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Manuscripts

A splicing variant of *TERT* identified by GWAS interacts with menopausal estrogen therapy in risk of ovarian cancer

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SHORT TITLE

GxE interactions with estrogen therapy in ovarian cancer

KEYWORDS

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ABBREVIATIONS USED

ET = estrogen-alone therapy

OCAC = Ovarian Cancer Association Consortium

HT = hormone therapy

NHANES = National Health and Nutrition Examination Survey

GWAS = genome-wide association study

OC = oral contraceptive

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SNP = single nucleotide polymorphism

COGS = Collaborative Oncological Gene-environment Study

LAMP = Local Ancestry in Admixed Populations

OR = odds ratio

CI = confidence interval

LRT = likelihood ratio test

ICR = interaction contrast ratio

ARTICLE CATEGORY

Cancer Epidemiology

NOVELTY AND IMPACT

This is the first study to present evidence of statistical interactions between postmenopausal estrogen-alone therapy use and confirmed ovarian cancer susceptibility alleles on risk of serous and endometrioid ovarian cancer, suggesting effects that may not be independent. Of particular interest is the interaction with rs10069690, a functional variant located in *TERT*, a gene involved in the formation of the enzyme telomerase and whose expression is upregulated by estrogen.

CONFLICT OF INTEREST DISCLOSURES

Dr. Usha Menon owns shares and received research funding from Abcodia Ltd, a University College London spin-out company with an interest in biomarkers and ovarian cancer screening.

Dr. Marc Goodman is a consultant to Johnson and Johnson.

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Accepted Article

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ABSTRACT

Menopausal estrogen-alone therapy (ET) is a well-established risk factor for serous and endometrioid ovarian cancer. Genetics also plays a role in ovarian cancer, which is partly attributable to 18 confirmed ovarian cancer susceptibility loci identified by genome-wide association studies. The interplay among these loci, ET use, and ovarian cancer risk has yet to be evaluated. We analyzed data from 1,414 serous cases, 337 endometrioid cases, and 4,051 controls across 10 case-control studies participating in the Ovarian Cancer Association Consortium (OCAC). Conditional logistic regression was used to determine the association between the confirmed susceptibility variants and risk of serous and endometrioid ovarian cancer among ET users and non-users separately and to test for statistical interaction. A splicing variant in *TERT*, rs10069690, showed a statistically significant interaction with ET use for risk of serous ovarian cancer (p_{int}=0.013). ET users carrying the T allele had a 51% increased risk of disease (OR=1.51, 95% CI 1.19-1.91), which was stronger for long-term ET users of 10+ years (OR=1.85, 95% CI 1.28-2.66, p_{int}=0.034). Non-users showed essentially no association (OR=1.08, 95% CI 0.96-1.21). Two additional genomic regions harboring rs7207826 (C allele) and rs56318008 (T allele) also had significant interactions with ET use for the endometrioid histotype (p_{int}=0.021 and p_{int}=0.037, respectively). Hence, a total of three confirmed susceptibility variants were identified whose associations with ovarian cancer risk are modified by ET exposure; follow-up is warranted given that these interactions are not adjusted for multiple comparisons. These findings, if validated, may elucidate the mechanism of action of these loci.

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INTRODUCTION

The etiology of ovarian carcinoma (ovarian cancer) is influenced by several hormonal factors, including menopausal hormone therapy (HT) use. Approximately five million women in the United States currently use HT, and according to the National Health and Nutrition Examination Survey (NHANES) in 2010, the most commonly used type of HT among women aged 40 years and older is estrogen-alone therapy (ET) (1,2). ET is a well-established risk factor for serous and endometrioid ovarian cancer (2-4). Most recently, Lee et al demonstrated that use of ET postmenopausally was associated with a 57% and 82% increased risk of serous and endometrioid ovarian cancer, respectively (5); the meta-analysis by the Collaborative Group on Epidemiological Studies of Ovarian Cancer showed these histotype effects as well (2).

