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Common Genetic Variation and Susceptibility to Ovarian Cancer: Current Insights and Future Directions

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Abstract

In this review, we summarize current progress in the genetic epidemiology of epithelial ovarian cancer (EOC), focusing exclusively on elucidating the role of common germline genetic variation in conferring susceptibility to EOC. We provide an overview of the more than 30 EOC risk loci identified to date by genome-wide association studies (GWAS) and describe the contribution of large-scale, cross-cancer type, custom genotyping projects, such as the OncoArray and the Collaborative Oncological Gene-Environment Study, to locus discovery and replication. We discuss the histotype-specific nature of these EOC risk loci, pleiotropy, or overlapping genetic effects between EOC and other hormone-related cancer types, and the application of findings to polygenic risk prediction for EOC. The second part of the article offers a concise review of primarily laboratory-based studies that have led to the identification of several putative EOC susceptibility genes using common variants at the known EOC risk loci as starting points. More global biological insights emerging from network- and pathway-based analyses of GWAS for EOC susceptibility are also highlighted. Finally, we delve into potential future directions, including the need to identify EOC risk loci in non-European populations and the next generation of GWAS functional studies that are likely to involve genome editing to establish the cell type–specific carcinogenic effects of EOC risk variants *Cancer Epidemiol Biomarkers Prev; 27(4); 395–404. ©2017 AACR.*

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Introduction

There were an estimated 239,000 new cases of ovarian cancer diagnosed and 152,000 deaths due to this disease worldwide in 2012 (1). Although there has been some improvement in survival trends over the past decade, 60% of women diagnosed with ovarian cancer in the United States are only diagnosed after the disease has already metastasized, and in this group, the 5-year relative survival rate is an abysmal 29% (2). Ovarian cancer remains the leading causing of death from gynecologic malignancy in the United States (3).

The majority of ovarian cancers are of epithelial origin and referred to as epithelial ovarian cancers (EOCs). Invasive EOCs account for 90% of cases and constitute an extraordinarily heterogeneous disease comprising five distinct histopathologic subtypes or histotypes (4): high-grade serous (HGSOC; 70% of invasive EOCs), low-grade serous (LGSOC; <5%), endometrioid (ENOC; 10%), clear cell (CCOC; 10%), and mucinous (MOC; 3%). Furthermore, there is borderline EOC, characterized by the absence of stromal invasion, with two histotypes: serous and mucinous. The histotypes of EOC may well be considered as different diseases as they differ significantly in their epidemiology, tumor IHC and molecular genetics, natural history, response to therapy, and prognosis (4). These differences likely reflect the underlying cell of origin and precursor lesions for each histotype. Multiple lines of evidence suggest that endometriosis or the presence of ectopic endometrial tissue is the precursor of ENOC and CCOC (5). HGSOC, which is the most aggressive of the histotypes, is now believed to begin in the fallopian tube as serous tubal intraepithelial carcinoma (STIC) that, in turn, is derived from fallopian tube secretory epithelial cells (FTSEC) via a series of intermediate precursors (6). In contrast, serous borderline tumors and LGSOCs potentially originate from larger masses of tubal-type epithelium that occur ectopically as ovarian cortical inclusion cysts (5).

In addition to endometriosis, which is associated with increased risks of ENOC, CCOC, and LGSOC (7), there are several well-established personal and lifestyle risks or protective factors for

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EOC in general. A positive family history of EOC is the strongest single risk factor known for EOC, while oral contraceptive pill (OCP) use, parity, breastfeeding, and tubal ligation have substantial protective effects (8). Women with a single first-degree relative affected with EOC have a 3-fold higher risk of developing EOC (9). Twin studies suggest that the excess familial risk for EOC is due to genetic rather than nongenetic factors shared between twins and the proportion of population variance in EOC risk attributable to genetic factors (i.e., the heritability of EOC) is estimated to be over 30% (10, 11). The average risk of developing EOC for a woman in the United States by the age of 80 years is 1.3% (2). Since 1994 (12), deleterious mutations have been identified in several genes that confer either high lifetime EOC risk (average risk >20% by age 80; *BRCA1* and *BRCA2*; ref. 13) or moderate risk [average risk of 3%–10% by age 80; *RAD51C* (14), *RAD51D* (15), *BRIP1* (16), *FANCM* (17), and the mismatch repair genes *MLH1*, *MSH2*, *MSH6*, and *PMS2* (13)]. However, such mutations are rare (found in <1% of the general population) and therefore account for only a small fraction of all EOC cases, explaining approximately 20% of the excess familial risk for this cancer (18).

Nearly all multicase, multigeneration families with EOC are explained by the high risk–conferring mutations in *BRCA1* and *BRCA2*, and it is unlikely that other EOC susceptibility genes carrying mutations that confer a similar magnitude of risk exist. The genetic architecture of EOC is far more compatible with a polygenic model that is underpinned by multiple common genetic variants [minor allele frequencies (MAF) > 1%] and rare variants (MAF < 1%), each conferring low or moderate EOC risk (18, 19). Over the past decade, the genome-wide association study (GWAS) has emerged as the preferred study design in the search for common genetic variants or SNPs associated with a wide range of common, complex diseases and traits. A GWAS involves using arrays to directly genotype several hundred thousand germline variants strategically distributed across the genome to capture much of the common genetic variation observed in distinct populations, such as those of European, Asian, and African ancestry. Allele frequencies of these variants are compared between cases of a disease and controls to identify variants significantly associated with susceptibility to the disease after strictly controlling for the massive multiple testing burden imposed by the very large number of variants evaluated in the GWAS. The development of comprehensive catalogues of genetic variation in specific human populations by the HapMap and 1000 Genomes Projects has further catalyzed GWAS discovery by enabling the indirect evaluation of an even larger number of SNPs beyond those genotyped on the array informed by the deeper knowledge of population-specific correlation structure between SNPs available through these catalogues (20, 21).

