and 23% for *BRCA2*) [34]. These genes are responsible for most families containing multiple cases of breast and ovarian cancer [35, 36] and combined they account for approximately a third of the heritable risk of ovarian cancer [37]. However, in a study of 283 ovarian cancer families, only 27 percent of families containing just two first degree relatives with EOC were due to *BRCA1* or *BRCA2* mutations, which demonstrated that other ovarian cancer susceptibility alleles were likely to exist [36].

Several studies have reported that risks of ovarian and breast cancer vary depending on the location of the predicted pathogenic mutation in both *BRCA1* and *BRCA2 [38-42]*. A recent study of ~12,000 *BRCA1* carriers and 7,000 *BRCA2* carriers with breast and/or ovarian cancer indicated there are

increases in ovarian cancer risks with a concomitant decrease in breast cancer risk for mutations in the central portion both *BRCA1* and *BRCA2 [32, 38-42]*. Consistent with these findings, germline *BRCA* murine models have shown different phenotypes for different *BRCA* mutations [43, 44]. Other studies have shown that common low penetrant susceptibility alleles in other genes can modify the risks of ovarian and breast cancer in *BRCA1* and *BRCA2* mutation carriers [45, 46].

Germline *BRCA1/BRCA2* mutations are observed in all non-mucinous histologic subtypes of ovarian cancer [37], but are most commonly associated with the development of the HGSOC histotype [36, 38, 47-49], with around 15% HGSOC patients carrying mutations in these genes. Typically, HGSOCs are highly genomically unstable and inevitably acquire somatic *TP53* mutations during the early stages of tumor development. The BRCA1 and BRCA2 proteins are involved in the maintenance of genome stability by regulating the expression of genes critical for the repair of DNA double-strand breaks (DNA-DSB) via homologous recombination and regulation of cell growth and division [50]. Double strand DNA breaks are usually introduced by DNA damaging agents such as free radicals or ionizing radiation and the conversion of single strand breaks into double strand breaks by the collapse of the replication fork during DNA replication leading to global genomic instability [51]. Next generation sequencing (NGS) approaches, including whole genome and exome sequencing and targeted gene sequencing in large epidemiological case-control series have recently identifed additional ovarian cancer susceptibility genes. Focusing particularly on DNA-DSB repair genes that complex with BRCA1 and/or BRCA2, these studies have identified *RAD51C*, *RAD51D, BRIP1* and *FANCM* as likely susceptibility genes particularly for the HGSOC histotype (**Figure 1**) [51-59]. Relative risk estimates for pathogenic mutations in these genes are more modest than BRCA1/BRCA2 ranging from ~2 for FANCM, ~4 for RAD51C, ~7 for RAD51D and ~11 for BRIP1 [51-59].

Another class of genes associated with susceptibility to ovarian cancer are the DNA mismatch repair genes (MMR). Mutations in these genes are more commonly associated with Lynch Syndrome, or hereditary non-polyposis colorectal cancer (HNPCC). This autosomal dominant syndrome is associated with increased risks of gynecological cancers, in particular endometrial cancer and the endometrioid and clear cell subtypes of ovarian cancer [60]. In the largest population-based study to estimate the prevalence of mutations in MMR genes in ovarian cancer cases, *MSH2* and *MSH6* in

particular showed increased prevalence of germline mutations, largely in non-serous ovarian cancer cases [61, 62], and more recently a small number of cases with mutations in *PMS2* [47] and *MLH1* [63] have been identified. Lifetime risk for ovarian cancer in Lynch Syndrome patients varies depending on the mutation. By age 70 risk in MLH1 is 4-20%, MSH2 (7.5-20% and MSH6 (0-13.5%) [64, 65].

Common low penetrance susceptibility alleles: There has been substantial progress in identifying common risk variants for ovarian cancer using genome wide association studies (GWAS). These studies have so far identified thirty-nine independant EOC risk regions (**Table 1**) [45, 46, 66-76], with each risk region associated with only modest increases in risk (relative risk less than 1.3 per risk allele carried). The majority of common variant risk alleles so far identified are associated with the HGSOC subtype, probably because this is most common subtype; but some loci identified confer risk to other subtypes including mucinous [74, 76], clear cell [69, 71, 76], endometrioid [76] and low-grade serous histotypes [70, 76] (**Figure 2**). There is also evidence of pleiotropy, in which the same genetic variants or different variants in the same genomic region confer risk to two or more ovarian cancer subtypes and even other cancers, particularly breast and prostate cancers [77-79]. These data suggest there may be common functional mechanisms underlying the development multiple phenotypes associated with some common variant susceptibility loci.

