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Research Article

Combined and Interactive Effects of Environmental and GWAS-Identified Risk Factors in Ovarian Cancer

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Abstract

Background: There are several well-established environmental risk factors for ovarian cancer, and recent genome-wide association studies have also identified six variants that influence disease risk. However, the interplay between such risk factors and susceptibility loci has not been studied.

Methods: Data from 14 ovarian cancer case–control studies were pooled, and stratified analyses by each environmental risk factor with tests for heterogeneity were conducted to determine the presence of interactions for all histologic subtypes. A genetic "risk score" was created to consider the effects of all six variants simultaneously. A multivariate model was fit to examine the association between all environmental risk factors and genetic risk score on ovarian cancer risk.

Results: Among 7,374 controls and 5,566 cases, there was no statistical evidence of interaction between the six SNPs or genetic risk score and the environmental risk factors on ovarian cancer risk. In a main effects model, women in the highest genetic risk score quartile had a 65% increased risk of ovarian cancer compared with women in the lowest [95% confidence interval (CI), 1.48–1.84]. Analyses by histologic subtype yielded risk differences across subtype for endometriosis ($P_{het} < 0.001$), parity ($P_{het} < 0.01$), and tubal ligation ($P_{het} = 0.041$).

Conclusions: The lack of interactions suggests that a multiplicative model is the best fit for these data. Under such a model, we provide a robust estimate of the effect of each risk factor that sets the stage for absolute risk prediction modeling that considers both environmental and genetic risk factors. Further research into the observed differences in risk across histologic subtype is warranted. *Cancer Epidemiol Biomarkers Prev; 22(5); 880–90. ©2013 AACR.*

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Introduction

Invasive epithelial ovarian cancer (EOC) is the most fatal malignancy of the female reproductive tract. Approximately 15,460 women died from ovarian cancer in 2011 in the United States, causing more deaths than any other cancer of the female reproductive system (1). Five-year survival with EOC is less than 50%, with the majority of cases diagnosed at advanced stages (1). Screening for EOC in the general population has thus far been unsuccessful, notably the recently reported results from the Prostate, Lung, Colorectal, Ovarian (PLCO) cancer screening trial showing no shift in stage at diagnosis among screen-detected cases and no reduction in mortality (2). It has thus become increasingly important to improve risk prediction models and to better understand the underlying etiology of EOC.

A number of reproductive risk factors have been confirmed for ovarian cancer. Oral contraceptives are effective chemopreventive agents; in a large pooled analysis, a 43% reduction in risk of ovarian cancer was seen with an average of 5.8 years of oral contraceptive use (3). Parity is also strongly protective with risk decreasing with increasing number of births (4–6). Tubal ligation is also associated with a 30% decreased risk (4, 7). Conversely, a history of endometriosis is associated with a 2- to 3-fold increased risk of low-grade serous, endometrioid, and clear cell EOC (8).

In addition, women with first-degree family histories of EOC are 2 to 3 times as likely to develop the disease (9). Mutations in genes involved in Lynch syndrome as well as in the highly penetrant *BRCA1* and *BRCA2* genes confer a high risk of ovarian cancer, but because they account for less than half of the excess familial risk (10), common lower penetrance susceptibility genes also are thought to play a role (11–15). Recent genome-wide association studies (GWAS) have successfully identified and confirmed 6 single-nucleotide polymorphisms (SNP) that seem to influence the risk of EOC (11–13). These SNPs lie in genomic regions not previously known to affect risk of ovarian cancer, underscoring our limited understanding of the biology of this disease. The confirmed susceptibility SNPs are rs3814113 (located at 9p22, near *BNC2*), rs2072590 (located at 2q31, which contains a family of HOX genes), rs2665390 (located at 3q25, intronic to *TIPARP*), rs10088218 (located at 8q24, 700 kb downstream of *MYC*), rs8170 (located at 19p13, near *MERIT40*), and rs9303542 (located at 17q21, intronic to *SKAP1*; refs. 11–13).

A logical next step in examining the role of confirmed genetic susceptibility loci and other accepted environmental risk factors is to understand the interplay between the two. To this end, the Ovarian Cancer Association Consortium (OCAC; ref. 16) has undertaken an effort to study interactions focusing on the 6 confirmed loci and 6 well-accepted environmental factors: history of endometriosis, first-degree family history of ovarian cancer, oral contraceptive use, parity, tubal ligation, and age.

Materials and Methods

All studies included in this report obtained Institutional ethics committee approval and all participating subjects provided written informed consent.

Data ascertainment

Epidemiological and clinical data. Included in this report are data from 14 ovarian cancer case–control studies conducted in the United States ($n = 8$; refs. 4, 17–24), Europe ($n = 5$; refs. 25–27), and Australia (n = 1; ref. 28; Table 1). Table 1 shows the study design elements as well as the numbers of controls and cases by histologic subtype. Eleven of the studies are population-based, 2 studies are hospital-based, and one study is clinic-based. Each study site was provided with detailed coding instructions for the preparation of a primary dataset that included case–control status, tumor histology (serous, mucinous, endometrioid, clear cell, mixed, other), tumor behavior (invasive or borderline), tumor grade (well differentiated, moderately differentiated, poorly differentiated, undifferentiated), race/ethnicity, age (diagnosis for cases, reference date for controls), duration of oral contraceptive use (continuous, in months), parity (number of full-term births), tubal ligation (yes/no), history of endometriosis (yes/no), and first-degree family history of ovarian cancer (mother, number of daughters and sisters with ovarian cancer). Full-term births were defined as pregnancies lasting 6 months or longer.

