Published in final edited form as:

Cancer Res. 2009 March 15; 69(6): 2349–2357. doi:10.1158/0008-5472.CAN-08-2902.

Single Nucleotide Polymorphisms in the *TP53* Region and Susceptibility to Invasive Epithelial Ovarian Cancer

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Abstract

The p53 protein is critical for multiple cellular functions including cell growth and DNA repair. We assessed whether polymorphisms in the region encoding TP53 were associated with risk of invasive ovarian cancer. The study population includes a total of 5,206 invasive ovarian cancer cases (2,829 of which were serous) and 8,790 controls from 13 case-control or nested case-control studies participating in the Ovarian Cancer Association Consortium (OCAC). Three of the studies performed independent discovery investigations involving genotyping of up to 23 single nucleotide polymorphisms (SNPs) in the TP53 region. Significant findings from this discovery phase were followed up for replication in the other OCAC studies. Mixed effects logistic regression was used to generate posterior median per allele odds ratios (ORs), 95% probability intervals (PIs) and Bayes factors (BFs) for genotype associations. Five SNPs showed significant associations with risk in one or more of the discovery investigations and were followed up by OCAC. Mixed effects analysis confirmed associations with serous invasive cancers for two correlated ($r^2 = 0.62$) SNPs: rs2287498 (median per allele OR = 1.30; 95% PI = 1.07-1.57) and rs12951053 (median per allele OR = 1.19; 95% PI = 1.01 - 1.38). Analyses of other histological subtypes suggested similar associations with endometrioid but not with mucinous or clear cell cancers. This large study provides statistical evidence for a small increase in risk of ovarian cancer associated with common variants in the TP53 region.

Keywords

TP53; polymorphisms; ovarian cancer; epidemiology

Introduction

The p53 protein, which is a transcription factor regulating multiple cellular functions critical for maintenance of genomic stability. The importance of *TP53* in carcinogenesis is evident in the high incidence of malignancies in the rare familial Li-Fraumeni Syndrome, which is most commonly characterized by germline mutations in the *TP53* gene.(1) Somatic mutations can inactivate *TP53* and are found in approximately one half of human cancers, including epithelial ovarian carcinomas.(2-4) Activation of p53 prevents the replication of damaged DNA until repair or apoptosis can be completed.(5)

There is evidence to suggest that minor alterations in the *TP53* gene may have a significant effect on its biological function. First, whereas cancer-causing mutations in most tumor suppressor genes result in truncated protein products, deleterious *TP53* mutations generally are missense changes. Although these mutations affect just a single amino acid, they usually are sufficient to abrogate the transcriptional regulatory function of p53. In addition, there is evidence that the common P72R (rs1042522) nonsynonymous single nucleotide polymorphism (SNP) in *TP53* affects its function.(6-9) In view of the known role of *TP53* inactivation in a majority of serous ovarian cancers, and the propensity for subtle genetic variations to affect its function, *TP53* is an appealing candidate as an ovarian cancer susceptibility gene.(2,10)

Epidemiological studies have evaluated ovarian cancer risks associated with *TP53* variants in intron 2 (rs1642785)(11), intron 3 (16bp insertion)(12-15), exon 4 (P72R or rs1042522)(14, 16-19), and intron 10 (rs9894946)(14,15,20); however, the results were inconclusive.

This report was motivated by results from three independent discovery studies focusing on *TP53* polymorphisms and risk of ovarian cancer: the North Carolina Ovarian Cancer Study (NCOCS),(21) the Mayo Clinic Case-Control Study (MAYO),(22) and the Polish Ovarian Cancer Study (POCS).(23) The NCOCS and the MAYO utilized a tagSNP approach while the POCS used re-sequencing data to assess common genetic variation in *TP53* and two flanking genes in linkage disequilibrium (LD)(24) in invasive ovarian cancer cases and population controls. We present these findings as well as results from a large-scale, confirmatory study conducted by the international Ovarian Cancer Association Consortium (OCAC).