The vast majority of confirmed common variant risk alleles are located in the non-protein-coding genome and the likely functional mechanisms are through epigenomic regulation of one or more target susceptibility genes. Where functional evidence for a target susceptibility gene at a risk locus has emerged, the data suggests that the biology of ovarian cancer development at common variant risk loci differs from that of the high and moderate pentrance genes, in that the genes are not directly involved in DNA repair. For example, functional studies have identified: *HNF1B* (hepatocyte nuclear factor 1 homeobox B) at the 17q12 locus as a target gene for serous and clear cell EOC subtypes, and for prostate cancer [71, 79]; the Homeobox gene *HOXD9* at 2q31 as a target in high-grade serous and mucinous ovarian cancer [74, 80]; *PAX8* (Paired box gene 8) on chromosome 2p13 associated with mucinous ovarian cancer [74]; *ABHD8* (abhydrolase domain containing 8 gene) on chromosome 19p13 associated with both ovarian and breast cancer development [81]; and *OBFC1* (oligonucleotide/ oligosaccharide-binding fold containing 1) at chromosome 10q24 associated with low-grade serous

ovarian cancer [76]. Of the thirty nine risk loci identified by GWAS evidence implicating a functional gene has been reported at eight loci (Table 1), demonstrating the significant amount of biology yet to be identified.

Missing Heritability: The studies summarized above report on a range of susceptibility genes and risk alleles for ovarian cancer of both varying allele frequency and risks in the population (**Figure 3**). However, the known susceptibility genes for ovarian cancer account for ~40% of the excess familial risks (narrow sense heritability), with common low risk variants found by GWAS contributing less than 5% [82] (**Figure 4**). Thus, less than half the heritable component of EOC has been characterized. The remaining risk is probably due to multiple alleles including common genetic variants (>5% in the population) conferring weak effects (relative risks <1.2), and uncommon (1-5%) and rare variants (<1%) conferring weak to moderate effects with relative risks less than ten

Germline genetic variation and clinical outcome in EOC patients*:* There is now substantial evidence that germline genetic alleles of *BRCA1* and *BRCA2* influence overall survival in EOC cancer cases, likely due to enhanced platinum sensitivity conferred through a breakdown in DNA repair mechanisms [37, 83, 84]. The most comprehensive of these studies showed that *BRCA1* and *BRCA2* mutation carriers have a more favorable short survival than non-carriers after adjusting for stage, grade, histology and age at diagnosis (*BRCA1*, HR=0.73, $P=2\times10^{-5}$; *BRCA2*, HR = 0.49, $P=3\times10^{-10}$) [84]. However, more recent studies have suggested that these survival advantages to not persist, particularly in *BRCA1* carriers [85-87]. To date, there is only weak evidence that that common, low penetrance susceptibility variants may also influence overall survival in ovarian cancer patients [88-92].

Finding EOC susceptibility alleles associated with disease risk and outcome could have significant impacts in the clinical management of ovarian cancer cases. For example, such findings could lead to the development of novel therapies for EOC and/or may influence their disease management after stratifying patients by their germline genotypes. Indeed, the functional characterization of *BRCA1*/*2,* has already led to the development of a novel therapy for *BRCA1/BRCA2* carriers based on synthetic lethality and inhibition of the poly (ADP-ribose) polymerase (PARP) DNA repair pathway. Phase I and II trials for PARP inhibitors (commonly known as olaparib) show that PARP inhibition significantly

reduces EOC tumour burden in *BRCA1/2* carriers, and Phase III trials are underway [93, 94]. Several PARP inhibitors now have FDA approval for use in EOC, for both treatment (NCT01286987)[95] and maintenance [96, 97], in platinum sensitive and platinum resistant EOC [98, 99].

Clincial Risk Predicton and Prevention of Epithelial Ovarian Cancers

One of the successful advances in reducing EOC mortality over the last few years has come from identifying germline genetic variants that substantially increase a woman's lifetime risk of disease. As discussed above, *BRCA1* and *BRCA2* genes are the strongest known genetic risk factors for ovarian cancer. The clinical utility of BRCA genetic testing in healthy women to inform risk reducing interventions is now well established; prophylactic bilateral salpingo-oophorectomy is commonly used to reduce EOC risks in mutation carriers, and is generally offered to BRCA1 carriers by age 40 and to BRCA2 carriers by age 45 (NCCN Guidelines 2.2017). The application of cascade testing in family members of probands has become an important intervention to prevent future cases of EOC [100]. However, the population benefits of genetic testing are limited by the low population frequency of *BRCA1*/*BRCA2* mutations; together they have a prevalence of approximately 1 in 400 in non-ashkenazi Jewish individuals in general populations of European decent and 1/40 for Ashkenazi Jewish individuals [101].