Data were sent by each study investigator to the consortium data coordinating center at Duke University (Durham, NC). The epidemiologic working group of the OCAC cleaned these data and any inconsistencies in the data were resolved with the study investigators. As a validation of the epidemiologic data, the associations between ovarian cancer risk and oral contraceptive use, parity, tubal ligation, history of endometriosis, and first-degree family history of ovarian cancer for each study site were assessed to ensure that the expected associations were observed in each dataset (where the data were

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Table 1. Description of study sites included in the analysis

Study name	Study abbreviation	Country	Study type	Years of collection	Number of controls	Number of cases	Serous[a]	Mucinous	Endometrioid	Clear cell	Other[b]
Australian Ovarian Cancer Study	AUS	Australia	Population-based	2002–2006	1122	1003	616	39	130	68	150
Diseases of the Ovary and their Evaluation Study	DOV	USA	Population-based	2002–2005	604	530	303	18	84	30	95
German Ovarian Cancer Study	GER	Germany	Population-based	1993–1996	433	203	106	21	22	6	48
Hawaii Ovarian Cancer Study	HAW	USA	Population-based	1993–2008	170	81	43	3	13	6	16
Novel Risk Factors and Potential Early Detection Markers for Ovarian Cancer	HOP	USA	Population-based	2003–2009	388	385	220	19	53	31	62
Malignant Ovarian Cancer Study	MAL	Denmark	Population-based	1994–1999	551	445	274	43	56	33	39
Mayo Clinic Ovarian Cancer Case Control Study[c]	MAY	USA	Clinic-based	2000–2007	422	319	205	11	63	22	18
North Carolina Ovarian Cancer Study	NCO	USA	Population-based	1999–2008	655	493	293	20	81	58	41
Nijmegen Ovarian Cancer Study	NTH	Netherlands	Hospital-based	2008	577	243	100	30	60	18	35
Polish Ovarian Cancer Case Control Study[c]	POL	Poland	Population-based	2000–2003	228	238	108	23	53	13	41
Family Registry for Ovarian Cancer and Genetic Epidemiology[c]	STA	USA	Population-based	1997–2001	413	295	184	18	38	23	32
University of California, Irvine Ovarian Cancer Study[c]	UCI	USA	Population-based	1993–2005	494	280	167	17	46	21	29
United Kingdom Ovarian Cancer Population Study[c]	UKO	United Kingdom	Hospital-based	2006–2010	852	710	359	71	121	71	88
University of Southern California, Study of Lifestyle and Women's Health	USC	USA	Population-based	1993–2005	465	341	183	26	44	15	73
				Total:	7374	5566	3161	359	864	415	767

[a]73.4% high-grade, 7.9% low-grade, 18.7% grade unknown.

[b]Includes mixed cell, other specified epithelial ovarian cancer, undifferentiated/poorly differentiated epithelial, and unknown but known to be epithelial.

[c]Missing data for nongenetic variables (MAY missing tubal ligation, UCI missing 30% tubal ligation, POL and STA missing endometriosis, UKO >20% missing oral contraceptive use, endometriosis, tubal ligation, and parity).

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available; see Table 1 footnote c); all expected associations were observed for each study (data not shown).

Genotype data. Individual-level genotype data were obtained for all subjects from the genotype coordinating center at Cambridge University (Cambridge, UK) for 6 SNPs that are confirmed susceptibility loci for ovarian cancer: rs3814113, rs2072590, rs2665390, rs10088218, rs8170, and rs9303542. For MAY, NCO, and UKO, rs9303542 was imputed from GWAS data (12).

The genotype data had previously been cleaned and the primary genetic association study results have been published (11–13). The results reported here are restricted to the 14 studies that also had data available on the environmental epidemiologic risk factors. Because these results are based on the subset of studies that had both epidemiologic and genetic data, we reanalyzed the genetic associations for the 6 SNPs in these 14 studies to ensure that we observed the expected genetic associations (see "Main effect: Current report" category in Table 2 and Supplementary Tables S1–S6).

Statistical analysis

All analyses were restricted to non-Hispanic white, Hispanic white, and black participants. Only invasive EOC cases were included.