Materials and Methods

Discovery Studies

Data from three studies, NCOCS, MAYO and POCS focusing on genetic variation in *TP53* and risk of ovarian cancer were compiled and analyzed. Details of these studies have been published elsewhere and are described briefly below.(21-23) An *a priori* decision by all three discovery analyses was made to restrict the discovery analysis to non-Hispanic white women with newly diagnosed, histologically confirmed, primary invasive epithelial ovarian cancer and to non-Hispanic white controls. Both the NCOCS and MAYO studies restricted analyses to serous cases while the POCS analyses were run overall and restricted to serous cases, because of the *a priori* belief that *TP53* variants might be more closely related to serous cancers.

All ovarian cancer cases were reviewed at each site respectively by an expert pathologist. The NCOCS is a population-based, case-control study. Cases between the ages of 20 and 74 years were identified from the North Carolina Central Cancer Registry from January 1999 to January 2007. Control subjects were matched by age and race and were identified through random digit dialing. The discovery analysis included 391 serous invasive ovarian cases and 786 controls.

The MAYO study included participants recruited at the Mayo Clinic between January 2000 and March 2006. Participation was limited to women from six states: Minnesota, Iowa, Wisconsin, Illinois, North Dakota, and South Dakota. Clinic-based controls frequency-matched to cases on age, race, and geographic region of residence were selected from women seeking general medical evaluation. The discovery analysis included 200 serous invasive cases and 458 controls.

The POCS is a population-based, case-control study among residents of Warsaw and Lodz (Poland) who were 20-74 years of age. Control women were frequency matched to cases on age and study site (Warsaw and Lodz), and were randomly selected within matching strata from population lists of Warsaw and Lodz residents. Discovery analyses were restricted to 264 invasive ovarian cases of which 118 are serous and 625 controls. The study protocols for the three discovery studies were approved by respective Institutional Review Boards (IRBs).

SNP Selection and Genotype Analysis—In all, up to 23 SNPs were genotyped in the three discovery studies. A full list of the polymorphisms along with their chromosomal positions is given in Supplemental Table 1. The POCS genotyped 20 SNPs, of which 8 were genotyped in the NCOCS and 9 were genotyped in the MAYO study. The NCOCS and MAYO studies genotyped 10 and 9 SNPs, respectively, of which 8 were the same. Supplemental Table 2 shows the genotype frequencies of the SNPs for each of the 13 participating case-control studies.

Both the NCOCS and the MAYO study identified sets of tagSNPs for the *TP53* region using releases 19 and 20, respectively, of the International HapMap Project's¹(25) CEU founder

¹<http://www.hapmap.org>

population and the ldSelect program.⁽²⁶⁾ ldSelect identified bins of SNPs with minor allele frequency (MAF) ≥ 0.05 using a pair-wise LD threshold of $r^2 \geq 0.8$. The samples were genotyped using an Illumina Golden Gate Assay™ at the Duke Institute of Genomic Science and Policy (IGSP) and the Mayo Clinic, respectively, with cases and controls randomly mixed within each plate.

For the NCOCS, one within- and one across-plate duplicate sample was included on each 96-well DNA plate to evaluate consistency in genotyping. The concordance rate for duplicates was 99.9%. In addition, six CEPH-Utah trios from the Coriell Institute, Camden, N.J. were distributed across six plates. Any SNP where more than 1% of samples within a batch failed genotyping on an Illumina BeadStudio file was disregarded and only the remaining SNPs were carried forward for statistical analysis. There was 95.8% concordance between HapMap calls on the CEPH data and the genotype calls for 9 of the SNPs evaluated. One SNP, rs8079544, showed 50% discordance and these data were excluded from additional analyses. A chi-square, 1 degree of freedom, test found only one SNP (rs2287499) in the *TP53* region that showed evidence ($p < 0.05$) for departure from Hardy-Weinberg-Equilibrium (HWE) among controls.

For the MAYO study, eight replicates of a CEPH family trio (mother, father, child) from the Coriell Institute, and replicates of an additional five standard DNAs were included in each 96-well plate ($n=10$ plates). The replicate and inheritance data were used to review and refine clustering. In addition, 2 samples per 96-well plate were blindly duplicated ($n=20$). Samples and SNPs with a call rate of $< 95\%$ were excluded: of the remainder the mean per-SNP call rate was 98.64, the mean per-sample call rate was 99.72, and reproducibility was 99.9%. All seven *TP53* tagSNPs that were attempted were successfully genotyped (mean call rate = 99.57). Genotyping details are provided elsewhere.⁽²²⁾