Ovarian cancer also has a strong genetic component. A large part is attributable to high-penetrance susceptibility mutations, but common variants identified using genome-wide association studies (GWASs) play important roles as well. There are currently 18 confirmed ovarian cancer common susceptibility loci that explain approximately 3.9% of the disease's excess familial risk (6-13). Each of these common variants is associated with extremely modest relative risk estimates, but it is possible that interactions between non-genetic and genetic risk factors exist, thereby putting some women at higher risk.

Pearce et al previously examined the interactive effects between six GWAS-identified common variants and five well-accepted non-genetic risk factors: first-degree family history of ovarian cancer, tubal ligation, parity, oral contraceptive (OC) use, and personal history of endometriosis (14). However, menopausal ET, which has consistently been shown to be associated with risk of serous and endometrioid ovarian cancer (2,5), was not included in these analyses. Using data from the Ovarian Cancer Association Consortium (OCAC), we have

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evaluated potential statistical interactions between menopausal ET use and the 18 confirmed

ovarian cancer common susceptibility alleles. To our knowledge, this is the first study to

investigate the interactions between menopausal ET use and ovarian cancer susceptibility loci on

disease risk.

MATERIALS AND METHODS

All studies included in this analysis had approval from ethics committees and written

informed consent was obtained from all study participants.

Study Populations

A total of 10 case-control studies participating in the OCAC

(http://apps.ccge.medschl.cam.ac.uk/consortia/ocac/index.html) were included in this analysis,

with seven in the United States and three in Europe. Specific details for each of these studies

have been published elsewhere (15-25), but their main study characteristics are presented in

Table 1.

We had a total of 5,403 serous and endometrioid cases and 13,337 controls across the 10

OCAC studies; only serous and endometrioid cases were included as most studies have shown

that only these histotypes are significantly associated with ET use (2,5,26). However, only a

proportion of these women had genetic data available, leaving us with 3,855 cases and 9,593

controls. Further exclusions included the following: women who were less than 50 years of age

at reference date, which was typically the date of diagnosis for cases and the date of interview for

controls, (871 cases and 2,532 controls), had past diagnoses of cancer (other than non-melanoma

skin cancer) (398 cases and 887 controls), had unknown or missing HT information (171 cases

and 365 controls), or had used HT in a combined estrogen-progestin form (664 cases and 1,758

controls). Hence, our final dataset included 1,414 serous cases, 337 endometrioid cases, and

4,051 controls.

Genotype Data

To date, 18 confirmed, genome-wide significant ovarian cancer susceptibility loci (p≤5.0

x 10^{-8}) have been identified (6-13). However, subsequent fine mapping efforts have shown that

in some instances, the originally published best "hit" in the confirmed region was no longer the

most strongly associated single nucleotide polymorphism (SNP). Table 2 presents the originally

published SNPs and, where applicable, the current best hits, which we used in the analysis

presented here (6).

Details regarding the genetic data have been previously described (9). Briefly, existing

genotype data from three GWASs, their replication efforts, and two large-scale arrays (the

Collaborative Oncological Gene-Environment Study (iCOGS) and the Exome chip) were

combined with data from the April 2012 release of the 1000 Genomes Project and imputation

using the program IMPUTE2 (27) was carried out for all OCAC participants. Subjects from two

studies, NCO and NEC, were split into two analytic sets based on the varying scope of genotype

data (genome-wide versus array) available for imputation. This resulted in a total of 12 analytic

sets for analysis (see Table 1 footnote).

Exposure and Covariate Data

Self-completed questionnaires and phone or in-person interviews were used to collect

information on HT use and other potential confounding variables including age, OC use, parity,

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hysterectomy, tubal ligation, endometriosis, and education. Given that use of ET increases risk of endometrial cancer in women with intact uteri (28), the majority of ET users were hysterectomized and hence, their true age at menopause was unknown. We therefore assumed that all women in our analysis had an age at menopause of 50, which is the average age at menopause for women in the Western world (29).