To evaluate the presence of statistical interactions, we stratified by each environmental risk factor and conducted a test for heterogeneity across the strata. All models were run by site and conditioned on race/ethnicity (non-Hispanic white, Hispanic white, and black) and age (<50, 50–54, 55–59, 60–64, 65+) except when the variable of interest was age. Genotype was modeled as an ordinal variable taking a value of 0 (homozygous for the major allele), 1 (heterozygous), or 2 (homozygous for the minor allele) except for imputed values that also ranged from 0 to 2 (explained below). The risk factors were modeled as follows: duration of oral contraceptive use (never use, <1, 1–1.99, 2–4.99, 5–9.99, 10+ years), parity (0, 1, 2+ full-term births), tubal ligation (yes/no), self-reported history of endometriosis (yes/no), first-degree family history of ovarian cancer (yes/no where "yes" corresponded to a positive ovarian cancer history among mother, sister, or daughter), and age at diagnosis (<50, 50–54, 55–59, 60–64, 65+). Grade was categorized as well differentiated versus moderately/poorly differentiated or undifferentiated. In addition, models were fit for each histologic subtype (high-grade serous, low-grade serous, mucinous, endometrioid, clear cell). The pooled OR was obtained by carrying out a fixed-effects meta-analysis of the individual site data.

In addition to fitting models for each SNP and risk factor separately, a genetic "risk score" was calculated to take into account the 6 SNPs simultaneously. We used mean substitution imputation stratified by study to impute missing genotypes to avoid loss of data (29), as subjects missing any one of the 6 genotypes would otherwise have been dropped from the analysis. Mean substitution imputation replaces a missing genotype with the mean genotype (twice the minor allele frequency in cases and controls combined) for that SNP. rs3814113 was not genotyped for the NTH study so we used the mean genotype for the MAL study given the similar genetic ancestry of these 2 populations. To reduce bias in creating the risk score, the beta-coefficient for each SNP was calculated from the ORs reported in the published papers that used the entire set of studies for which genotype data is available, that is, the beta-coefficients used to calculate the risk score were not derived solely from the studies with epidemiologic data. This limits concerns related to the "winner's curse" and further, the beta-coefficient resulting from an analysis limited to studies without epidemiologic data (i.e., studies independent from those used in the gene–environment interaction analysis) was more extreme than that obtained from the analysis using all of the available data. The beta-coefficient for each SNP was multiplied by the genotype value (0–2) for each subject and then these values for the 6 SNPs were summed to obtain the risk score for each individual. A risk score was calculated for all invasive and for each histologic subtype. To determine whether the risk score captured all of the genetic risk information, we fit separate models that included risk score and each of the individual SNPs in turn. In all cases, the effect of the individual SNP was near 1.0 and not statistically significant when risk score was included in the model (data not shown). The genetic risk score was modeled as a continuous variable with regard to interactions with the environmental risk factors. Serous ovarian cancers could not be separated on the basis of grade for this analysis because no published data on the beta-coefficients by grade were available.

In addition to examining the gene–environment interactions, a single logistic regression model was fit to simultaneously examine the main effect associations between 5 of the environmental risk factors and the 6 SNPs with ovarian cancer risk (because most studies were broadly matched on age, it was not possible to assess main effect ORs associated with age). All models were fit by site and conditioned on age and race/ethnicity, and these environmental risk factors were modeled as described above. The genetic risk score was modeled in quartiles (based on the distribution in controls) for ease of interpretation. Histologic-specific subtype analyses were also carried out, but serous cases could not be evaluated on the basis of the grade for this analysis because it included genetic risk score.

The pooled OR for each risk factor was obtained by carrying out a fixed-effects meta-analysis of the individual site data. Some sites did not have data available for a particular risk factor (see Table 1 footnote), therefore those studies did not contribute to the pooled estimate for that risk factor. To avoid loss of data because of missing information across risk factors (i.e., a subject would be excluded from the analysis because she was missing data for just one risk factor), a missing indicator category was created for each risk factor. The P_{het} value for each risk factor from the fixed-effects meta-analysis was evaluated.

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Table 2. Association between each SNP and invasive ovarian cancer among all women and by environmental factors