The POCS study selected SNPs based on re-sequence analysis of over 7200 base pairs including the flanking 5', 3', conserved regions and all exons in *TP53* in 94 Norwegian women and 102 individuals in the SNP500Cancer panel².⁽²⁴⁾ SNPs with a minor allele frequency > 0.03 were then genotyped using genomic DNA from participants in the POCS. These included 11 SNPs in *TP53* and nine additional SNPs in the two flanking, neighboring genes, *ATP1B2* and *WDR79* (see Supplemental Tables 2 and 3). A description of the methods for each genotype assay can be found at the SNP500 website.²⁽¹⁹⁾ Duplicate DNA pairs from 70 subjects in the study showed 100% concordance for all but one assay (rs17885803) which showed 99% concordance. Completion was $\geq 98\%$ for all assays.

Statistical Analyses—Plots of LD that were drawn using Haploview version 4.1⁽²⁷⁾ are in Supplemental Figures 1 and 2, for those of European and African ancestry, respectively. SNP data for all three studies were independently analyzed fitting unconditional logistic regression models adjusted for age, assuming a log-additive genetic model to estimate per allele odds ratios (ORs) and corresponding 95% confidence intervals (95% CI) for associations between genotype and case status. SNPs with the lowest p-values were nominated for evaluation in the replication study. The decision to move forward on the results of the NCOCS and MAYO was an *a priori* decision to achieve homogeneity likely depicted by serous histology especially in the context of the *TP53* gene where p53 mutations are the common among serous cases. The POCS analyses were run overall and restricted to serous cases because of the *a priori* belief that *TP53* variants might be more closely related to serous cases. In the PCOS study, the selection of SNPs for replication was based on SNPs with significant associations for all tumors or for serous tumors only.

²<http://snp500cancer.nci.nih.gov>

Replication Study

Study Participants—Ten additional sites contributed data for the *TP53* replication study: the Australian Ovarian Cancer Study (AOCS) and the Australian Cancer Study (ACS) presented together as AUS,(28) the Family Registry for Ovarian Cancer (FROC, presented as STA),(29) the Hawaiian Ovarian Cancer Study (HAW),(30) the Malignant Ovarian Cancer Study Denmark (MALOVA),(31) the New England Case-Control Study (NEC),(32) the Nurses' Health Study (NHS),(33) SEARCH Cambridge (SEA),(34) the Los Angeles County Case-Control Study of Ovarian Cancer (LAC-CCOC, presented here as USC),(35) the University of California at Irvine study (UCI),(36) and the United Kingdom Ovarian Cancer Population Study (UKOPS, presented here as UKO).(37) Characteristics of the study populations are shown in Supplemental Table 3. Of the ten replication case-control studies, nine used population-based ascertainment for cases and controls and one was a nested case-control study (NHS). All studies received ethical committee approval and all study subjects provided informed consent. Key clinical and questionnaire data on study participants were merged into a common dataset, including case-control status, ethnicity, race, tumor behavior, histologic subtype, age at diagnosis/interview, and history of prior cancers. Among the epithelial ovarian cancer cases across all OCAC sites, 293 had missing data on histologic subtype and were omitted. Race/ethnicity was missing for nine cancer cases. There was no missing data for any of the other variables. Centralized pathology review was conducted for HAW, NEC, and a sample of STA and AUS cases. The remaining sites used pathology reports only.

The combined data set (discovery and replication) comprised 5,206 white, non-Hispanic invasive epithelial ovarian cancer cases, of which 2,829 were classified as serous invasive ovarian cancer, and 8,790 white non-Hispanic controls. Analyses were restricted to serous invasive ovarian cancer cases to achieve a homogenous subgroup likely to have a common etiology.

SNPs found to be associated with risk of serous ovarian cancer in the replication study also were analysed in endometrioid, mucinous, and clear cell invasive ovarian cancer. Additionally, we conducted analyses on potentially associated SNPs in 73 invasive serous ovarian cancer cases and 189 controls who self-reported themselves to be of African descent from nine centers.