Given the importance of menopause to ovarian cancer etiology, the effects of ET use prior to menopause when endogenous estrogen levels are naturally high could be inherently different from its effects after menopause (30). Therefore, we only considered women as ET users if they used ET after age 50 for at least one year. Non-users were women who had never used ET after age 50 (including women who only used ET before age 50) or had only used ET after age 50 for less than one year as the effect of such short-term use is likely to be minimal. However, a sensitivity analysis was conducted using a true "never" user baseline group, and the results did not change. Duration of postmenopausal ET use was assessed in the following categories: 1 to <5 years, 5 to <10 years, and 10+ years.

Statistical Analysis

All models were conditioned on analytic set, five-year age category (50-54, 55-59, 60-64, 65-69, 70-74, and 75+ years), and genetic ancestry (European, Asian, African, and other) as determined by the program LAMP (Local Ancestry in Admixed Populations) (31). Women with >90% European ancestry were classified as European, >80% Asian or African ancestry were classified as Asian or African, respectively, and those with mixed ancestry were classified as other (9). In addition, all models were adjusted for OC use (never [including <1 year of use], 1 to <2 years, 2 to <5 years, 5 to <10 years, and 10+ years), parity (never, 1 birth, 2+ births),

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hysterectomy (yes/no), endometriosis (yes/no), tubal ligation (yes/no), and education (less than

high school, high school, some college, college graduate or higher) since they were judged to be

potentially important confounders a priori. Missing categories were created for women missing

any of the covariates so their data could be included in the analysis. Data on hysterectomy status

was not available from all sites, but sensitivity analyses showed that hysterectomy status did not

substantially impact the estimates for ET or any of the SNPs.

Weighted genetic risk scores, which took into account the 18 confirmed SNPs

simultaneously, were calculated by taking the beta coefficients for each SNP's association with

risk of serous and endometrioid ovarian cancer using all OCAC studies in which genotype data

was available (43 OCAC studies, which included 18,174 cases and 26,134 controls (9)) and

multiplying them by the genotype value (0-2) for each subject (i.e., beta coefficients were

derived from a much larger dataset). These values for the 18 SNPs were then summed to obtain

each individual's total risk score, which was then categorized into quartiles according to the

distribution in controls for ease of interpretation.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the main effect

association between each SNP or genetic risk score quartile and disease risk using conditional

logistic regression. This was done for the serous and endometrioid histotypes separately.

Previous analyses that evaluated ET's main effect on risk of serous ovarian cancer showed no

difference by grade so all serous cases were combined in our analysis (5). These genetic

associations were further stratified by whether or not ET was used after age 50. Because these

gene-environment interaction analyses were primarily focused on understanding disease

etiology, we tested for statistical interaction (i.e., departure from a multiplicative model) between

the 18 ovarian cancer susceptibility loci or genetic risk score and ET use on risk of serous and

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endometrioid ovarian cancer using the likelihood ratio test (LRT) comparing models with and

without interaction terms (32). A similar approach was used to analyze the effect of duration

categories of ET use for the associations showing a significant interaction with ever/never ET

use. For completeness, we also assessed interactions on the additive scale by calculating

interaction contrast ratios (ICRs) and 95% CIs for the ICRs; ICR values greater than zero with

95% CIs that excluded zero indicated greater than additive effects.

All p-values reported were two-sided and considered significant at p≤0.05. An adjusted

p-value that factored in the number of tests for interaction conducted was considered as well. All

analyses were performed using STATA release 14.0.

RESULTS

A total of 5,802 women were included in these analyses, with 1,414 serous cases, 337

endometrioid cases, and 4,051 controls (Table 1). Approximately 13.6%, 20.0%, and 15.1% of

the controls, serous cases, and endometrioid cases reported using ET after age 50. In addition, 18

confirmed ovarian cancer SNPs were investigated here and their characteristics are presented in

Table 2. For nine of the 18 SNPs, their corresponding previously reported best hits are listed as

well (Table 2).

Although the main effects of each of the 18 SNPs have been previously published, Table

3 shows their main effects as well as the effects of genetic risk score in quartiles with serous

ovarian cancer. There was a statistically significant interaction between ET use and the T allele

of rs10069690 on chromosome 5 on risk of serous ovarian cancer that showed departure from

both additivity and multiplicativity (ICR=0.55, 95% CI 0.16-0.94; p_{int} for LRT=0.013) (Table 3).