	rs3814113		rs2072590		rs2665390		rs10088218		rs8170		rs9303542	
	OR[a] (95% CI)	P_{het}[b]	OR[a] 95% CI	P_{het}[b]	OR[a] 95% CI	P_{het}[b]	OR[a] 95% CI	P_{het}[b]	OR[a] 95% CI	P_{het}[b]	OR[a] 95% CI	P_{het}[b]
Main effect: Previously published result (11–13)	0.82 (0.79–0.86)		1.16 (1.12–1.21)		1.19 (1.11–1.27)		0.84 (0.80–0.89)		1.12 (1.07–1.17)		1.11 (1.06–1.16)	
Main effect: Current report[c]	0.82 (0.77–0.88)		1.13 (1.07–1.19)		1.25 (1.14–1.38)		0.84 (0.78–0.91)		1.07 (1.01–1.14)		1.11 (1.04–1.17)	
Endometriosis												
Yes	0.84 (0.60–1.16)		1.45 (1.14–1.85)		1.73 (1.10–2.73)		0.78 (0.61–1.01)		1.06 (0.82–1.36)		0.93 (0.71–1.23)	
No	0.83 (0.76–0.91)	0.98	1.12 (1.06–1.19)	0.05	1.23 (1.10–1.37)	0.15	0.84 (0.78–0.90)	0.60	1.12 (1.05–1.19)	0.69	1.05 (0.98–1.13)	0.41
First-degree family history												
Yes	0.67 (0.46–0.99)		1.01 (0.73–1.38)		0.98 (0.54–1.77)		0.74 (0.47–1.16)		1.07 (1.00–1.15)		1.10 (1.04–1.17)	
No	0.83 (0.78–0.88)	0.30	1.13 (1.07–1.19)	0.49	1.25 (1.13–1.37)	0.43	0.84 (0.78–0.92)	0.56	0.92 (0.65–1.32)	0.42	1.08 (0.75–1.57)	0.93
Oral contraceptive use												
Never	0.77 (0.70–0.86)		1.06 (0.96–1.16)		1.22 (1.03–1.43)		0.84 (0.73–0.96)		1.10 (0.99–1.23)		1.11 (1.00–1.22)	
<1 year	0.82 (0.66–1.02)		1.18 (0.97–1.44)		1.24 (0.88–1.75)		0.79 (0.59–1.04)		0.83 (0.67–1.04)		1.21 (0.99–1.48)	
1–1.99 years	1.03 (0.80–1.33)		1.31 (1.03–1.68)		1.68 (1.05–2.67)		0.86 (0.60–1.25)		1.19 (0.89–1.60)		1.27 (0.98–1.65)	
2–4.99 years	0.80 (0.67–0.96)		1.15 (0.99–1.34)		1.36 (1.03–1.79)		0.73 (0.58–0.93)		1.00 (0.83–1.20)		1.00 (0.85–1.18)	
5–9.99 years	0.87 (0.74–1.03)		1.10 (0.94–1.27)		1.31 (1.01–1.69)		0.80 (0.64–0.99)		1.13 (0.94–1.36)		1.16 (1.00–1.35)	
10+ years	0.92 (0.78–1.09)	0.27	1.19 (1.02–1.38)	0.52	1.41 (1.08–1.83)	0.81	0.98 (0.78–1.22)	0.63	1.11 (0.93–1.33)	0.24	1.16 (0.99–1.36)	0.56
Tubal ligation												
Yes	0.91 (0.78–1.06)		1.22 (1.06–1.39)		1.23 (0.97–1.54)		0.74 (0.60–0.91)		1.04 (0.97–1.13)		1.13 (1.05–1.20)	
No	0.81 (0.76–0.87)	0.21	1.10 (1.03–1.17)	0.21	1.32 (1.18–1.49)	0.55	0.86 (0.78–0.95)	0.19	1.22 (1.04–1.43)	0.09	1.05 (0.92–1.21)	0.42
Parity												
No births	0.82 (0.70–0.96)		1.07 (0.93–1.24)		1.20 (0.94–1.53)		0.83 (0.68–1.02)		1.08 (0.91–1.28)		1.08 (0.93–1.26)	
1 birth	0.78 (0.66–0.93)		1.15 (0.99–1.33)		1.46 (1.10–1.93)		0.87 (0.69–1.10)		1.05 (0.88–1.26)		1.07 (0.91–1.26)	
2–3 births	0.86 (0.79–0.94)		1.12 (1.04–1.21)		1.21 (1.05–1.38)		0.84 (0.75–0.94)		1.11 (1.01–1.22)		1.11 (1.03–1.21)	
4–5 births	0.74 (0.61–0.89)		1.25 (1.04–1.49)		1.30 (0.96–1.74)		0.68 (0.52–0.89)		0.96 (0.78–1.17)		1.09 (0.91–1.30)	
6+ births	1.23 (0.71–2.14)	0.31	1.28 (0.72–2.27)	0.31	2.26 (0.98–5.19)	0.48	0.80 (0.38–1.69)	0.68	0.74 (0.43–1.30)	0.48	1.09 (0.64–1.87)	0.99
Age												
<50 years old	0.83 (0.73–0.94)		1.20 (1.07–1.35)		1.33 (1.08–1.64)		0.82 (0.70–0.97)		0.96 (0.83–1.10)		1.12 (1.00–1.26)	
50–54 years old	0.83 (0.71–0.98)		1.12 (0.97–1.30)		1.25 (0.96–1.63)		0.94 (0.75–1.17)		1.07 (0.89–1.28)		1.21 (1.04–1.40)	
55–59 years old	0.77 (0.67–0.90)		1.07 (0.94–1.23)		1.17 (0.93–1.47)		0.94 (0.78–1.14)		1.18 (1.01–1.39)		1.03 (0.89–1.18)	
60–64 years old	0.80 (0.68–0.93)		1.12 (0.98–1.27)		1.38 (1.10–1.74)		0.84 (0.69–1.02)		1.13 (0.97–1.32)		0.99 (0.86–1.14)	
65+ years old	0.87 (0.78–0.98)	0.77	1.11 (1.00–1.23)	0.78	1.25 (1.04–1.50)	0.87	0.78 (0.67–0.91)	0.52	1.09 (0.97–1.22)	0.34	1.17 (1.05–1.30)	0.20

[a]OR conditioned on race/ethnicity, individual models by site; estimate derived from meta-analysis of individual site models.