The Ovarian Cancer Association Consortium (OCAC) is an international, multidisciplinary forum for investigators working on the genetic epidemiology and molecular biology of EOC. Since its formation in April 2005, the OCAC has led the conduct of large-scale genetic association, replication, and meta-analytic studies to identify common EOC susceptibility variants. In 2012, we reviewed the progress made by the OCAC up to that point with a particular focus on candidate gene association studies and the first common EOC risk locus identified by a GWAS (22). In this review, we discuss the more than 30 EOC susceptibility loci identified since then, and the novel insights into EOC biology that are rapidly emerging from these discoveries.

GWASs of EOC Susceptibility

The first GWAS of EOC susceptibility was published in 2009, reporting the identification of the 9p22.2 risk locus (23). Since then, a total of 37 common SNP loci (MAF > 1%) associated with EOC risk at the genome-wide threshold for statistical significance ($P < 5 \times 10^{-8}$) have been identified. The association at each of these loci varies considerably by histotype, and at the power to detect histotype-specific associations in the largest and most recent EOC GWAS meta-analysis (24), most loci appear to either predispose to one histotype or to specific combinations of histotypes. The genetic discoveries have thus supported the existing epidemiologic, pathologic, and clinical evidence that the histotypes of EOC are indeed distinct diseases. All EOC risk loci identified so far have been identified in populations of European ancestry, except for 9q22.33 and 10p11.21 that were found in a GWAS of about 2,500 cases and 4,000 controls of Han Chinese descent (25). Details of all currently known EOC risk loci with corresponding references are summarized in Tables 1–3. The EOC SNPs discovered to date all have an MAF of at least 5% each and confer a less than 50% change in risk per allele with two exceptions [rs62274041 at 3q25.31 for association with HGSOC; OR, 1.63; 95% confidence interval (CI), 1.53–1.74; $P = 4 \times 10^{-49}$ and rs150293538 at 8q21.11 for association with LGSOC and borderline serous EOC; OR, 2.19; 95% CI, 1.65–2.90; $P = 2.0 \times 10^{-9}$].

Table 1. New EOC risk loci identified by the OncoArray meta-analysis at $P < 5 \times 10^{-8}$ (ref. 23)[a]

Locus	Lead SNP	Phenotype	Effect allele	EAF	OR (95% CI)	*P*
3q22.3	rs112071820	Mucinous	GCCAG	0.28	1.29 (1.20–1.37)	1.5E−13
3q28	rs9870207	S. borderline + LGSOC	A	0.69	1.19 (1.12–1.27)	4.5E−08
4q32.3	rs13113999	S. borderline	T	0.52	1.23 (1.14–1.32)	4.7E−08
5q12.3	rs555025179	Endometrioid	GACAC	0.53	1.18 (1.11–1.26)	4.5E−08
8q21.11	rs150293538	S. borderline + LGSOC	T	0.98	2.19 (1.65–2.90)	2.0E−09
9q31.1	rs320203[b]	Mucinous	A	0.85	1.29 (1.18–1.41)	1.7E−08
10q24.33	rs7902587	S. borderline + LGSOC	T	0.10	1.29 (1.18–1.41)	4.0E−08
18q11.2	rs8098244	S. borderline + LGSOC	A	0.28	1.19 (1.12–1.27)	3.9E−08
22q12.1	rs6005807	HGSOC	C	0.90	1.17 (1.10–1.23)	1.2E−08
2q13	rs2165109	HGSOC	C	0.25	1.09 (1.05–1.12)	2.0E−08
8q24.21	rs9886651	HGSOC	G	0.46	1.08 (1.05–1.11)	1.9E−09
12q24.31	rs7953249	HGSOC	G	0.42	1.08 (1.06–1.11)	4.5E−10

Abbreviations: EAF, effect allele frequency; S. borderline, serous borderline.
[a]In European ancestry populations.
[b]All risk loci listed except rs320203 had BFDP <10%.

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Table 2. Previously published EOC risk loci confirmed by the OncoArray meta-analysis at $P < 5 \times 10^{-8}$ (ref. 23)[a,b]

Locus	Lead SNP	Phenotype	Effect allele	EAF	OR (95% CI)[c]	*P*	Ref.
1p34.3	rs58722170	Serous	C	0.22	1.10 (1.07–1.13)	1.4E−09	25
2q14.1	rs752590	Mucinous	G	0.21	1.30 (1.21–1.39)	2.2E−12	53
2q31.1	rs711830	Mucinous	A	0.32	1.27 (1.20–1.35)	1.1E−14	53
2q31.1	rs6755777	Serous	T	0.32	1.12 (1.09–1.15)	2.7E−15	28
3q25.31	rs62274041	HGSOC	G	0.05	1.57 (1.48–1.66)	2.1E−57	22
5p15.33	rs10069690	Serous	T	0.26	1.13 (1.09–1.17)	1.5E−12	37
5p15.33	rs7705526	S. borderline	A	0.33	1.38 (1.29–1.48)	5.5E−19	37
8q21.13	rs76837345	HGSOC	G	0.07	1.20 (1.13–1.28)	9.0E−10	26
8q24.21	rs1400482	Serous	G	0.87	1.23 (1.19–1.28)	7.4E−26	28
9p22.2	rs10962692	HGSOC	G	0.80	1.36 (1.30–1.42)	1.4E−47	22
9q34.2	rs8176685	HGSOC	G	0.19	1.15 (1.10–1.19)	5.2E−12	25
10p12.31	rs144962376	Serous	TCCCT	0.31	1.10 (1.06–1.13)	6.6E−09	26
17q12	rs7405776	Serous	G	0.41	1.10 (1.07–1.14)	1.9E−10	35
17q12	rs11651755	Clear cell	C	0.49	0.79 (0.73–0.86)	6.8E−09	35
17q21.31	rs7207826	Serous	C	0.27	1.14 (1.10–1.18)	1.2E−14	36
17q21.32	rs1879586	HGSOC	G	0.18	1.15 (1.10–1.19)	2.5E−12	26
19p13.11	rs4808075	HGSOC	C	0.30	1.20 (1.16–1.24)	3.3E−24	29
19q13.2	rs688187	Mucinous	A	0.31	1.43 (1.33–1.53)	1.2E−22	53
In Han Chinese ancestry populations only							
9q22.33	rs1413299	Serous	C	0.40	1.53 (1.25–1.86)	1.9E−08	24
10p11.21	rs1192691	Serous	A	0.36	0.81 (0.70–0.95)	2.6E−08	24