While the T allele of rs10069690 was associated with a 51% increased risk of serous ovarian

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cancer among ET users (OR=1.51, 95% CI 1.19-1.91), there was essentially no risk among non-users (OR=1.08, 95% CI 0.96-1.21).

Table 4 presents the same information as Table 3, but for the endometrioid histotype. Two statistically significant interactions between the genetic variants rs7207826 and rs56318008 and ET use on risk of disease that showed departure from multiplicativity were observed (p_{int} for LRT=0.021 and p_{int} for LRT=0.037, respectively) (Table 4). Rs7207826 (T allele) on chromosome 17 was positively associated with the endometrioid histotype among non-users of ET (OR=1.32, 95% CI 1.09-1.61), but showed a decreased risk of disease among ET users (OR=0.71, 95% CI 0.43-1.18). Similarly, non-users of ET carrying the C allele for rs56318008 on chromosome 1 showed an increased risk of endometrioid ovarian cancer (OR=1.53, 95% CI 1.21-1.92) whereas ET users showed a decreased risk (OR=0.82, 95% CI 0.46-1.45). Genetic risk score did not appear to interact with ET use on risk of either histotype (p_{int} for LRT=0.52 for serous, p_{int} for LRT=0.25 for endometrioid) (Tables 3 and 4).

For each of the three SNPs that showed a statistically significant interaction with postmenopausal ET use on serous or endometrioid ovarian cancer risk at a p≤0.05 level on a multiplicative scale, the association between the SNP and risk of disease was assessed by duration of ET use. Rs7207826 and rs56318008 did not have significant interactions with duration for endometrioid ovarian cancer (p_{int} for LRT=0.18 and p_{int} for LRT=0.087, respectively). However, rs10069690 did have a significant interaction for serous ovarian cancer (p_{int} for LRT=0.034); women who carried the T allele and had used ET for 10+ years had close to a two-fold increased risk relative to non-users of ET who carried the C (reference) allele (OR=1.85, 95% CI 1.28-2.66) (Table 5).

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With 18 SNPs plus a genetic risk score for two histotypes and three additional duration interactions, we conducted a total of 41 tests for interaction in the analyses presented here. Four of these interactions were considered statistically significant at a p≤0.05 level. Although this is twice as many interaction associations as would be expected by chance at the p≤0.05 level, none of the them met a Bonferroni threshold for multiple comparisons of p=1.22 x 10^{-3} (0.05/41 tests).

DISCUSSION

We have shown evidence of statistical interactions between postmenopausal ET use and three confirmed ovarian cancer susceptibility alleles with risk of serous and endometrioid ovarian cancer. Although none of the interactions we report here remained significant after adjusting for multiple comparisons, these results may still be relevant as they could contribute to our understanding of the mechanism of action for these loci.

The most significant and biologically plausible interaction identified was rs10069690 for serous ovarian cancer, a SNP whose main effect has only been observed for the serous histotype (13). Rs10069690 is located in the *TERT-CLPTM1L* region of chromosome 5p15.33, a multi-cancer susceptibility locus that encodes the reverse transcriptase subunit (hTERT) of telomerase, an enzyme known to help maintain telomere length and integrity. Telomere shortening is often associated with genetic instability and hence increased risk of cancer and death, but telomerase has been shown to counteract this process, making the expression of *TERT* important in preventing tumorigenesis. Evidence has suggested that sex steroid hormones, such as estrogen, may be good candidates as physiological regulators of *TERT* (33). Some findings have shown telomerase activity to be under hormonal control in estrogen-targeted tissues, including the

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endometrium (34) and the ovary (35); the expression of *TERT* has been shown to be upregulated

by estrogen (36,37).