Advances in next generation sequencing technologies now enable very rapid cost-effective sequence analysis of susceptibility genes for clinical use. Panel testing for known or suspected susceptibility genes is already commonly used in clinical practice, and gene panel tests for ovarian cancer have been marketed by many companies. Two different models of testing are in place; traditional gene or panel testing ordered by the patients' physician and often billed through insurance, and a direct-to-consumer model has more recently been developed where the test is ordered by the provider and the consumer meets testing costs. The development of panel testing to include *BRCA1* and *BRCA2* genes after the U.S. Supreme Court invalidated claims of Myriad Genetics with respect to the patenting of these genes in 2013, and the development of next generation sequencing methods has driven down sequencing costs has resulted in broader panels of genes being available for testing. However, there are important issues in the application of panel testing [102]. For example, for many genes included in these panels the evidence that predicted pathogenic mutations are truly associated with disease is

often weak (e.g. *PALB2, BARD1, NBN*) [56]. For other recently identified susceptibility genes (e.g. *BRIP1*, *RAD51C*, *RAD51D, MSH6*) [47, 56, 57], the evidence of association with ovarian cancer risk may be strong, but the published estimates of disease penetrance associatd with mutations are imprecise, which diminishes their utlity for genetic counselling of identified carriers. Recent updates to the NCCN Guidelines recommend the consideration of risk reducing salpingo-oophorectomy in carriers of such moderate risk genes [103], although it has been suggested that this intervention be delayed until the lifetime risk of such mutation carriers exceeds 2.6%, the lifetime risk of a woman with a non-BRCA family history of ovarian cancer [104].

The clincial utility of genetic data is further hampered by the lack of functional 'proof' that germine genetic variants are disease causing, even if they are predicted to lead to protein truncation. Large population based targeted sequencing studies performed by the research community have amplified these concerns. A recent aggregation analysis of high-quality exome sequencing of the protein-coding genomes in 60,706 mainly disease free individuals identified more than 7 million high-quality sequence variants [105]. Of these, 179,774 different variants were predicted with high-confidence to be protein truncating variants (PTVs) through the introduction of a stop codon, frameshift, or the disruption of an essential splice site. This corresponded to an average of 85 heterozygous and 35 homozygous PTVs per individual [105]. The implication is that the human genome can tolerate a multitude of PTVs without obvious consequences on health, and so there can be no assumption of pathogencitiy when a protein coding variant is classified as a PTV.

Recent genetic epidemiological studies in which thousands of ovarian cancer cases and controls have been sequenced for panels of genes, have highlighted this issue [56, 57]. Sequence analysis of several genes that function in the same DNA double strand DNA break repair pathway as *BRCA1* and *BRCA2* (*BRIP1, NBN1, PALB2, BARD1, RAD51B, RAD51C* and *RAD51D*), were found to have PTVs in ovarian cancer cases. In some genes (e.g. *NBN1*) there was no difference in the frequency of PTVs between cases and controls, suggesting that coding mutations do not confer disease susceptibility. For other genes (e.g. *PALB2*, *BARD1* and *RAD51B*) there was some evidence of slightly increased ovarian cancer risks associated with PTVs, but because mutations in these genes were very rare, extremely large sample sizes will be needed to determine if mutations in these genes are truly

associated with ovarian cancer risk [56].

Another outstanding issue is the variable penetrance associated with different PTVs in the same gene and the impact this might have on clinical risk prediction. As described above, different mutations in *BRCA1* and *BRCA2* based on their location appear to confer different risks of breast and ovarian cancer. While most PTVs in *BRCA1* and *BRCA2* generally confer high penetrant disease risks, other PTVs in these genes may be associated with much lower risks. For example the average cumulative risk estimates by age 70 years for PTVs in the *BRCA2* gene range from 45% for breast cancer to 11% for ovarian cancer. There are, however, examples of PTVs, particularly those towards to the 3' end of the gene, such as K3326X, a nonsense mutation located at the 3' end of *BRCA2,* being associated with much lower breast and ovarian cancer risks. A recent analysis that included more than ~76,000 cancer patients and ~84,000 controls, found the K3326X variant to be a low pentrance susceptibility allele for triple-negative breast cancer (OR = 1.52) and serous invasive ovarian cancer (OR = 1.46) [106] which are considerable lower risk estimates than for other PTVs throughout this gene. It is likely that this tolerance of K3326X is reflective of the potential tolerance of proteins missing a small number of amino acids from the terminal of the BRCA2 protein, highlighting the difficulty in interpretation of PTVs, particularly those towards the 3' end of the coding region of the gene.

Polygenic and epidemiological risk prediction: Ultimately, a womans risk of ovarian cancer will be determined by a combination of genetic and epidemiological risk factors. The known susceptibility alleles identified so far account for less than half of the heritable component of ovarian cancer. It is likely that population based next generation sequencing studies will continue to identify alleles of moderate penetrance for ovarian cancer, although it is unlikely that other high penetrance genes similar to *BRCA1* and *BRCA2* exist. It is also anticipated that hundreds or even thousands of additional common variants conferring marginal risk associations for ovarian cancer remain to be identified [107]. Establishing a polygenic risk score (PRS) that incorporates a multitude of genetic variants could have significant clinical value in risk prediction and prevention approaches to ovarian cancer in the population.