Abbreviations: EAF, effect allele frequency; ref., reference; S. borderline, serous borderline.
[a]In European ancestry populations unless otherwise specified.
[b]All risk loci listed had BFDP <10%.
[c]All ORs, CIs, and *P* values from the OncoArray meta-analysis (ref. 23).

Factors driving the discovery of EOC susceptibility loci

There have been two key factors that have driven the identification of common germline variation associated with EOC risk. First, sample sizes studied have increased from 1,817 to 26,293 for European-ancestry cases of invasive EOC analyzed between the first or genome-wide discovery stage of the first GWAS published (23) and the most recent meta-analysis of genetic association studies (24). Sample sizes have been increased by bringing more studies into the OCAC, but also through collaborations with the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) that added over 3,000 EOC cases in *BRCA1* or *BRCA2* mutation carriers (24, 26). The result has been an over 20-fold increase in total invasive serous cases studied (HGSOC + LGSOC) and a greater than 5-fold jump in the number of invasive nonserous cases (ENOC + CCOC + MOC), enabling a progressively deeper dissection of EOC heterogeneity at the genetic level. The GWAS meta-analysis by Phelan and colleagues also included 3,103 borderline (serous and mucinous) EOC cases (24), leading to the identification of five new loci associated with borderline serous EOC susceptibility in addition to the identification of seven new risk loci for invasive EOC histotypes (Table 1).

The second key driver of EOC GWAS discovery has been the inclusion of this cancer in the OncoArray Consortium and in its predecessor, the Collaborative Oncological Gene-Environment Study (COGS). The COGS project involved genotyping of over 150,000 individuals, including breast, ovarian, and prostate cancer cases, *BRCA1/2* mutation carriers, and controls using an Illumina Infinium custom chip, the iCOGS array, that included 211,155 SNPs (27). The OncoArray Consortium expanded on these efforts by genotyping just under 450,000 individuals, including breast, ovarian, prostate, colon, lung, and endometrial cancer cases, *BRCA1/2* mutation carriers, and controls using another custom platform from Illumina, the OncoArray, that included 494,763 SNPs (28). The application of the same custom array to samples from international consortia studying the different cancer types allowed these two large-scale genotyping projects to be cost-effective. This, in turn, enabled robust identification and/or replication of associations with EOC risk in the largest feasible sample size and has offered an unprecedented opportunity to explore the extent to which susceptibility loci are shared between EOC and other cancer types. The OncoArray included dense SNP coverage of genomic regions that contained previously identified EOC risk loci to facilitate fine-scale mapping, suggestive associations ($5 \times 10^{-8} < P < 10^{-5}$) from prior GWAS for potential replication of these signals, SNPs associated with cancer-related traits, SNPs known to be associated with other cancers not being profiled on the array, candidate functional variants, SNPs in certain candidate genes and pathways, SNPs with

Table 3. Previously published EOC risk loci not confirmed by OncoArray meta-analysis at $P < 5 \times 10^{-8}$ (ref. 23)[a,b]

Locus	Lead SNP	Phenotype	Effect allele	EAF	OR (95% CI)[c]	*P*	Ref.
1p36.12	rs56318008	All invasive EOC	T	0.15	1.08 (1.04–1.12)	8.4E−05	25
4q26	rs17329882	All invasive EOC	C	0.24	1.08 (1.04–1.11)	2.5E−06	25
4q32.3	rs4691139	*BRCA1* mutation+	G	0.47	1.16 (1.09–1.23)	4.3E−07	41
6p22.1	rs6456822	All invasive EOC	T	0.69	1.07 (1.04–1.10)	1.2E−06	25
17q11.2	rs143663961	All invasive EOC	A	0.73	1.08 (1.05–1.11)	1.3E−07	25

Abbreviations: EAF, effect allele frequency; ref., reference; S. borderline, serous borderline.
[a]In European ancestry populations.
[b]All risk loci listed had BFDP >10%.
[c]All ORs, CIs, and *P* values from the OncoArray meta-analysis (ref. 23).

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pharmacogenetic associations, as well as some rare variants selected from exome chip and sequencing experiments (28). The iCOGS array was similar in principle but far less comprehensive than the OncoArray. Critically, the OncoArray included a "GWAS backbone" or a set of roughly 260,000 genotyped SNPs that when coupled with SNPs imputed from the 1000 Genomes reference panel provided coverage of most common germline variation across the whole genome.