Recently, Killedar et al reported rs10069690 as a likely functional SNP since its risk-

associated T allele was shown to result in the co-production of full length-hTERT as well as an

alternatively spliced transcript, which encodes a catalytically inactive protein that inhibits

telomerase activity; this was thought to be due to a dominant negative effect of the protein since

telomerase exists as a dimer and its catalytic activity requires both hTERT active sites to be

functional (38). The decreased enzymatic activity may result in shorter telomeres, which could

lead to an increased risk of genetic instability and subsequent carcinogenesis. Given the evidence

suggesting estrogen's role in the transcriptional regulation of hTERT, the elevated risk of serous

ovarian cancer may be attributable to the inhibition of telomerase activity from higher levels of

estrogen with prolonged ET use (OR=1.85, 95% CI 1.28-2.66 for 10+ years).

Cancer cells have also been shown to activate telomerase to stabilize telomeres for

continued proliferation and cellular immortalization. However, from this perspective, the

inhibition of telomerase associated with rs10069690 would result in cell death of cancer cells and

hence a decreased risk of disease particularly among ET users, which is contrary to our findings.

Presently, it is unclear whether telomerase activation helps in the uncontrolled cellular

proliferation of existing cancer cells or in the preservation of a non-malignant phenotype by

maintaining the replicative longevity of ovarian cells (35). Our results appear to support the

latter.

The additional two interactions observed with ET use were rs56318008 and rs7207826

for endometrioid ovarian cancer. Rs56318008 is located near *WNT4*, a gene involved in

steroidogenesis (39) and implicated in GWASs for risk of endometriosis (40), an estrogen-

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related gynecologic condition strongly associated with the endometrioid histotype (41).

Rs7207826 is located near *SKAP1*, a gene that does not appear to be directly related to female

sex hormones and is primarily involved in T cell signaling and the regulation of the lymphocyte

function-associated antigen 1 gene (*LFA-1*). It should be noted though that *WNT4* and *SKAP1*

have not been shown to be the targets of risk SNPs at these loci.

Although this study is the largest of its kind, it still has a modest sample size in which to

attempt to discover interactions. In addition, the self-reported nature of the exposure and

covariate data used could be considered a limitation. However, studies have shown high

agreement between information collected using interviews versus records for HT use (42) as well

as other reproductive factors (43,44). Our results may be due to chance as these interactions do

not survive correction for multiple hypothesis testing, but the fact that these are confirmed

susceptibility alleles adds support to our findings. Given the role of estrogen in *TERT* activation

and expression, rs10069690 is of particular interest. From a biological standpoint, this SNP

appears to affect telomerase activity and hence, telomere maintenance, actions that could

promote tumorigenesis if improperly regulated (38). Although we cannot rule out that the

observed interaction may be due to a SNP in the region that is in linkage disequilibrium with

rs10069690, the fact that rs10069690 is functional with biological plausibility supporting its

interaction with ET use makes it a strong candidate. The other two SNPs implicated in this

analysis are intriguing as well in that they are confirmed ovarian cancer susceptibility loci.

However, as previously mentioned, the target genes for these SNPs are unknown and hence their

relevance remains uncertain at this time.

Our results highlight the complexity of ovarian cancer etiology. In addition, they provide

evidence that the roles of ET and the 18 ovarian cancer common variants in ovarian

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carcinogenesis may be beyond their independent effects. This is the first study, to our

knowledge, to suggest potential gene-environment interactions in ovarian cancer in the context

of HT use with confirmed susceptibility alleles. These findings, if replicated, may be critical for

future risk prediction modeling.

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Table 1. Description of studies included in analysis