One recent study estimated the impact on the risk estimates of *BRIP1* mutation carriers after incorporating additional genetic and epidemiological risk factor information [56]. Assuming the best

estimate to be the point estimate from segregation analysis performed in familes carrying *BRIP1* mutations, the lifetime risk of epithelial ovarian cancer in *BRIP1* carriers was estimated to be 5.8%. After, incorporting information for eighteen common risk alleles for ovarian cancer, women at the 80th centile of the polygenic risk distribution based on those 18 alleles would have an expected lifetime risk of 7.2% per cent. After incorporating other risk factors for ovarian cancer into the polygenic model, specifically oral contraceptive pill use, tubal ligation, parity, a history of endometriosis and family history after removing the component due to the known genes, the lifetime risk at the 80th centile of the risk distribution increased 8.2% [56].

In summary, the clinical benefits of genetic risk prediction for carriers of high penetrance mutations in *BRCA1* and *BRCA2* cannot be questioned; over the last two decades, risk reducing surgery in *BRCA1/BRCA2* mutation carriers has probably had a greater impact than any other clinical intervention in reducing mortality due to ovarian cancer. However, major challenges remain in translating *BRCA1* and *BRCA2* testing on a population scale, and in incorporating the information from for additional genetic and epidemiological risk factors for more refined risk prediction strategies. For risk alleles of more moderate pentrance, many clinical questions remain including, including: (1) Are disease risk estimates substantial and accurate enough to warrant clinical inteventions given that the only recommended clincial intervention is risk reducing surgery? (2) In the future, will functional analyses improve our understanding of the clinical significance of ovarian cancer risk variants to improve the accuracy of genetic risk prediction? (3) For individuals at more intermediate risk, what are the clinical options to reduce those risks? For example are chemopreventive strategies (e.g. oral contraceptive use) an alternative option to risk reducing surgery where the size of the elevated risks are not suffficent to warrant surgical intervention?

Table 1. Confirmed common variant susceptibility regions identified for epithelial ovarian cancer, by subtype.

Locus	Subtype[#]	Top SNP	OR (95%CI)	P-value	Coding Gene[§]	Ref.
1p36.12	Invasive EOC-BRCA1	rs56318008	1.11 (1.07-1.16)	7.6×10^{-9}	***CDC42***	[46, 80]
1p34.3	Invasive EOC-BRCA1	rs58722170	1.08 (1.04-1.12)	2.7×10^{-12}	***CDCA8***	[46, 80]
2q13	BrCa-PrCa-OvCa	rs17041869	0.94 (0.93–0.96)	5.1×10^{-9}	BCL2L11	[77]