Pleiotropic risk loci shared between ovarian cancer and other cancer types

Pleiotropy is the phenomenon where a single genetic variant or gene has an effect on more than one phenotype. Since the earliest GWAS of EOC susceptibility, it has become increasingly apparent that some EOC risk loci are found in regions of the genome that are within 1-megabase of risk loci for other cancer types. The first such examples observed for EOC risk loci were at 8q24.21 and 19p13.11 (29, 30). The lead SNP from the original publication rs8170 (as also the fine-mapped lead SNP rs4808075; ref. 31) at the 19p13.11 HGSOC risk locus is also a genome-wide significant lead SNP for estrogen receptor (ER)-negative and triple-negative breast cancer risk in the general population as well as for breast cancer risk among *BRCA1* mutation carriers (30–33). This SNP has the same direction of allelic effect between breast and ovarian cancer and thus demonstrates pleiotropic effects at the variant level. For 8q24, it is now known that the region harbors several independent or partially correlated risk loci for at least 10 different cancer types with some of the loci being shared by two or more cancers (34). Although the three independent serous EOC risk loci at 8q24 do not overlap SNPs associated with other cancer types (24), they may represent examples of pleiotropy acting through the same gene or mechanism and act via enhancer-mediated regulation of the nearby *MYC* proto-oncogene as has been suggested for the breast, prostate, and colon cancer associations at 8q24 (35).

As described above, one of the specific aims of the COGS was to characterize susceptibility regions potentially shared between ovarian, breast, and prostate cancer. The COGS publications and the subsequent OCAC-CIMBA COGS EOC meta-analysis identified several new regions that contain associations within a megabase of each other (26, 27, 36–38): for all three cancer types (5p15.33 and 6p22.1), for ovarian and breast cancer (10p12.31 and 17q11.2), and for ovarian and prostate cancer (17q12 and 17q21.31). Some of these loci, such as 5p15.33 (*TERT*) and 17q12 (*HNF1B*), are also known to overlap risk loci for other cancer types, including endometrial cancer (39, 40). The COGS project culminated in the largest cross-cancer type genome-wide association meta-analysis for hormone-related cancers to date (41). This study included over 112,000 cases of breast, ovarian, and prostate cancers and 116,000 controls drawn from the COGS and from all previously reported GWAS in European-ancestry populations for these three cancer types. Combining summary data for association with risk of each cancer type, all together and in pairs, identified five new pleiotropic risk loci involving EOC and demonstrated that pleiotropy itself can be leveraged to identify completely new risk loci common to multiple cancers. As described in Table 4, three of the risk loci were shared between all three cancer types (2q13, 11q12.3, and a new 19p13.11 locus) and two between ovarian and breast cancer only (9q31.1 and 15q26.1). Each locus was >1 Mb away from any previously published risk locus for these cancers individually. In addition to these five loci, a total of 17 of the 37 common SNP loci so far known to be associated with EOC risk at genome-wide significance harbor variants associated with at least one other cancer type within 1 Mb (42). The number of potentially pleiotropic cancer risk loci involving EOC may grow as OncoArray data for other cancers are analyzed and published. These independent variants occurring within 1 Mb of each other and associated with EOC and other cancer types may overlap tissue-specific enhancers in the relevant cell types that regulate the same target susceptibility genes (41).

OncoArray results and polygenic risk prediction for EOC

The OncoArray project generated genotype data on approximately 18,000 invasive EOC cases, 2,500 borderline EOC

Table 4. Pleiotropic cancer risk loci shared between EOC and breast and/or prostate cancers identified at $P < 10^{-8}$ specifically by cross-cancer type meta-analysis in European ancestry populations (ref. 40)[a]

Locus	Lead SNP	Effect allele, EAF	Cancer type	OR (95% CI)	*P*
Associations with ovarian, breast, and prostate cancer risk with the same direction of effect					
2q13	rs17041869	A	Breast cancer	0.97 (0.94–0.99)	7.1×10^{-3}
		0.88	Ovarian cancer[b]	0.93 (0.88–0.97)	5.3×10^{-4}
			Prostate cancer	0.92 (0.89–0.95)	2.6×10^{-6}
			Meta-analysis	0.94 (0.93–0.96)	5.1×10^{-9}
11q12.3	rs7937840	T	Breast cancer	1.04 (1.02–1.06)	3.6×10^{-5}
		0.26	Ovarian cancer	1.05 (1.01–1.09)	5.8×10^{-3}
			Prostate cancer	1.05 (1.02–1.08)	8.9×10^{-4}
			Meta-analysis	1.05 (1.03–1.06)	5.0×10^{-9}
19p13.11	rs1469713	A	Breast cancer	0.95 (0.94–0.97)	9.9×10^{-8}
		0.64	Ovarian cancer	0.96 (0.93–0.99)	6.3×10^{-3}
			Prostate cancer	0.97 (0.94–0.99)	1.0×10^{-2}
			Meta-analysis	0.96 (0.95–0.97)	3.4×10^{-10}
Associations with ovarian and breast cancer risk with the same direction of effect					
9q31.1	rs200182588	G	Breast cancer	0.96 (0.94–0.98)	1.9×10^{-5}
		0.56	Ovarian cancer	0.93 (0.89–0.96)	2.8×10^{-6}
			Meta-analysis	0.95 (0.94–0.97)	8.9×10^{-9}
15q26.1	rs8037137	T	Breast cancer	1.07 (1.04–1.10)	1.8×10^{-7}
		0.86	Ovarian cancer	1.09 (1.04–1.14)	2.1×10^{-4}
			Meta-analysis	1.07 (1.05–1.10)	9.1×10^{-10}

Abbreviations: EAF, effect allele frequency; ref., reference.
[a]This meta-analysis did not include data from the OncoArray project (ref. 23).
[b]Ovarian cancer refers to all invasive EOCs.

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cases, and 24,000 controls from the OCAC and 23,000 *BRCA1* and *BRCA2* mutation carriers from the CIMBA, over 3,000 of whom were affected by EOC. The joint OCAC–CIMBA meta-analysis by Phelan and colleagues combined results from the OncoArray with results of nonoverlapping samples from previously reported GWAS and from the COGS to yield a dataset of over 22,000 invasive EOC cases, 3,000 borderline EOC cases, and 40,000 controls from the OCAC and over 27,000 *BRCA1* and *BRCA2* mutation carriers from the CIMBA, including just under 4,000 EOC cases (24). Associations between 11 million variants with MAF >1% across the genome and nine phenotypes defined from the histotypes of EOC were investigated (all invasive, serous invasive, HGSOC, LGSOC, serous borderline, LGSOC and serous borderline combined, ENOC, CCOC, and MOC). Twelve new EOC risk loci were identified, representing a third of all EOC risk loci uncovered so far, and this includes nine for serous EOC histotypes, two for MOC, and one for ENOC (Table 1).