Study Name	Study Abbrev.	Country	Study Period	Method of Data Collection	Number of Controls [a]	Number of Serous Cases [a]	Number of Endometrioid Cases [a]
Disease of the Ovary and their Evaluation Study (23)	DOV	USA	2002-2009	In-person interview	547 (123)	218 (65)	53 (10)
German Ovarian Cancer Study (15)	GER	Germany	1992-1998	Self-completed questionnaire	232 (39)	66 (11)	11 (4)
Hawaii Ovarian Cancer Study (17)	HAW	USA	1994-2007	In-person interview	229 (28)	68 (13)	23 (6)
Hormones and Ovarian Cancer Prediction (18)	HOP	USA	2003-2008	In-person interview	694 (68)	168 (28)	48 (7)
Malignant Ovarian Cancer Study (24)	MAL	Denmark	1994-1999	In-person or phone interview	363 (47)	96 (11)	17 (2)
North Carolina Ovarian Cancer Study [b] (19)	NCO	USA	1999-2008	In-person interview	401 (70)	189 (60)	47 (10)
New England Case-Control Study of Ovarian Cancer [b] (21)	NEC	USA	1999-2008	In-person interview	394 (28)	211 (26)	56 (3)
New Jersey Ovarian Cancer Study (25)	NJO	USA	2002-2008	Phone interview	112 (6)	63 (3)	20 (0)
United Kingdom Ovarian Cancer Population Study (16)	UKO	United Kingdom	2006-2007	In-person interview	490 (47)	27 (1)	9 (0)
University of Southern California, Study of Lifestyle and Women's Health (20,22)	USC	USA	1993-2008	In-person interview	589 (95)	308 (65)	53 (9)
				Total:	4,051 (551)	1,414 (283)	337 (51)

[a] Number in parentheses indicates the number of postmenopausal ET users.

[b] Subjects were split into two different analytic sets.

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Table 2. Characteristics of the 18 SNPs included in the analysis and their previously reported best hits

SNP	Previously Published Best Hit [a]	Chromosome Band	Position	Reference Allele(s)	Tested Allele [b]	Tested Allele Frequency [c]
rs58722170 (6)		1p34.3	38096421	G	C	0.15
rs10069690 (13)		5p15.33	1279790	C	T	0.35
chr10:21878831:D	rs1243180 (9)	10p12.31	21878831	CCCTTC	-	0.14
rs17329882 (6)		4q26	119949960	A	C	0.15
rs1879586	rs12942666 (12)	17q21.31	43567337	C	G	0.08
rs56318008 (6)		1p36	22470407	C	T	0.20
rs4808075	rs2363956 (7)	19p13.11	17390291	T	C	0.16
chr9:136138765:D (6)		9q34.2	136138765	CGCCCACCACTA	-	0.13
rs7207826	rs9303542 (9)	17q21.32	46500673	T	C	0.31
rs76837345	rs11782652 (9)	8q21.13	82668818	A	G	0.04
rs62274042	rs7651446 (9)	3q25.31	156435952	G	A	0.01
rs635634 (6)		9q34.2	136155000	C	T	0.14
rs3744763 (10)		17q12	36090885	G	A	0.69
chr17:29181220:I (6)		17q11.2	29181220	-	T	0.13
rs6755777	rs2072590 (8)	2q31.1	177043226	T	G	0.82
rs117224476	rs3814113 (11)	9q22.2	16907967	T	G	0.16
rs1400482	rs10088218 (8)	8q24.21	129541931	G	A	0.09
rs116133110 (6)		6q22.1	28480635	T	C	0.46

Note: chr10:21878831:D and chr17:29181220:I are listed as rs1449962376 and rs199661266, respectively, in 1000 Genomes.

[a] If not specified, the previously published best hit is the same as the current best hit considered.

[b] "-" refers to a deletion.

[c] Based on 1000 Genomes for all populations. For chr9:136138765:D (rs587729126), the tested allele frequency was based on the controls in the full OCAC dataset since the SNP is not listed in 1000 Genomes.

Table 3. Association between each of the 18 SNPs and genetic risk score and risk of serous ovarian cancer, stratified by ET use after age 50