2q13	MOC	rs752590	1.34 (1.21–1.49)	3.3×10^{-8}	PAX8	[74]
2q13	Invasive EOC-BRCA1	rs2165109	1.09 (1.05 – 1.12)	4.2×10^{-8}	ACOXL	[76]
2q31	HGSOC	rs2072590	1.14 (1.10-1.19)	3.7×10^{-13}	***HOXD9***	[67, 80]
	MOC	rs711830	1.30 (1.20–1.40)	7.5×10^{-12}		[74]
3q22.3	MOC	rs112071820	1.29 (1.20 – 1.37)	1.5×10^{-13}	BPESC1	[76]
3q25	HGSOC	rs7651446	1.59 (1.48-1.70)	1.5×10^{-38}	TiPARP	[69]
3q28	LMP-SOC	rs9870207	1.19 (1.12 – 1.27)	4.5×10^{-8}	GMNC	[76]
4q32.3	Invasive EOC-BRCA1	rs4691139	1.20 (1.17–1.38)	3.4×10^{-8}	TRIM61	[45]
4q32.3	LMP-SOC	rs13113999	1.23 (1.14 – 1.32)	4.7×10^{-8}	TLL1	[76]
4q26	Invasive EOC	rs17329882	1.09 (1.06-1.13)	1.4×10^{-8}	SYNPO2	[46]
5p15.15	HGSOC	rs10069690	1.14 (1.10-1.19)	7.6×10^{-11}	TERT	[70]
	LMP-SOC	rs7705526	1.51 (1.36–1.67)	1.34×10^{-11}		
5q12.3	EnOC	rs555025179	1.18 (1.11 – 1.26)	4.5×10^{-8}	MAST4	[76]
6p22.1	Invasive EOC-BRCA1	rs116133110[4]	0.93 (0.91-0.97)	3.0×10^{-8}	GPX6	[46]
8q21	HGSOC	rs11782652	1.24 (1.16-1.32)	5.6×10^{-11}	CHMP4C	[69]
8q21.11	LMP-SOC	rs150293538	2.19 (1.65 – 2.90)	2.0×10^{-9}	ZFHX4	[76]
8q24	HGSOC	rs10088218	0.77 (0.73-0.82)	1.6×10^{-20}	***MYC***	[67, 80]
8q24.21	Invasive EOC-BRCA1	rs9886651	1.08 (1.05 – 1.11)	3.5×10^{-9}	PVT1	[76]
9p22	HGSOC	rs3814113	0.79 (0.76-0.82)	2.7×10^{-34}	BNC2	[66]
9q22.33	Invasive EOC	rs1413299	1.53 (1.25–1.86)	$1.88\ 10^{-8}$	COL15A1/ TGFBR1	[73]
9q31	BrCa-OvCa	rs200182588	0.96 (0.94–0.98)	8.9×10^{-9}	SMC2	[75]
9q31.1	MOC	rs320203	1.29 (1.18 – 1.41)	1.7×10^{-8}	GRIN3A	[76]
9q34.2	Invasive EOC-BRCA1	rs635634	1.11 (1.07-1.16)	4.4×10^{-9}	ABO	[46]
10p11.21	Invasive EOC	rs1192691	0.89 (0.73–1.07)	$2.62\ 10^{-8}$	NAMPTL/ ANKRD30A	[73]
10p12	HGSOC	rs1243180	1.10 (1.06-1.14)	1.2×10^{-9}	MLLT10	[69]
10q24.33	LMP-SOC	rs7902587	1.29 (1.18 – 1.41)	4.0×10^{-8}	***OBFC1***	[76]
11q12	BrCa-PrCa-OvCa	rs7937840	1.05 (1.03–1.06)	5.0×10^{-9}	INCENP	[75]
12q24.31	Invasive EOC-BRCA1	rs7953249	1.08 (1.06 – 1.11)	1.1×10^{-9}	HNF1A	[76]
15q26	BrCa-OvCa	rs8037137	1.07 (1.05–1.10)	9.1×10^{-10}	RCCD1	[75]
17q11.2	Invasive EOC-BRCA1	chr17:29181220:I5	0.91 (0.88-0.94)	2.6×10^{-9}	ATAD5	[46]
17q12	CCOC	rs11651755	0.80 (0.72-0.88)	2.9×10^{-8}	***HNF1B***	[69, 71, 79]
	HGSOC	rs757210	1.11 (1.07-1.15)	8.2×10^{-9}		
17q21.31	HGSOC	rs183211	1.11 (1.07-1.16)	1.6×10^{-7}	PLEKHM1	[72]
17q21.32	HGSOC	rs9303542	1.14 (1.10-1.19)	4.0×10^{-12}	SKAP1	[69]
18q11.2	LMP-SOC	rs8098244	1.19 (1.12 – 1.27)	3.9×10^{-8}	LAMA3	[76]
19p13	Br, Pr, Ov	rs1469713	0.96 (0.95–0.97)	3.4×10^{-10}	GATAD2A	[75]
19p13	HGSOC	rs4808075	1.18 (1.13-1.23)	2.9×10^{-14}	***ABHD8***	[68, 81]
19q13.2	MOC	rs688187	0.67 (0.60–0.75)	6.8×10^{-13}	IFNL3	[74]
22q12.1	HGSOC	rs6005807	1.17 (1.11 – 1.23)	4.5×10^{-9}	CHEK2	[76]