[b]P_{het} = heterogeneity across strata of environmental factor.

[c]Main effect of genotype based on a log-additive model.

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If heterogeneity was present, based on a $P \leq 0.05$, a systematic evaluation to determine the source was undertaken by removing one site at a time until the source(s) of heterogeneity were identified.

All P values reported are two-sided.

Results

Details of the 14 studies are given in Table 1. The case–control analysis included 7,374 controls and 5,566 cases. As expected, the majority of cases were serous, followed by the endometrioid, clear cell, and mucinous subtypes.

The main effect of each SNP with risk of ovarian cancer has been presented elsewhere (11–13) for the larger dataset of all OCAC studies, but is shown again in the first line in Table 2 and Supplementary Tables S1–S6 under the heading "Main effect: Previously published result". The main effect of the SNP is given for the 14 studies in the current report in Table 2 and Supplementary Tables S1–S6 under the heading "Main effect: Current report". The results are consistent with the previously published results with all SNPs showing a significant main effect association with the risk of ovarian cancer.

There was no evidence of statistical interaction between any of the 6 SNPs and the 6 ovarian cancer environmental risk factors (endometriosis, first-degree family history of ovarian cancer, oral contraceptive use, parity, tubal ligation, and age at diagnosis) on overall risk of ovarian cancer (i.e., when all histologic subtypes were combined). These results are presented in Table 2 and Supplementary Tables S1–S6.

The genetic risk score captures the combined effects of the 6 susceptibility SNPs. This risk score is based on beta-coefficients and can have a positive or negative value depending on the genotypes for each subject. The range of risk scores for the controls was −0.744 to 0.800 units and for cases was −0.744 to 0.923 units. The main effect of the genetic risk score and ovarian cancer risk is shown in Table 3; the OR for a one-unit increase in genetic risk was 2.56 (95% CI, 2.14–3.06). As with the individual SNP effects, we found no statistically significant interactions between the environmental risk factors and the combined

Table 3. Association between genetic risk score and ovarian cancer among all women and by environmental factors

	Invasive		Serous		Mucinous		Endometrioid		Clear cell	
	OR[a] (95% CI)	P_{het}[b]	OR[a] 95% CI	P_{het}[b]	OR[a] 95% CI	P_{het}[b]	OR[a] 95% CI	P_{het}[b]	OR[a] 95% CI	P_{het}[b]
All women	2.56 (2.14–3.06)		2.50 (2.13–2.94)		2.61 (1.41–4.81)		3.49 (2.18–5.59)		3.11 (1.31–7.39)	
Endometriosis										
Yes	4.35 (2.09–9.05)		6.50 (3.10–13.63)		2.88 (0.06–143.62)		6.86 (1.32–35.66)		2.03 (0.13–30.77)	
No	2.47 (2.02–3.02)	0.14	2.31 (1.93–2.77)	0.01	2.50 (1.24–5.01)	0.94	3.86 (2.24–6.67)	0.52	3.73 (1.31–10.61)	0.68
First-degree family history										
Yes	2.48 (0.87–7.08)		3.02 (1.22–7.44)		0.33 (0.00–61.92)		0.22 (0.01–5.00)		—	
No	2.51 (2.09–3.01)	0.98	2.44 (2.06–2.88)	0.65	2.70 (1.44–5.06)	0.43	3.72 (2.29–6.04)	0.08	3.69 (1.53–8.91)	
Oral contraceptive use										
Never	2.61 (1.92–3.54)		2.76 (2.09–3.63)		1.99 (0.74–5.34)		4.84 (2.24–10.43)		2.02 (0.46–8.91)	
<1 year	2.54 (1.36–4.75)		2.35 (1.37–4.03)		4.63 (0.17–123.03)		1.47 (0.19–11.27)		15.18 (0.48–478.27)	
1–1.99 years	2.99 (1.40–6.37)		3.03 (1.51–6.06)		15.72 (0.07–3522.25)		0.73 (0.09–6.29)		0.64 (0.01–43.62)	
2–4.99 years	2.61 (1.55–4.39)		2.48 (1.55–3.98)		2.67 (0.20–36.47)		1.54 (0.31–7.60)		16.95 (1.17–244.76)	
5–9.99 years	2.66 (1.64–4.32)		2.14 (1.37–3.35)		2.93 (0.64–13.43)		5.87 (1.45–23.76)		0.54 (0.03–8.67)	
10+ years	2.49 (1.53–4.07)	1.00	1.88 (1.19–2.97)	0.74	0.76 (0.11–5.14)	0.84	6.89 (1.64–28.91)	0.33	0.32 (0.01–11.28)	0.32
Tubal ligation										
Yes	2.93 (1.89–4.55)		2.47 (1.69–3.62)		2.18 (0.24–20.32)		5.48 (1.24–24.20)		2.28 (0.13–41.13)	
No	2.52 (2.04–3.12)	0.54	2.46 (2.03–2.99)	0.98	2.79 (1.40–5.58)	0.84	4.05 (2.34–7.00)	0.71	5.55 (2.06–14.94)	0.57
Parity										
No births	2.15 (1.38–3.36)		2.19 (1.45–3.31)		4.23 (1.07–16.78)		1.40 (0.49–3.97)		2.71 (0.49–14.92)	
1 birth	3.07 (1.85–5.10)		2.60 (1.64–4.10)		4.28 (0.79–23.30)		7.07 (1.87–26.69)		3.47 (0.17–69.26)	
2–3 births	2.36 (1.84–3.02)		2.29 (1.83–2.87)		2.39 (0.97–5.92)		2.71 (1.32–5.59)		2.30 (0.55–9.72)	
4–5 births	4.05 (2.28–7.20)		3.52 (2.14–5.79)		5.39 (0.20–142.90)		9.03 (1.73–47.26)		19.43 (0.31–1206.17)	
6+ births	1.91 (0.43–8.59)	0.40	2.04 (0.55–7.56)	0.59	—	0.86	1.58 (0.02–116.21)	0.24	–	0.82
Age										
<50 years old	2.64 (1.83–3.80)		2.53 (1.77–3.60)		4.25 (1.39–12.99)		4.64 (1.85–11.61)		4.18 (0.64–27.11)	
50–54 years old	2.63 (1.62–4.27)		2.11 (1.36–3.29)		1.30 (0.19–8.79)		3.31 (0.97–11.27)		2.30 (0.18–28.95)	
55–59 years old	2.16 (1.41–3.31)		2.16 (1.46–3.18)		3.08 (0.60–15.75)		4.13 (1.32–12.94)		4.86 (0.80–29.46)	
60–64 years old	2.61 (1.69–4.04)		2.68 (1.84–3.90)		0.91 (0.15–5.66)		1.85 (0.47–7.34)		4.44 (0.47–42.19)	
65+ years old	2.63 (1.88–3.69)	0.96	2.68 (1.99–3.61)	0.84	2.95 (0.88–9.95)	0.63	2.54 (1.01–6.38)	0.80	1.28 (0.15–10.80)	0.89