	Main Effect		No ET Use (N=1,131 cases/3,500 controls)		ET Use (N=283 cases/551 controls)		
	OR[a,b]	95% CI	OR[a]	95% CI	OR[a]	95% CI	p-value for interaction
SNP							
rs58722170	1.25	1.11 – 1.40	1.21	1.06 – 1.38	1.41	1.07 – 1.85	0.31
rs10069690	1.14	1.03 – 1.26	1.08	0.96 – 1.21	1.51	1.19 – 1.91	**0.013**
chr10:21878831:D	1.14	1.03 – 1.26	1.15	1.03 – 1.29	1.09	0.86 – 1.38	0.68
rs17329882	1.14	1.02 – 1.28	1.17	1.03 – 1.32	1.05	0.81 – 1.37	0.47
rs1879586	1.15	1.01 – 1.30	1.17	1.02 – 1.34	1.04	0.78 – 1.37	0.44
rs56318008	1.16	1.03 – 1.31	1.22	1.06 – 1.39	0.93	0.698 – 1.25	0.099
rs4808075	1.18	1.07 – 1.31	1.20	1.07 – 1.34	1.13	0.90 – 1.42	0.64
chr9:136138765:D	1.08	0.93 – 1.26	1.14	0.96 – 1.34	0.89	0.63 – 1.26	0.21
rs7207826	1.17	1.06 – 1.29	1.19	1.06 – 1.33	1.06	0.84 – 1.35	0.39
rs76837345	1.19	0.98 – 1.44	1.27	1.03 – 1.57	0.88	0.55 – 1.39	0.14
rs62274042	1.65	1.36 – 2.01	1.59	1.28 – 1.97	1.98	1.24 – 3.14	0.40
rs635634	1.14	1.01 – 1.29	1.16	1.01 – 1.33	1.06	0.80 – 1.40	0.56
rs3744763	0.89	0.81 – 0.97	0.89	0.80 – 0.98	0.88	0.72 – 1.09	0.97
chr17:29181220:I	0.89	0.80 – 0.99	0.88	0.78 – 0.99	0.93	0.72 – 1.19	0.71
rs6755777	0.98	0.89 – 1.09	0.98	0.88 – 1.10	0.99	0.80 – 1.24	0.94
rs117224476	0.73	0.64 – 0.84	0.76	0.65 – 0.88	0.62	0.45 – 0.85	0.26
rs1400482	0.80	0.69 – 0.92	0.81	0.69 – 0.95	0.77	0.54 – 1.09	0.79
rs116133110	0.86	0.78 – 0.95	0.87	0.78 – 0.97	0.83	0.66 – 1.04	0.69
Risk score quartile							
2nd vs. 1st quartile	1.15	0.94 – 1.41	1.18	0.95 – 1.48	0.98	0.61 – 1.59	
3rd vs. 1st quartile	1.56	1.29 – 1.90	1.53	1.24 – 1.90	1.77	1.12 – 2.81	0.52
4th vs. 1st quartile	2.26	1.87 – 2.72	2.31	1.88 – 2.85	2.00	1.30 – 3.08	

Note: OR=odds ratio, CI=confidence interval. P-values significant at a ≤ 0.05 level are indicated in bold.

[a] Adjusted for OC use (never (including <1), 1 to <2, 2 to <5, 5 to <10, 10+ years), parity (0, 1, 2+ births), hysterectomy, endometriosis, tubal ligation, and education (less than high school, high school graduate, some college, college graduate or more); conditioned on age (50-54, 55-59, 60-64, 65-69, 70-74, 75+), genetic ancestry (European, African, Asian, other), and analytic set.

[b] All SNP main effects show genome-wide significance ($p \leq 5.0 \times 10^{-8}$) in the full OCAC dataset.

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Table 4. Association between each of the 18 SNPs and genetic risk score and risk of endometrioid ovarian cancer, stratified by ET use after age 50