Genotype Analyses—Eight of the ten replicating OCAC sites used the 5' nuclease TaqMan allelic discrimination assay (Taqman; Applied Biosystems, Foster City, CA, USA) according to manufacturer's instructions. Samples from the AOCS and ACS studies (AUS) in Australia were genotyped using the iPLEX Sequenom MassArray system (Sequenom Inc., San Diego, CA, USA). The MAYO study additionally used the TaqMan assay for the follow-up of rs9894946, and rs2287498. To ensure quality control across laboratories, the *TP53* SNPs were genotyped at each site using the HAPMAPPT01 panel of CEPH-Utah trios-standard plate by Coriell.³ The panel includes 90 unique DNA samples, five duplicate samples, and a negative template control. The concordance on these plates across plate was > 98%. HWE was checked among controls. Deviations of genotype frequencies in the controls from those expected under HWE were assessed by chi squared tests (1 degree of freedom). The frequency distributions of the genotypes of all *TP53* SNPs according to the OCAC sites are found in Supplemental Table 2.

Statistical Analyses—For the replication analysis, we used a mixed effects logistic regression, fit using Bayesian methods to appropriately handle heterogeneity in risks across studies. Each model associating case-control status to a SNP was adjusted for study site,

³<http://ccr.coriell.org/Sections/Search/>

reference age, and personal history of breast cancer. Study site, age and SNP were treated as random effects with study site-specific distributions allowing for heterogeneity in effects across sites. In particular, the site-specific log ORs for each SNP were independently normally distributed with mean μ_{TP53} and variance σ^2_{TP53} , with the overall population level log OR, μ_{TP53} , assigned a proper but relatively non-informative normal distribution with mean 0 and variance 10. For the variance component σ^2_{TP53} , the precision $1/\sigma^2_{TP53}$ was given a gamma prior distribution with shape parameter 1 and rate 0.05. This choice was based on assuming a range for the OR of between 0.5 and 2, leading to a prior expectation for the precision of approximately 1/0.05. The shape parameter of 1 corresponds to adding two sites in terms of degrees of freedom *a priori*. The same hierarchical distributions were used for the other random effects. The variable 'previous breast cancer' was treated as a fixed effect with a common coefficient across all sites, which was *a priori* normally distributed with mean 0 and variance 10. Posterior inference was based on running 50,000 iterations of a Markov chain Monte Carlo (MCMC) algorithm using WinBUGS version 1.4.3.(38) We computed Bayesian 95% posterior probability intervals (PIs) by taking the 2.5th and 97.5th percentiles of the sampled values from the MCMC output. Point estimates of ORs were estimated by the median of the sampled values. We summarized strength of association by computing the posterior probability that the OR was greater than one, $P(OR > 1.0 | \text{Data})$. This quantity was estimated by the frequency of ORs greater than 1.0 in the MCMC samples. We also computed Bayes Factors (BFs) as a measure of the strength of associations for each SNP in the replication study. This BF is the ratio of the posterior probability for an OR > 1.0 to the posterior probability for an OR < 1.0. Based on Jeffreys' scale of evidence, (39,40) BFs between 3.2 and 10 provide substantial evidence of a positive association, BFs between 10 and 100 provide strong positive evidence for an association, and BFs greater than 100 provide decisive evidence of a positive association.

This Bayesian mixed effects model is comparable to a mixed effects logistic regression and may be viewed as a limiting case of the meta-analytic approach of DerSimonian and Laird. (41) Both approaches are more appropriate for a multi-center study evaluation than a fixed effects analysis as each allows for center-to-center heterogeneity in effects. We also present the results from comparable frequentist mixed effects model fits using SAS PROC GLIMMIX.⁴ The wider, more conservative, Bayesian intervals reflect the additional uncertainty in the estimation of the variance component.

Results

Using the log-additive model, analyses of the three discovery studies led to the selection of five SNPs for replication (rs2287498, rs12951053, rs1042522, rs16258595, and rs9894946). Two SNPs, rs2287498 and rs12951053, showed the strongest association with serous invasive tumors in the NCOCS and showed similar associations in either POCS (rs12951053) or MAYO (rs2078486, which was in high LD with rs2287498; $r^2=0.98$, MAYO and POCS data). The other three SNPs were selected based only on analyses from the POCS (NCOCS and MAYO were not available at the time of selection) which showed significant associations ($p < 0.05$) with all invasive cancers and/or serous cancers in the POCS. Other SNPs, including rs2078486 in the NCOCS and MAYO and rs2909430 and rs1642785 in the POCS, which also showed association in these discovery studies, were not genotyped because they had high correlations in the control populations with the SNPs that were selected for replication. In the POCS controls, rs1042522 was in strong LD with rs1642785 ($r^2=0.94$) and rs2909430 was in strong LD with rs16258595 ($r^2=0.92$).