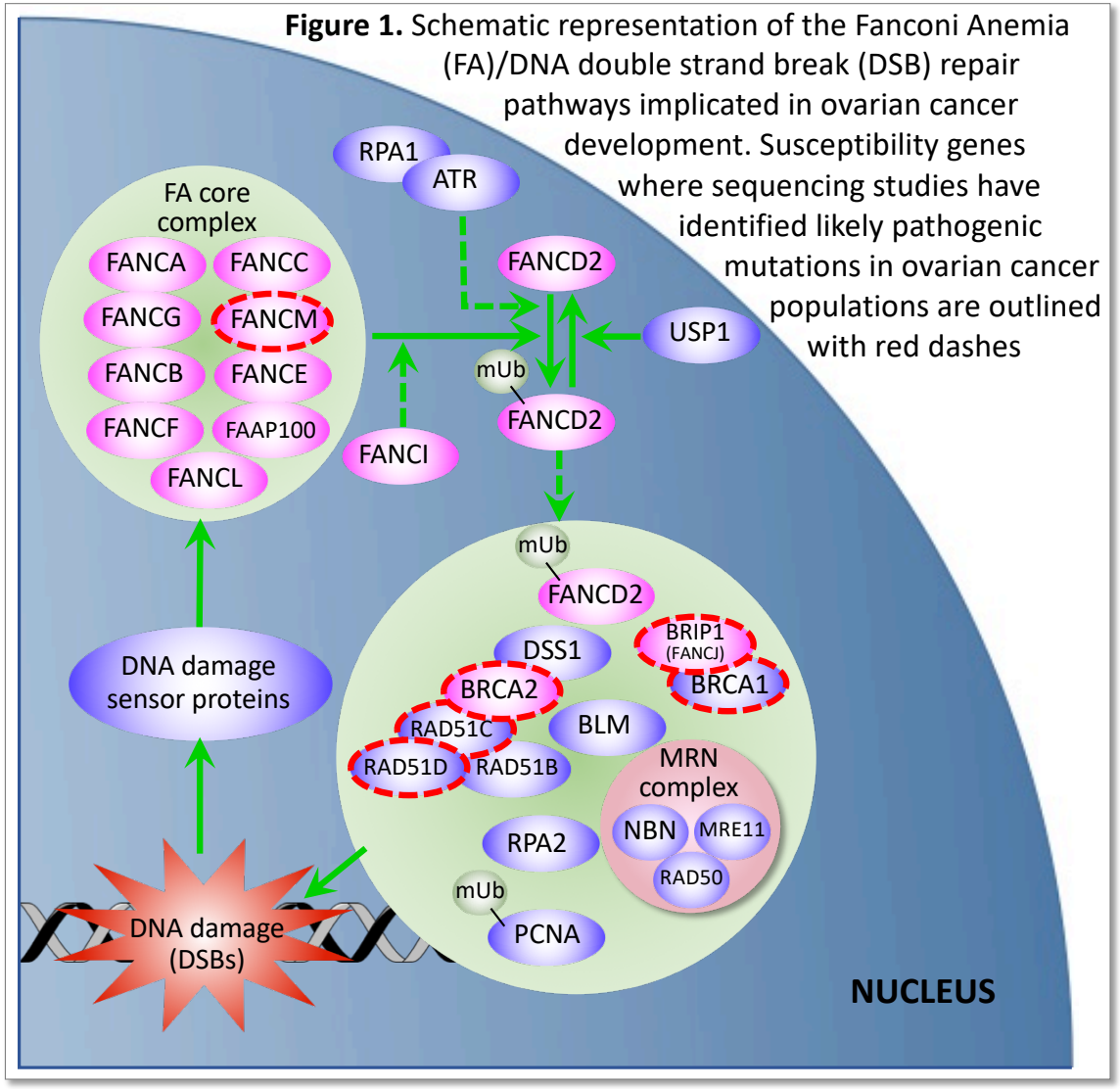
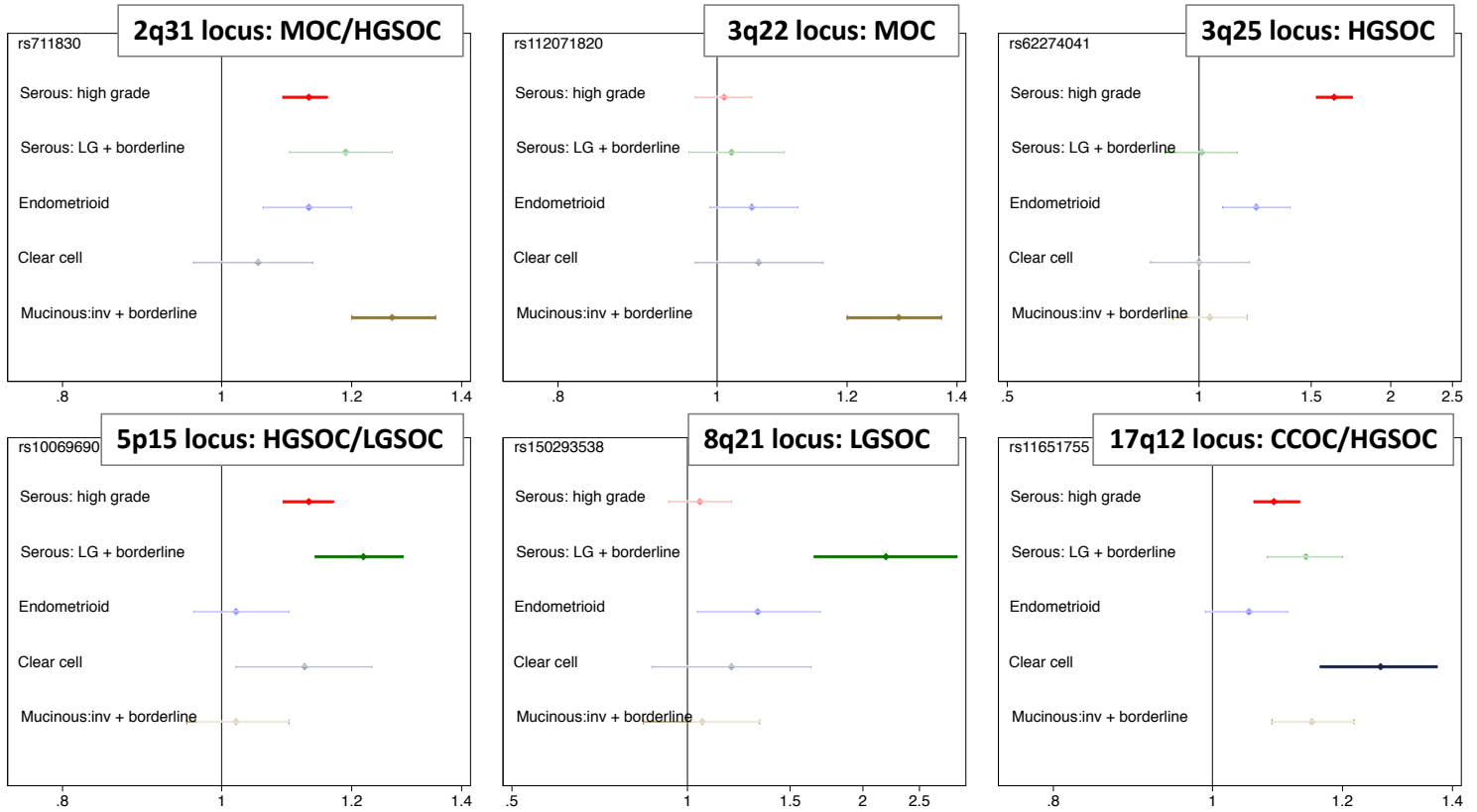