The OncoArray has also offered the opportunity to replicate associations first identified by the COGS and older GWAS. Although the vast majority of these risk loci were replicated, it is worth noting that five associations (at 1p36.12, 4q26, 6p22.1, and 17q11.2 reported in ref. 26 and at 4q32.3 reported in ref. 43; Table 3) failed to replicate at genome-wide significance ($P < 5 \times 10^{-8}$) in the meta-analysis by Phelan and colleagues (24). Applying the Bayesian false discovery probability (BFDP; ref. 44), a measure for assessing the noteworthiness of an observed association, with a conservative prior probability of association of 0.0001 and a plausible per-allele OR of 1.2 revealed that 11 of the 12 loci identified by the OncoArray meta-analysis (Table 1) and 18 of the 23 previously published susceptibility loci for EOC in European-ancestry populations (Table 2) had a BFDP <10% (24). Of the 29 associations with BFDP <10%, 27 were associated with invasive EOC susceptibility at $P < 0.01$. When taken together with the five pleiotropic cancer risk loci involving EOC (Table 4; ref. 41), these 27 currently confirmed EOC risk loci explain an estimated 6.4% of the polygenic risk of EOC in the general population (24). The magnitude of the associations with EOC susceptibility is similar between the general population and among *BRCA1* and *BRCA2* mutation carriers, suggesting that common risk alleles and *BRCA1/2* mutations interact multiplicatively on the relative risk scale to confer susceptibility to EOC (26). A polygenic risk score (PRS) based on 18 common EOC risk loci that explain just under 4% of the polygenic risk of EOC in the population was recently shown to be strongly associated with EOC risk among *BRCA1/2* mutation carriers (45). Among women carrying a *BRCA2* mutation, those at the 10th percentile of this common variant EOC PRS had a 6% risk of developing EOC by age 80 as against a 19% risk for those at the 90th percentile. These findings indicate that incorporation of a PRS. particularly a PRS that is updated to include new variants identified by the OncoArray. into cancer risk prediction models will potentially improve clinical decision making for *BRCA2* mutation carriers. In the general population, the PRS may better define an at-risk group for EOC who might benefit from screening, should an effective screening method be identified, or from lifestyle interventions. Analysis of data from the OCAC indicates that relative risks associated with common genetic variants (based on 11 EOC risk loci evaluated at the time) interact multiplicatively with various lifestyle risk/protective factors (46). For example, a nulliparous woman in the highest PRS quintile with no family history of EOC and no history of endometriosis who has not used an OCP and not had a tubal ligation has a lifetime risk of 4.3%, which is over three times the average lifetime risk of 1.3%. If this same woman had used OCPs for 5 years or longer, her lifetime risk would have been reduced to 1.7% (46). With the development of appropriate statistical tools and ever-larger genetic and epidemiologic datasets, it will also become possible to identify new gene–environment or gene–lifestyle multifactor interactions (47).

From Genetic Associations to Biological Mechanisms in Ovarian Cancer

It is estimated that close to 90% of SNP loci identified by GWAS lie in regions of the genome that do not code for proteins, and indeed, all EOC SNP loci identified so far are either intronic or intergenic (48). This suggests that for most diseases and traits, associated common genetic variation does not disrupt protein structure itself but instead acts by regulating genes. Although SNPs, or rather the regulatory elements in which they might lie, may affect the promoter of the gene closest to them, experimental evaluation of the SNP–gene interaction landscape both at genome scale and at some of the earliest loci identified by GWAS suggests that SNPs can affect one or more genes up to a megabase away from them and perhaps at even greater distances (49, 50). Given that the human genome on average contains 12–15 genes per megabase, pinpointing the target gene(s) through which each risk locus acts therefore presents a particularly hard problem.

Unlike coding mutations that lead to a truncation of the protein product, unravelling the effect of SNPs in noncoding regions has necessitated the development of new bioinformatics tools and assays to assign functional significance. Thus, a pipeline of approaches has emerged alongside GWAS over the past decade to deal with this problem. The pipeline, summarized in Fig. 1, often requires state-of-the-art laboratory technologies that are rapidly evolving. These include chromosome conformation capture (3C/4C/5C/Hi-C), luciferase reporter assays, electrophoretic mobility shift assays, chromatin immunoprecipitation, and genome editing using the clustered regularly interspaced short palindromic repeats (CRISPR)–Cas9 system. The pipeline with its component technologies and their role in generating the substantial experimental evidence needed to establish GWAS variants and their target genes as causal for cancer are extensively reviewed elsewhere (48, 51, 52). Critical to the success of the pipeline have been two genetic epidemiology tools. First, because the SNPs originally identified by GWAS usually simply "tag" the underlying "causal" variant due to linkage disequilibrium, it is imperative to fine map and perform conditional analysis to prioritize "candidate causal" risk peaks and their constituent SNPs that demonstrate the clearest statistical evidence for association at each locus (53). The second tool is expression quantitative trait locus (eQTL) analysis to link germline EOC susceptibility alleles with the expression of nearby genes as profiled in ovarian tumors or tumor precursor tissues from the same individual (54).

GWAS functional characterization of EOC risk loci

In many respects, the identification of risk SNPs by GWAS is just the beginning of extensive laboratory research. A few specific examples of EOC susceptibility loci that have been subjected to bioinformatics and laboratory-based assays can illustrate the process needed to identify target genes and the likely mechanisms of effect on EOC pathogenesis.