[a]OR conditioned on race/ethnicity, individual models by site; estimate derived from meta-analysis of individual site models.
[b]P_{het} = heterogeneity across strata of environmental factor.

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genetic risk score with the exception of endometriosis and serous ovarian cancer (Table 3). The relative risk for serous ovarian cancer associated with a one unit change in genetic risk score was 6.50 among women with a history of endometriosis compared with 2.31 for women with no such history ($P_{het} = 0.01$), but this was the only statistically significant association across the entire analysis.

Table 4 shows the effect of 5 environmental risk factors, and the quartiles of the genetic risk score modeled jointly (multiplicatively) with the risk of ovarian cancer, given that there was little evidence of a departure from multiplicativity. We had minimal evidence of heterogeneity in effect across sites. No heterogeneity ($P > 0.05$ for all comparisons) was present for invasive ovarian cancer and any of the risk factors. For serous ovarian cancer, there was heterogeneity of effect in genetic risk score, but this was driven entirely by the GER site in which the effect estimate for one SNP (rs2665390) went in the opposite direction from all other sites. This was true in the published article on the main effect of this SNP (12). We also observed heterogeneity of effect for the endometrioid subtype related to oral contraceptive use (2–4.99 years of use; $P = 0.04$) and parity (2+ births, $P = 0.03$). This was driven by instability in the estimate for sites with small numbers of cases for this subtype.

Genetic risk score, endometriosis, and first-degree family history of ovarian cancer were associated with an increased risk whereas tubal ligation, oral contraceptive use, and parity were associated with a decreased risk of ovarian cancer (Table 4). For invasive cases, the OR for endometriosis was 1.53 (95% CI 1.30–1.81), but as we have previously reported, this association was restricted to endometrioid and clear cell ovarian cancer where the risk was substantially higher (Table 4). Women with a reported first-degree family history of ovarian cancer were twice as likely to develop invasive ovarian cancer (OR = 2.09, 95% CI 1.70–2.57) and this did not vary by subtype. The association with family history was not attenuated with the addition of genetic risk score to the model (OR without genetic risk score = 2.11 and OR with genetic risk score as shown in Table 4 = 2.09). Likewise, the association with genetic risk score quartile was not attenuated when family history was added to the model (data not shown). The risk associated with genetic risk quartile was linear and did not vary by subtype (Table 4). The associations with the other environmental risk factors were consistent across histologic subtype with respect to direction of effect, though some differences in magnitude were observed. Risk of ovarian cancer was decreased among oral contraceptive users in a duration-dependent manner, with increasing years of use associated with a greater reduction in risk across all subtypes. Tubal ligation was also associated with a 26% lower risk of invasive ovarian cancer (95% CI 0.67–0.83), and this reduced risk was seen for all subtypes, though some heterogeneity of effect was observed with regard to the magnitude of the reduction ($P_{het} = 0.041$). A significant protective effect of parity was also observed across all subtypes of invasive ovarian cancer, but the magnitude of effect varied ($P_{het} < 0.01$).