A mixed effects SNP-at-a-time analysis of five SNPs (rs2287498, rs12951053, rs1042522, rs16258595, rs9894946,) was performed in up to 10 additional OCAC studies (Table 1). Eight

⁴<http://support.sas.com/rnd/app/da/glimmix.html>

studies that included a total of 1,859 serous invasive ovarian cancer cases and 5,927 controls participated in the follow-up of SNP rs2287498. The results of the analyses, including the discovery studies, showed a significant overall posterior median per allele OR of 1.30 (95% PI=1.08-1.57; $P(\text{OR} > 1 \mid \text{Data})=0.99$; BF=165.7). When the discovery datasets were omitted, the per allele overall posterior median OR was 1.23 (95% PI=0.94-1.58), with a posterior probability $P(\text{OR} > 1 \mid \text{Data})=0.94$. The BF for this analysis was 16.3 indicating that the evidence is still in favor of a positive association between the SNP and case-control status. Using Proc GLIMMIX, we found the overall per allele OR for the association between serous invasive ovarian cancer and rs2287498 using all sites was 1.30 (95% CI=1.10 – 1.53; $p=0.0059$). Omitting the discovery datasets, the per allele OR was 1.23 (95% CI=0.99 – 1.54; $p=0.0573$). Figure 1 is a forest plot of study specific ORs and CIs generated using a mixed effects model and fixed effects model, illustrating the shrinkage of the point estimates.

Follow-up analysis of rs12951053 included nine studies in the final analysis (Table 1). The results showed a significant association between SNP rs12951053 with a posterior median per allele OR of 1.19 (95% PI= .01 – 1.38; $P(\text{OR} > 1 \mid \text{Data}) = 0.98$; BF=47.8). When the data from the three discovery studies were omitted, the posterior median per allele OR was 1.14 (95% PI = 0.93 – 1.36; $P(\text{OR} > 1 \mid \text{Data}) = 0.90$). The BF for this analysis was 9.2 indicating that the evidence is still in favor of the hypothesis that the $\text{OR} > 1.0$ when the discovery data sets were omitted. Using Proc GLIMMIX, the overall per allele OR for rs12951053 for all sites combined from the frequentist mixed effects analysis was 1.20 (95% CI=1.06 – 1.36; $p=0.0081$). Omitting the three discovery datasets, the per allele OR was 1.16 (95% CI=1.00 – 1.35; $p=0.056$). These per allele MLEs of ORs are comparable to Bayesian median ORs (differing by less than 0.02). Figure 2 is a forest plot of study specific ORs and CIs generated using a mixed effects model and fixed effects models, illustrating the shrinkage of the point estimates.

We found no evidence of association for rs9894846, rs1625859, or rs1042522 (Table 1). We also analyzed the combined data for five additional SNPs included in two or more datasets (see Supplemental Table 4). A significant finding in these analyses was for the association between ovarian cancer and SNP rs2078486, which was highly correlated with SNP rs2287498 among controls in the combined OCAC data ($r^2 = 0.99$) and therefore not a surprising finding. The per allele posterior median OR for rs2078486 was 1.49 (95% PI=1.04 – 2.15; $P(\text{OR} > 1 \mid \text{Data})=0.98$).

In Table 2 we provide results of combined analyses of rs2287498 and rs12951053 with other histologic subtypes of invasive epithelial ovarian cancer. Analysis of rs2287498 found an overall per allele OR of 1.25 (95% PI=0.94 – 1.65; $P(\text{OR} > 1 \mid \text{Data})=0.93$; BF=14.0) with a positive association for endometrioid invasive cancers. Evidence for a decisive association between SNP rs12951053 and endometrioid cancers was detected, with an overall per allele median OR of 1.31 (95% PI=1.05 – 1.62; $P(\text{OR} > 1 \mid \text{Data})=0.99$; BF=109.6). No relationship was observed with mucinous or clear cell invasive cancers and either of these SNPs.