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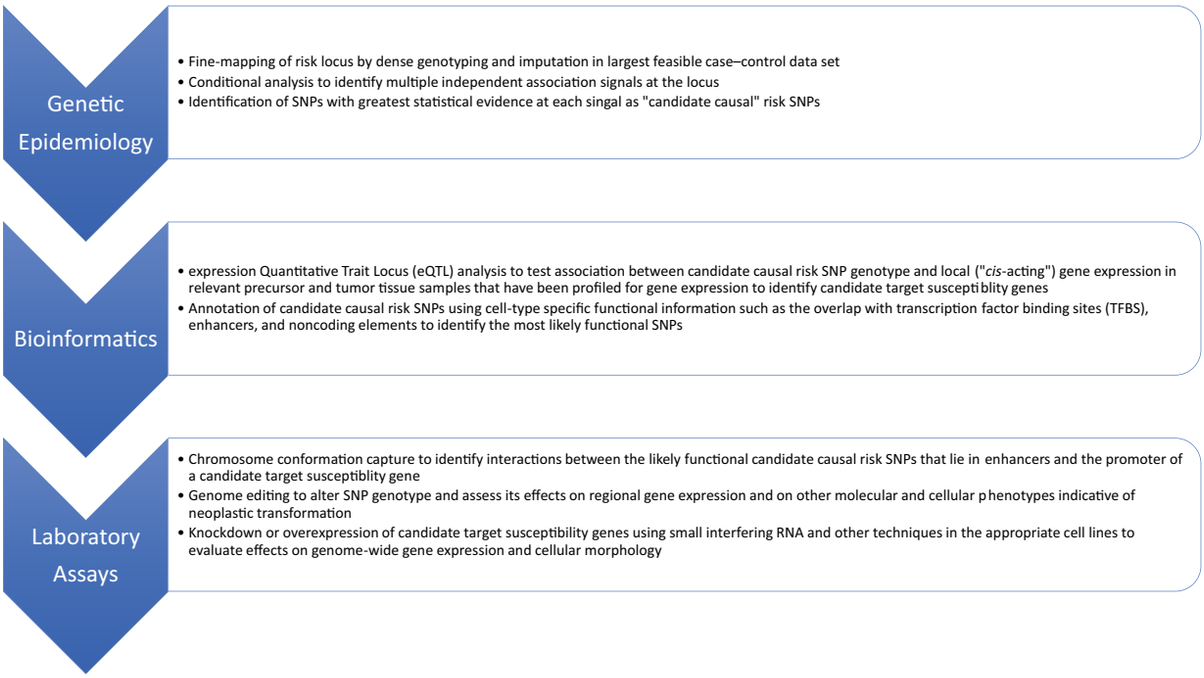

Figure 1.
An outline of the most common steps applied in the functional characterization of cancer risk loci. The aim of this pipeline is to identify the genes and associated molecular and cellular pathways through which cancer risk SNPs at each locus are most likely to exert their effects on cancer susceptibility.

HOXD9. Functional studies carried out by OCAC investigators suggest that *HOXD9* is a likely target EOC susceptibility gene of the 2q31.1 risk locus in both serous and mucinous histotypes (55, 56). Fine mapping of the 2q31.1 serous (HGSOC, LGSOC, and borderline) EOC risk signal identified 19 candidate causal SNPs clustered around *HOXD3* and *HAGLR*, approximately 45 kb telomeric to *HOXD9* (55). These variants were found to represent a significant eQTL for *HOXD9* expression in HGSOC tumors from 340 European ancestry patients in The Cancer Genome Atlas (TCGA), with the cancer risk alleles associated with increased expression of the gene. Systematic evaluation of each of the 19 SNPs using 3C performed in the HEY ovarian cancer cell line revealed that one of the SNPs, rs2857532, interacted with the *HOXD9* promoter. The G allele of this variant was shown *in silico* to create a binding site for three transcription factors (TFs), HOMEZ, BEN, and RelA-p65, all of which are expressed in HGSOC, suggesting that these TFs may regulate *HOXD9* expression in serous EOC by binding at this risk locus. On overexpression of *HOXD9*, immortalized p53-deficient ovarian surface epithelial cells (OSEC) and FTSECs demonstrated significant increase in anchorage-independent growth, shortening of cellular population doubling time, and reduction in contact inhibition and apoptosis. The 2q31.1 locus is also independently a genome-wide significant risk locus for MOC (invasive and borderline), with the same 19 SNPs underlying the association as for the serous histotypes. The most likely serous EOC functional variant, rs2857532, and two other SNPs, rs2072590 and rs4972504, were shown to interact with the *HOXD9* promoter in the EFO-27 MOC cell line on 3C analysis (56). HOXD9 is a little studied transcription factor, and its transcriptional target genes are largely uncharacterized. Whole-genome transcriptomic profiling has revealed that genes with significant change in expression after *HOXD9* overexpression in OSECs and in FTSECs are enriched for SNPs nominally ($P < 10^{-3}$) associated with serous EOC risk and for several cancer-related pathways (most notably focal adhesion), suggesting a more global role for this TF in mediating EOC development (55).