Discussion

In this comprehensive analysis of gene–environment interactions between confirmed ovarian cancer lifestyle/reproductive factors and genetic susceptibility loci, we found no evidence that these environmental variables modified the SNP associations with ovarian cancer risk with the possible exception of genetic risk score and endometriosis. However, given the number of comparisons in this analysis, this finding is likely due to chance.

The risk associated with each individual SNP is quite modest, on the order of 10% to 20% increased or decreased risk. We have reported for the first time on the combined effect of the 6 confirmed ovarian cancer susceptibility loci and the combined effect of these SNPs is somewhat larger. In a main effects model, a one-unit increase in genetic risk score was associated with a 2.56-fold increased risk of ovarian cancer (95% CI 2.14–3.06; Table 3). Although some women are at a very high genetic risk, few individuals fall into either the lowest or highest category of risk score units, and results across quartiles of the observed risk score distribution suggest that the combined effects of these 6 susceptibility alleles are associated with somewhat less than a 2-fold increase in risk comparing the lowest with the highest quartile. The adjusted results (Table 4) indicate that the effect of genetic risk score is not accounted for by a positive family history of ovarian cancer and vice versa. This suggests that other yet to be discovered genetic variants remain. Efforts to identify other genetic susceptibility loci are ongoing and will likely yield additional variants related to ovarian cancer risk.

Given the observed multiplicative nature of the data, the results shown in Table 4 provide the current best estimate of the joint effects of these risk factors on ovarian cancer risk. In addition to the 65% increased risk of ovarian cancer associated with being in the highest compared with the lowest quartile of genetic risk, a personal history of endometriosis and a first-degree family history of ovarian cancer were also associated with increased risk. Risk of ovarian cancer was lower for women who have used oral contraceptives, have borne children, or have had a tubal ligation.

Importantly, we have been able to show the risks associated with specific histologic subtypes with this large dataset. We have previously shown that the risk of ovarian cancer associated with endometriosis is restricted to the clear cell, endometrioid, and low-grade serous subtypes (8). However, we were unable to separate low- and high-grade serous cancers for the current analysis due to the inclusion of genetic risk score for which data by grade were not available. The observed associations for serous carcinoma presented in Table 4 more generally relate to high-grade serous ovarian cancer because this subtype is far more common than the low-grade serous subtype.

We observed no heterogeneity of effect across subtype for family history of ovarian cancer, oral contraceptive

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Table 4. Association between environmental and genetic factors and ovarian cancer risk in a multiplicative joint effects model

	Invasive		Serous		Mucinous		Endometrioid		Clear cell		P_{het} across histology
	OR[a] (95% CI)	*P*	OR[a] 95% CI	*P*	OR[a] 95% CI	*P*	OR[a] 95% CI	*P*	OR[a] 95% CI	*P*	
Endometriosis											
Yes vs. no	1.53 (1.30–1.81)	<0.001	1.17 (0.95–1.44)	0.143	1.54 (0.86–2.74)	0.145	2.40 (1.78–3.23)	<0.001	3.59 (2.50–5.15)	<0.001	<0.001
First-degree family history											
Yes vs. no	2.09 (1.70–2.57)	<0.001	2.29 (1.81–2.89)	<0.001	2.40 (1.25–4.61)	0.009	1.96 (1.28–3.00)	0.002	2.15 (0.94–4.92)	0.071	0.929
Oral contraceptive use											
1–1.99 years vs. never	0.70 (0.59–0.83)	<0.001	0.80 (0.65–0.98)	0.031	0.75 (0.36–1.57)	0.451	0.64 (0.45–0.92)	0.016	0.76 (0.46–1.24)	0.272	0.798
2–4.99 years vs. never	0.57 (0.50–0.65)	<0.001	0.65 (0.56–0.77)	<0.001	0.56 (0.35–0.90)	0.016	0.45 (0.34–0.60)	<0.001	0.55 (0.37–0.83)	0.004	0.167
5–9.99 years vs. never	0.48 (0.42–0.55)	<0.001	0.53 (0.45–0.62)	<0.001	0.68 (0.46–1.01)	0.054	0.41 (0.31–0.54)	<0.001	0.40 (0.27–0.58)	<0.001	0.097
10+ years vs. never	0.34 (0.30–0.39)	<0.001	0.39 (0.33–0.46)	<0.001	0.48 (0.32–0.72)	<0.001	0.28 (0.21–0.38)	<0.001	0.28 (0.18–0.44)	<0.001	0.083
Tubal ligation											
Yes vs. no	0.74 (0.67–0.83)	<0.001	0.84 (0.74–0.95)	0.007	0.65 (0.42–0.99)	0.043	0.57 (0.44–0.73)	<0.001	0.68 (0.47–0.99)	0.046	0.041
Parity											
1 birth vs. no births	0.76 (0.66–0.88)	<0.001	0.89 (0.75–1.06)	0.175	0.76 (0.49–1.17)	0.214	0.69 (0.53–0.91)	0.009	0.39 (0.26–0.58)	<0.001	0.002
2 or more births vs. no births	0.58 (0.51–0.65)	<0.001	0.66 (0.58–0.76)	<0.001	0.52 (0.37–0.73)	<0.001	0.42 (0.34–0.53)	<0.001	0.25 (0.18–0.33)	<0.001	<0.001
Risk score quartile											
Second vs. first quartile	1.25 (1.12–1.40)	<0.001	1.33 (1.15–1.53)	<0.001	1.72 (1.20–2.48)	0.004	1.25 (0.98–1.59)	0.068	1.19 (0.84–1.69)	0.329	0.463
Third vs. first quartile	1.29 (1.16–1.44)	<0.001	1.36 (1.19–1.56)	<0.001	1.31 (0.91–1.90)	0.151	1.13 (0.89–1.43)	0.321	1.20 (0.86–1.69)	0.289	0.577
Fourth vs. first quartile	1.65 (1.48–1.84)	<0.001	1.85 (1.62–2.11)	<0.001	1.76 (1.24–2.48)	0.001	1.64 (1.31–2.05)	<0.001	1.59 (1.15–2.21)	0.006	0.728