To further elucidate the relationship between genetic variation in *TP53* and ovarian cancer risk, we examined the association between rs2287498 and rs12951053 and ovarian cancer among a small number of subjects of African ancestry using mixed effects logistic regression. For rs12951053 the analysis included 73 serous invasive ovarian cancer cases and 189 controls enrolled in nine participating OCAC sites. The results are in Table 3. For rs2287498, 69 serous invasive cases and 173 controls among six OCAC sites were included. The association between rs12951053 in intron 7 of *TP53* and serous ovarian cancer was stronger in magnitude and consistent in direction with the corresponding association in non-Hispanic whites, while this was not true for rs2287498 in exon 2 of the neighboring gene *WDR79*. In particular, the median per allele OR for rs12951053 was 1.79 (95% PI=0.96 – 3.25; $P(\text{OR} > 1 \mid \text{Data})=0.97$; BF=29.4)

while the median per allele OR for rs2287498 was 0.71 (95% PI=0.40 – 1.27; P (OR < 1 | Data) =0.88; BF=0.1). These markers were essentially uncorrelated in these samples ($r^2=0.01$), while they were in LD in the non-Hispanic white samples ($r^2=0.62$). This suggests that there may be a single functional locus that it is closer to SNP rs12951053 than SNP rs2287498.

Discussion

This large investigation of 13 individual studies identified regions in or near *TP53* associated with increased risk of serous ovarian cancer in non-Hispanic white women. The strongest association was seen with rs2287498, a synonymous amino acid change in exon 2 (F150F) of the 5' neighboring gene *WDR79* (median per allele OR=1.30 (95% PI = 1.07-1.57)). The posterior probability and BF indicate that the evidence for an association is strong. SNP rs12951053 also showed evidence of association in non-Hispanic white women (median per allele OR = 1.19 (95% PI = 1.01-1.38). Similar associations were found for endometrioid tumors with weak or no evidence for the other histologic subtypes. Of note, endometrioid cancers are often a mixture of endometrioid and serous which may account for the consistent findings in only these two subtypes.

The r^2 between rs12951053 and rs2287498 is 0.62, making determination of the location of the association, assuming there is a single risk variant, difficult. To shed light on this, we examined evidence for association separately in OAC samples of African descent. Although our power was limited, it showed an increased risk with rs12951053, located in intron 7 of *TP53*, and not with rs2287498 or any other marker in LD with rs12951053 in samples for non-Hispanic whites. The contrasting results between women of African descent and non-Hispanic whites are consistent with a single risk-associated marker at or near rs12951053. However, the lack of evidence for an association with rs2287498 may be a chance finding due to the small sample of women with African ancestry.

Of the SNPs evaluated in the replication study, only rs1042522 (P72R) has been previously assessed in relation to ovarian cancer risk. Several small studies have suggested that there may be an association between this common amino-acid changing polymorphism and ovarian cancer risk.(11,14,19,42) A higher frequency of the variant R allele among cases compared to controls has been reported, however these differences were not statistically significant. Two additional small studies, one of 45 cases in South Africa among women with *BRCA1* or *BRCA2* mutations(18) and the other of 51 cases in Greece,(16) did not find a greater frequency of the R allele among cases than controls. Likewise, we also were not able to confirm an association between the P72R polymorphism and ovarian cancer.

Few other *TP53* polymorphisms have been previously investigated in relation to ovarian cancer risk. The intron 2 polymorphism (rs1642785) was evaluated in a study of 184 cases in Denmark with no evidence for a higher frequency of the variant allele in ovarian cancer cases than in controls.(11) In the current study rs1042522 tagged rs1642785 ($r^2=0.94$, in POCS) but was not confirmed in the replication phase.

Two case-control studies of 310 cases in Germany(15) and 225 cases in the United Kingdom (20) found an approximately two-fold increase in ovarian cancer risk associated with the intron 10 variant rs9894946. We were not able to replicate this finding although a 16 basepair insertion in intron 3, not measured in our study, was also related to risk and strongly correlated with rs9894946 in the German study population.(15) This finding was not replicated in two other studies.(12,13)

The strengths of this study include a comprehensive tagging approach for identifying potentially relevant polymorphisms, the large sample size, and stringent quality control requirements that included a high proportion of blinded samples and high concordance and

genotyping rates. Additionally, restricting the analysis to non-Hispanic whites reduces the likelihood of significant population-stratification or confounding bias by race or ethnicity. Our ability to characterize the SNP association within the histologic subtypes of ovarian cancer is an additional strength of this study, although the power to detect associations in the less frequent subtypes was limited.