Figure 1. Schematic representation of the Fanconi Anemia (FA)/DNA double strand break (DSB) repair pathways implicated in ovarian cancer development. Susceptibility genes where sequencing studies have identified likely pathogenic mutations in ovarian cancer populations are outlined with red dashes

Figure 2. Histotype-specific associations (odds ratios) of the top SNP in six EOC susceptibility regions. The forest plots show the point estimates of odds ratios with the 95% confidence interval around each estimate. For each locus, the highlighted odds ratios and confidence intervals correspond to histotype associations at genome side significance ($P< 5x10^{-8}$). Key to ovarian cancer (OC) histotypes: M, mucinous; HGS, high grade serous; LGS, low grade serous; clear cell.



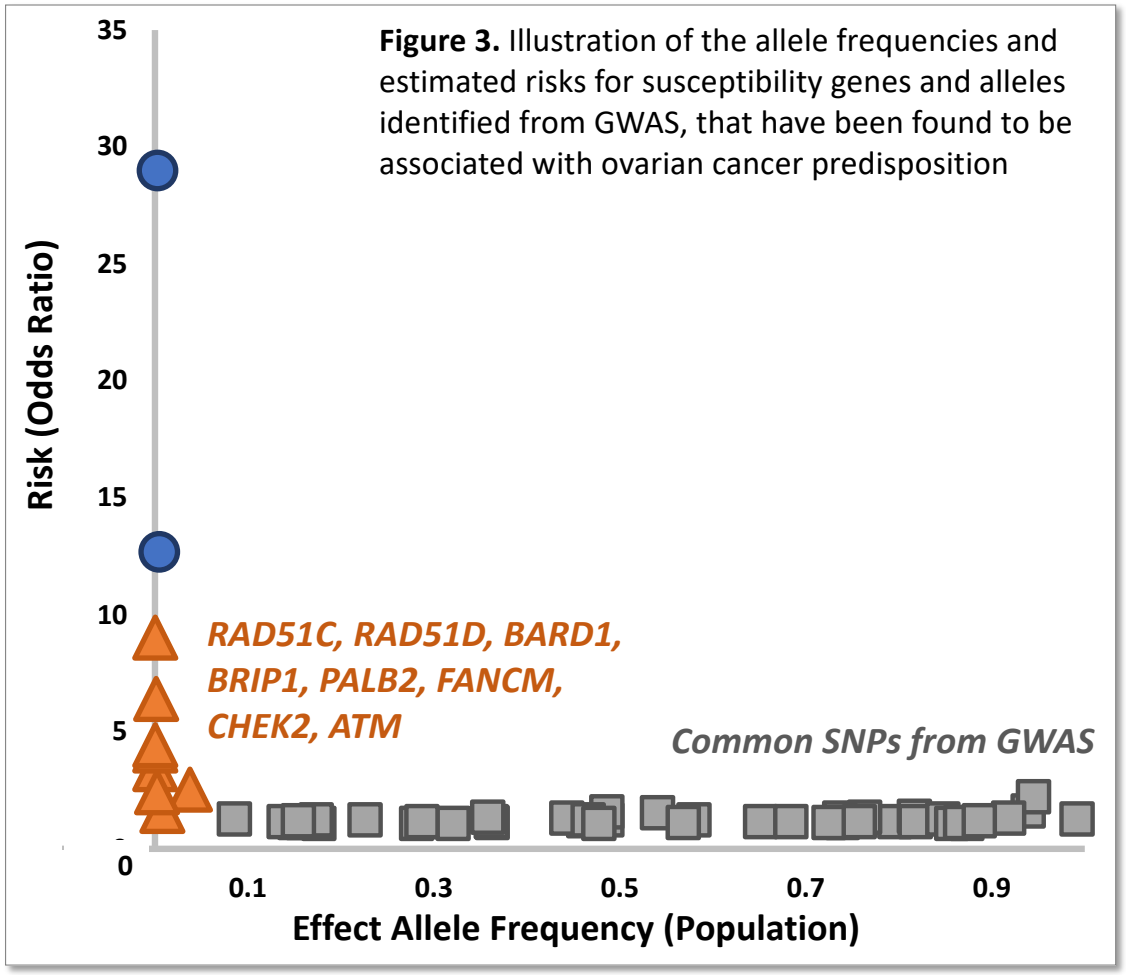


Figure 3. Illustration of the allele frequencies and estimated risks for susceptibility genes and alleles identified from GWAS, that have been found to be associated with ovarian cancer predisposition

Figure 4. Illustration of the proportional contributions of BRCA1 and BRCA2 gene mutations, mismatch repair (MMR) gene mutations, BRIP1, RAD51C and RAD51 genes and common risk SNPs from GWAS studies to ovarian cancer risk. The know genes and risk alleles account for less than 50% of of the estimated heritable component of ovarian cancer