TERT and OBFC1. GWAS findings have shed new light on the etiology of borderline serous EOC and suggest that mechanisms regulating telomere length have a central role specifically in this histotype. The COGS analysis found that the minor allele of rs7705526 in intron 2 of *TERT* (5p15.33 locus) was associated at $P < 5 \times 10^{-8}$ with increased borderline serous EOC risk and with longer telomeres (38). Inclusion of this minor allele in luciferase reporter constructs in A2780 ovarian cancer cells significantly increased *TERT* promoter activity, suggesting that rs7705526 lies in a putative regulatory element that acts *in cis* as a transcriptional enhancer of *TERT*, which encodes the catalytic subunit of telomerase, the enzyme that lengthens telomeres (38). The OncoArray analysis identified a borderline serous EOC risk locus at 10q24.33 that was also shown to be the strongest local eQTL for *OBFC1* using gene expression data from 535 serous EOC tumors (24). This locus has previously been reported to be associated with telomere length with the cancer risk alleles correlating with longer telomeres (57). *OBFC1* is also known to function in a telomere-associated complex that binds telomeric single-stranded DNA *in vitro* and localizes at telomeres *in vivo* (58). Finally, a recent Mendelian randomization study using all SNPs thus far known to be strongly associated with telomere length in the general population as an instrumental variable and GWAS summary statistics for several cancer types showed that

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for every 1-SD increase in genetically determined telomere length, there was a 4.35-fold increase in risk of serous borderline EOC (59).

ABHD8 and ANKLE1. Risk alleles with pleiotropic effects on multiple cancer types hint at the existence of common underlying cancer susceptibility genes and pathways. The 19p13.11 serous EOC and ER-negative breast cancer risk locus (described above) was fine mapped in roughly 10,000 serous EOC cases, 15,000 *BRCA1* mutation carriers, 7,000 ER-negative breast cancer cases and 73,000 controls (31). This extensive cross-cancer type fine mapping powered the identification of a single clear peak of association comprising 13 highly correlated SNPs that accounted for the risk signal in both cancer types. The SNPs spanned *BABAM1*, *ABHD8*, and *ANKLE1* and constituted a significant eQTL for *ABHD8* in 340 HGSOCs and 135 normal breast tissue samples, and for *ANKLE1* in 60 OSEC samples. Five of the 13 SNPs coincided with a variety of regulatory annotations in OSECs, FTSECs, and/or human mammary epithelial cells. Details of the functional analysis have been published (31), but briefly, interaction between some of these SNPs and the *ABHD8* promoter was confirmed by 3C analysis in normal ovary (IOSE11) and breast (Bre80) and in ovarian (A2780) and breast (MCF7) cancer cell lines. The proximity of the peak SNPs to the *ANKLE1* promoter precluded its evaluation by 3C. Luciferase assays indicated that risk alleles at this locus increase transactivation of the *ABHD8* promoter, and overexpression of this gene led to significant changes in migration and invasion in both ovarian and breast cells. Conversely, targeted deletion by CRISPR-Cas9 genome editing of one of the 13 SNPs, rs56069439, which overlapped enhancer marks in both cell types, induced reductions in *ANKLE1* expression in both ovarian and breast epithelial cell lines but did not affect *ABHD8* expression. Collectively, these findings paint a complex picture of the functional landscape of this region likely underpinned by two genes that, similar to *HOXD9* at 2q31.1, have little prior support for their role in cancer biology based on the published literature. It is noteworthy that none of the series of experiments conducted on this locus provided any evidence for a role of *BABAM1*, which encodes a protein (previously known as MERIT40) that interacts with a complex containing BRCA1 to control the retention and stability of BRCA1 at sites of double-stranded breaks in DNA (60, 61).

HNF1B. *HNF1B* at 17q12 is downregulated in most HGSOCs in TCGA (frequently by promoter methylation) but overexpressed in CCOCs (36, 62). These histotype-specific differences prompted an evaluation of *HNF1B* as a candidate EOC susceptibility gene using the iCOGS array, leading to the identification of a genome-wide significant risk locus for serous (HGSOC and borderline) EOC and for CCOC spanning 22 kb from the 5′ untranslated region to intron 4 of *HNF1B* (36). Consistent with the observed difference in expression between histotypes, the alleles conferring serous EOC risk were protective for CCOC, and there was evidence of distinct histotype-specific signals underlying the association in this region. The serous EOC risk alleles were associated with *HNF1B* promoter methylation and the histotype-specific patterns of expression were confirmed at the protein level by IHC profiling of over a 1,000 tumors from the Ovarian Tumor Tissue Analysis consortium. Overexpression of *HNF1B* in endometriosis epithelial cells, which may represent the cell of origin for CCOC, led to changes in cellular morphology, suggestive of neoplastic transformation. The 17q12 locus is also associated with endometrial cancer risk, and initial analyses suggest that *HNF1B* is a likely candidate susceptibility gene for endometrial cancer as well (63).

Global mechanistic insights from EOC susceptibility variants

In addition to the identification of putative target genes at EOC risk loci, results from EOC GWAS are beginning to unravel potential genome-wide biological features and master regulatory networks that may underpin EOC development in susceptible women. Genome-wide profiling of gynecologic epithelial cell types for H3K4me1 and H3K27ac histone marks (indicative of poised and active or engaged enhancers, respectively) and of localized nucleosome depletion (another characteristic of enhancers) show that "candidate causal" HGSOC risk SNPs are twice as likely to lie within enhancers (versus outside) than expected by chance (64). This enrichment of HGSOC risk SNPs in regulatory elements is particularly pronounced in OSECs and FTSECs but not seen in cell types completely unrelated to EOC. The recent OncoArray study has further emphasized this tissue specificity by demonstrating that candidate causal risk SNPs at the 12q24.31 and 10q24.33 loci are located in H3K27ac hotspots in cell lines relevant to EOC (24). There is also emerging evidence that EOC risk SNPs may overlap other types of biofeatures across the genome, such as long noncoding RNAs (65).