	Main Effect		No ET Use (N=286 cases/3500 controls)		ET Use (N=51 cases/551 controls)		
	OR[a,b]	95% CI	OR[a]	95% CI	OR[a]	95% CI	p-value for interaction
SNP							
rs58722170	0.95	0.76 – 1.20	0.97	0.75 – 1.25	0.87	0.50 – 1.52	0.73
rs10069690	0.98	0.81 – 1.20	0.93	0.75 – 1.16	1.32	0.82 – 2.15	0.20
chr10:21878831:D	1.08	0.89 – 1.30	1.03	0.84 – 1.27	1.30	0.81 – 2.08	0.39
rs17329882	1.07	0.87 – 1.32	1.11	0.88 – 1.39	0.90	0.52 – 1.56	0.48
rs1879586	0.97	0.76 – 1.24	0.99	0.77 – 1.29	0.83	0.46 – 1.52	0.59
rs56318008	1.40	1.13 – 1.74	1.53	1.21 – 1.92	0.82	0.46 – 1.45	**0.037**
rs4808075	1.01	0.83 – 1.22	1.02	0.83 – 1.25	0.97	0.60 – 1.56	0.84
chr9:136138765:D	0.99	0.74 – 1.31	1.03	0.76 – 1.41	0.74	0.35 – 1.55	0.41
rs7207826	1.21	1.01 – 1.45	1.32	1.09 – 1.61	0.71	0.43 – 1.18	**0.021**
rs76837345	1.25	0.89 – 1.75	1.14	0.78 – 1.68	1.69	0.83 – 3.46	0.35
rs62274042	1.12	0.75 – 1.68	1.10	0.70 – 1.70	1.34	0.47 – 3.75	0.73
rs635634	1.04	0.83 – 1.31	1.10	0.86 – 1.41	0.76	0.41 – 1.42	0.28
rs3744763	1.06	0.89 – 1.26	1.07	0.89 – 1.28	1.00	0.65 – 1.54	0.79
chr17:29181220:I	0.81	0.66 – 0.99	0.81	0.65 – 1.01	0.80	0.49 – 1.32	0.97
rs6755777	1.01	0.84 – 1.21	0.98	0.81 – 1.20	1.14	0.73 – 1.78	0.56
rs117224476	0.79	0.62 – 1.02	0.85	0.65 – 1.11	0.54	0.28 – 1.06	0.21
rs1400482	0.98	0.76 – 1.26	0.92	0.70 – 1.21	1.36	0.73 – 2.52	0.26
rs116133110	1.04	0.87 – 1.24	1.08	0.89 – 1.31	0.85	0.55 – 1.31	0.32
Risk score quartile							
2nd vs. 1st quartile	1.49	1.04 – 2.14	1.40	0.94 – 2.09	1.98	0.79 – 4.94	
3rd vs. 1st quartile	1.69	1.18 – 2.40	1.65	1.12 – 2.42	2.04	0.80 – 5.17	0.25
4th vs. 1st quartile	1.73	1.22 – 2.46	1.85	1.27 – 2.70	1.10	0.42 – 2.91	

Note: OR=odds ratio, CI=confidence interval. P-values significant at a ≤0.05 level are indicated in bold.

[a] Adjusted for OC use (never (including <1), 1 to <2, 2 to <5, 5 to <10, 10+ years), parity (0, 1, 2+ births), hysterectomy, endometriosis, tubal ligation, and education (less than high school, high school graduate, some college, college graduate or more); conditioned on age (50-54, 55-59, 60-64, 65-69, 70-74, 75+), genetic ancestry (European, African, Asian, other), and analytic set.

[b] All SNP main effects show genome-wide significance ($p \leq 5.0 \times 10^{-8}$) in the full OCAC dataset.

Table 5. Association between rs10069690 and risk of serous ovarian cancer by duration of ET use after age 50

SNP	1 to <5 years (N=70 cases/193 controls)		5 to <10 years (N=82 cases/168 controls)		10+ years (N=131 cases/190 controls)	
	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI
rs10069690	1.41	0.90 – 2.23	1.21	1.09 – 2.32	1.85	1.28 – 2.66
					p-value for interaction = 0.034	

Note: OR=odds ratio, CI=confidence interval. The reference group consists of women who did not use ET after age 50 and carried the C (reference) allele.

[a] Adjusted for OC use (never (including <1), 1 to <2, 2 to <5, 5 to <10, 10+ years), parity (0, 1, 2+ births), hysterectomy, endometriosis, tubal ligation, and education (less than high school, high school graduate, some college, college graduate or more); conditioned on age (50-54, 55-59, 60-64, 65-69, 70-74, 75+), genetic ancestry (European, African, Asian, other), and analytic set.