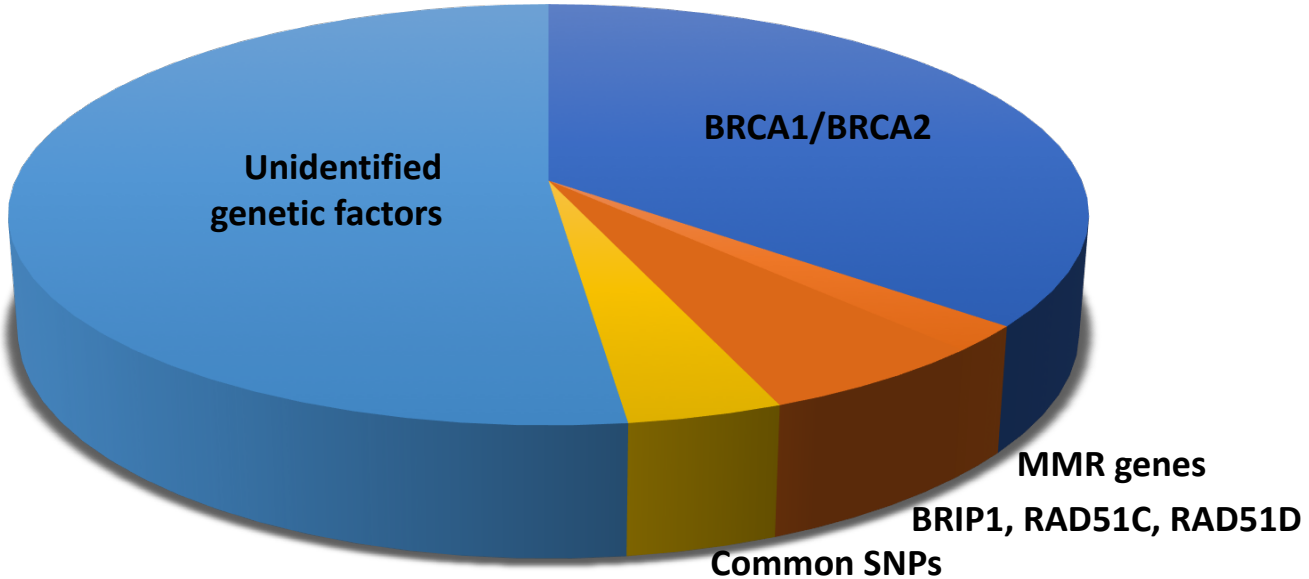


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TABLE AND FIGURE LEGENDS

Table 1.

[#]Susceptibility regions identified for different subtypes as classified by the different analyses: **(1) Invasive EOC-BRCA1**: Invasive epithelial ovarian cancer (EOC) cases from meta analyses that included BRCA1 carriers from the CIMBA consortium; **(2) BrCa-PrCa-OvCa** and **BrCa-OvCa:** Susceptibility loci identified from a meta-analysis of breast cancer (BrCa), prostate cancer (PrCa) and ovarian cancer (OvCa) datasets; **(3) MOC:** Mucinous ovarian Cancer; **(4) HGSOC:** High Grade Serous Ovarian Cancer; **(5) LMP-SOC:** Low malignant potential (borderline) and or low grade serous ovarian cancer; **(6) EnOC:** Endometrioid ovarian cancer; **(7) CCOC:** Clear Cell Ovarian Cancer. [§]The gene in closest proximity to the most significant ovarian cancer risk variant at each locus, or where the gene is bold and italicized, there is published functional evidence that this is the likely target gene at a locus although the gene may not be the closest in proximity to the risk associated SNP at that locus.

Figure 1. Schematic representation of the Fanconi Anemia (FA)/DNA double strand break (DSB) repair pathways implicated in ovarian cancer development. Susceptibility genes where sequencing studies have identified likely pathogenic mutations in ovarian cancer populations are outlined with red dashes.

Figure 2. Histotype-specific associations (odds ratios) of the top SNP in six EOC susceptibility regions. The forest plots show the point estimates of odds ratios with the 95% confidence interval around each estimate. For each locus, the highlighted odds ratios and confidence intervals correspond to histotype associations at genome side significance ($P< 5x10^{-8}$). Key to ovarian cancer (OC) histotypes: M, mucinous; HGS, high grade serous; LGS, low grade serous; clear cell.

Figure 3. Illustration of the allele frequencies and estimated risks for susceptibility genes and alleles identified from GWAS, that have been found to be associated with ovarian cancer predisposition.

Figure 4. Illustration of the proportional contributions of BRCA1 and BRCA2 gene mutations, mismatch repair (MMR) gene mutations, BRIP1, RAD51C and RAD51 genes and common risk SNPs from GWAS studies to ovarian cancer risk. The know genes and risk alleles account for less than 50% of of the estimated heritable component of ovarian cancer.