Another emerging theme from GWAS is the role of transcription factors in EOC biology. Genes such as *HOXD9* and *HNF1B* that encode TFs and are located near EOC susceptibility loci are turning out to be the most likely regulatory targets of EOC risk SNPs (36, 55). Large-scale epigenomics projects, such as the Encyclopedia of Regulatory Elements (ENCODE), have not profiled genome-wide transcription factor–binding sites (TFBS) in EOC and related precursor tissues (66). This coupled with the fact that several TFs with possible roles in EOC have partial or complete homeodomain motifs (*HOXD9*, *HNF1B*, *HOXB7*, *PAX8*) that exhibit promiscuous DNA binding *in vitro* has made identification of the appropriate downstream transcriptional target genes of these TFs particularly challenging (67). This has led to the adoption of alternative strategies to elucidate the role of TFs and their gene networks in EOC susceptibility. For example, coexpression was used as a proxy for TF-target gene coregulation in the TCGA HGSOC dataset to construct a network of genes coexpressed across the genome with members of the *HOXB* and *HOXD* TF gene clusters that lie at the 17q21.32 and 2q31.1 serous EOC risk loci, respectively (68). Genes in this network were found to be highly enriched for SNPs associated with EOC risk at more modest levels of significance than standard GWAS significance (i.e., they had P values between 0.05 and 5×10^{-8}).

Beyond TFs encoded by genes at currently identified EOC risk loci, other TFs that lie elsewhere, such as PAX8, may also act as global master regulators of EOC susceptibility. PAX8 is essential for the development of the fallopian tube, and almost all HGSOCs exhibit PAX8 expression and dependence (69). Although there is a mucinous EOC risk locus near *PAX8* (56), there is no evidence for a serous EOC risk locus in this region. However, it was recently shown that target genes of PAX8, initially defined from motif analysis but containing several genes later validated by silencing *PAX8* expression in EOC cell lines, are found at six genome-wide significant serous EOC risk loci, and this PAX8 transcriptional network was most significantly associated with serous EOC risk out of 615 TF-target gene networks assessed by pathway analysis of all pre-OncoArray serous EOC

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genetic association data (70). Overall, such pathway-based studies suggest that the observed polygenicity of EOC susceptibility may have its roots in coherent gene networks that are gradually perturbed over the course of carcinogenesis, although these findings must be treated with great caution until deeper functional interrogation is undertaken.

Future Directions and Conclusions

The OncoArray was also used to genotype approximately 2,000 African American and 7,000 Asian EOC cases and controls. It is anticipated that ongoing analyses of these data by the OCAC will result in the identification of novel EOC susceptibility loci that begin to unravel the genetic architecture of this cancer in populations of African and Asian ancestry. These sample sizes also underscore the need to increase enrollment of EOC patients from other racial and ethnic groups. Additional locus discovery in European ancestry populations is likely to come from a combination of further increases in sample size, particularly for the less common histotypes, and better imputation of variants, especially rarer variants, across the genome. This improvement in imputation may be made possible by leveraging reference panels, such as the one recently developed by the Haplotype Reference Consortium (HRC; ref. 71). The HRC includes nearly 65,000 haplotypes obtained from over 32,000 samples with low-coverage, whole-genome sequencing data that allows variants with MAF as low as 0.1% to be accurately imputed from the present generation of genotyping arrays used in GWAS. The OncoArray, with its coverage of ovarian, breast, prostate, lung, colon, and endometrial cancers has also set the stage for an even larger cross-cancer type meta-analysis of more than 0.5 million individuals that is likely to yield multiple new pleiotropic loci shared between ovarian and other cancers.

Each EOC risk locus identified, be it exclusive to EOC or overlapping with other cancer types, offers a unique glimpse into the biology of ovarian cancer. The most challenging of the future directions for the OCAC will be to progress from common allelic associations to cell-type–specific regulatory elements and their target genes and from these genes to pathways contributing to EOC susceptibility. It is only through an understanding of the molecular and cellular processes affected by each association signal will it be possible to eventually translate these discoveries into clinically meaningful interventions to treat, and possibly prevent, ovarian cancer. This review has highlighted the deep experimental characterization of five EOC risk loci, but there are over 25 loci yet to be followed up. Additional candidate susceptibility genes at EOC risk loci may be identified *in silico* using frameworks, such as Predixcan, that first model the association between multiple SNPs and the expression of a gene and then test association of the same set of potentially functional SNPs with disease risk (72). We believe that the next generation of the functional pipeline will rely heavily on CRIPSR-Cas9–based genome editing to generate isogenic ovarian and fallopian cell lines that differ from each other only in the genotype of single, non–protein-coding, "candidate causal" risk SNPs (73). The isogenicity will provide the template for an unbiased evaluation (i) of transcription factor binding and epigenetic changes at this risk SNP; (ii) of the effects of modifying the SNP genotype on regional gene expression; and (iii) of the effects of modified gene expression on molecular pathways and cellular phenotypes indicative of neoplastic initiation. Functional studies of EOC risk loci will necessitate the generation of genome-scale gene expression, TFBS, and chromatin interaction profiles in cells that most closely represent the cell of origin of each histotype of EOC as well as in primary EOC tumors. Appropriate mouse models will also have to be established to test the tumorigenic impact of ovarian cancer risk SNPs that lie in enhancer elements and TFBS conserved across species, as has been done with mouse studies investigating the role of *MYC* at the 8q24 colorectal cancer risk locus (50). It is envisioned that the addition of biological information in the form of eQTLs, TFBS, and chromatin interactions will in itself aid the identification of additional EOC risk loci that fail to reach genome-wide significance at present due to sample size constraints but are nevertheless modestly associated with the disease (55). The addition of such "biological priors" to SNP-level association statistics may also help improve polygenic risk prediction for EOC by separating genuine sub–genome-wide significant susceptibility signals from noise. The work carried out by the OCAC so far in elucidating the role of common genetic variation in susceptibility to EOC has thus laid the foundation for a future of increasingly interdisciplinary studies that must seamlessly blend genetic epidemiology and functional genomics to address the causal significance of EOC-associated alleles.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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