[a]OR conditioned on age and race/ethnicity, individual models by site; estimate derived from meta-analysis of individual site models.

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use, or genetic risk score. Several studies have suggested an increased risk or no association between mucinous ovarian cancer and oral contraceptive use (30–33), but this was not the case in our analysis or in another smaller pooled analysis (34). A total of 1,834 invasive cases and 7,484 controls were included in this earlier, smaller pooled analysis, which consisted of 9 case–control studies conducted in the 1970s and 1980s that do not overlap with those in our study and one case–control study that does overlap with our study (STA; ref. 34). Risk decreased in a similar manner with respect to years of oral contraceptive use for all of the subtypes (Table 4). Previous studies have also suggested no association between mucinous ovarian cancer and family history of ovarian cancer (30, 35), but in this large pooled analysis, we found a strong association (OR = 2.40, $P = 0.009$). The smaller pooled analysis is also consistent with our finding (OR = 1.80, 95% CI 1.10–3.20; ref. 34).

We found a decreased risk associated with tubal ligation for all of the subtypes (OR = 0.74), however significant heterogeneity was present ($P = 0.041$). This was driven by the difference in effect estimates between the serous (OR = 0.84) and endometrioid (OR = 0.57) subtypes. The mechanism for such a difference is unclear, but could lie in tubal ligation eliminating retrograde menstruation, which may be more strongly associated with the endometrioid subtype compared with the serous subtype. Similarly, although parity was associated with a decreased risk of all subtypes, significant heterogeneity of effect was also present ($P < 0.01$). This is largely driven by a stronger protective effect for clear cell and to a lesser extent endometrioid compared with the serous and mucinous subtypes. Interestingly, in the smaller pooled analysis of Kurian and colleagues (34), a stronger protective effect of pregnancy was observed for clear cell ovarian cancer. The underlying reason for these histologic differences is not obvious. Differences in risk associations across subtypes have been reported for smoking and menopausal hormone therapy (30, 31), but these data were not available in this analysis.

We chose to limit our gene–environment interaction analyses to ovarian cancer risk factors for which there is little controversy as to their role in ovarian cancer. Parity, oral contraceptive use, endometriosis, tubal ligation, family history, and age are all accepted risk/protective factors. Likewise, we studied genetic loci that have been shown to be associated with ovarian cancer risk within a large number of studies. The fact that we did not identify any clear gene–environment interactions may not be that surprising. These are the first 6 loci to be identified for ovarian cancer and are likely the "lowest hanging fruit" that are not influenced by any environmental risk factor. Of note is the absence of interaction between age and these genetic variants, which is contrary to the widely held view that ovarian cancers diagnosed in younger women are more genetic in nature. It may be that major genes, such as *BRCA1* and *BRCA2*, are associated with age, but common genetic variants do not influence age at diagnosis.

Although the study designs differ (see Table 1), the associations with each of the environmental risk factors were observed in each individual study (data not shown) suggesting that substantial bias according to study design is unlikely. Although the studies included here are only a subset of those used in the primary main effect genetic analyses, we have shown that the SNP associations were also robust in this dataset (see Table 2 and Supplementary Tables S1–S6, "Main effect: Current report"). The sample size available for this study was large, with more than 5,000 cases and 7,000 controls. Nevertheless, when looking at specific histologic subtypes, the numbers for clear cell, endometrioid, and mucinous cancer were modest (Table 1) making it more difficult to detect interactions with these subtypes.

In this study, the effect of the 6 confirmed ovarian cancer susceptibility loci did not differ across a range of ovarian cancer lifestyle/reproductive factors thus suggesting that a simple multiplicative model incorporating the joint effects of each of these factors is appropriate. Tubal ligation, oral contraceptive use, and parity are protective for ovarian cancer, whereas genetic risk score, a history of endometriosis, and a first-degree family history of ovarian cancer increase risk. The evidence of heterogeneity across histologic subtypes of ovarian cancer and parity and tubal ligation was related to a higher magnitude of the protective effects for some of the subtypes. Investigation into the biology underlying these differences is needed.

Disclosure of Potential Conflicts of Interest

U. Menon has financial interests in Abcodia. No potential conflicts of interest were disclosed by the other authors.

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