We used a staged design for the discovery and replication of a subset of the most promising findings in order to reduce genotyping costs. The consequence of this may have been loss of power to localize the putative SNP(s) compared to an approach where all SNPs are genotyped in all samples. A more powerful approach would have been for all centers to genotype all variants to more fully characterize the variation in *TP53* associated with ovarian cancer risk.

Overall, this evaluation of common genetic variation in *TP53* by an international ovarian cancer consortium indicates that certain SNPs in this gene are likely to be related to an increase in risk of serous and endometrioid invasive ovarian cancer. Although the removal of the three discovery datasets for the analysis of rs12951053 and rs2287498 represents a very conservative approach, evidence for an association with both SNPs remained evident. As described by Jeffrey's, (39) Bayes factors greater than 10 indicate "strong confidence that a result would survive further investigation." Although it is possible that common variants not selected by the replication strategies we used are related to disease, these are likely to be captured by the tag SNPs. Fine mapping studies around the regions of interest will be needed to address this question.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Genotyping for the replication of findings was supported by a grant from the Ovarian Cancer Research Fund provided by the family and friends of Kathryn Sladek Smith. Additional support was provided by: U.S. Public Health Service grant CA58598 and contracts N01-CN-55424 and N01-67001 from the National Cancer Institute, NIH, Department of Health and Human Services (Hawaii), the Roswell Park Alliance and the National Cancer Institute CA71966 and Core Grant CA16056 (FROC), Intramural Funds from the National Cancer Institute, NIH, Bethesda, MD (POCS), the California Cancer Research Program grants 00-01389V-20170 and 2110200, U.S. Public Health Service grants CA122443 (MAYO), CA76016 (NCOCS), NCA76016, CA14089, CA17054, CA61132, CA63464, N01-PC-67010 and R03-CA113148, Department of Defense grant DAMD17-02-1-0666, and California Department of Health Services sub-contract 050-E8709 as part of its statewide cancer reporting program (USC), R01 CA 58598 and N01 PC 35137 (Hawaii), CA54419, CA105009(NECC,) CA49449 and CA087969(NHS). HS was funded by a grant from WellBeing. The AOCs Management Group (D Bowtell, G Chenevix-Trench, A deFazio, D Gertig, A Green, P Webb) gratefully acknowledges the contribution of all the clinical and scientific collaborators. AOCs and the ACS Management Group (A Green, P Parsons, N Hayward, P Webb, D Whiteman) also thank all of the project staff, collaborating institutions and study participants. Financial support was provided by: U.S. Army Medical Research and Materiel Command under DAMD17-01-1-0729, the Cancer Council Tasmania and Cancer Foundation of Western Australia (AOCs study); The National Health and Medical Research Council of Australia (199600) (ACS study); GCT and PW are supported by the NHMRC. SEARCH is funded through a program grant from Cancer Research UK (CRUK). Dr. Paul Pharoah is a CRUK Senior Clinical Research Fellow. The Polish Breast Cancer study thanks Meredith Yeager from the Core Genotyping Facility, both at the National Cancer Institute (USA), Szeszenia-Dabrowska of the Nofer Institute of Occupational Medicine and W. Zatonski of the Department of Cancer Epidemiology and Prevention, Cancer Center and M. Skłodowska-Curie Institute of Oncology, 02-781 Warsaw, Poland for their contribution to the POCS. Anita Soni (Westat, Rockville, MD) for her work on study management; Pei Chao (IMS, Silver Spring, MD) for her work on data and sample management; Douglas Richesson for statistical analyses; Meredith Yeager and Robert Welch for genotyping; and Neonila Szeszenia-Dabrowska and Witold Zatonski for their work during study design and data collection. Finally, we would like to express our profound thanks to all the study participants who contributed to this research.

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Figure 1.

Odds ratios and 95% confidence intervals by OCAC site for rs2287498 for the mixed effects (solid squares) and fixed effect (open diamonds) models and overall odds ratio and confidence interval with (dotted line) and without (dashed line) the discovery datasets; NCO = NCOCS, MAY = MAYO, POC = POCS, MAL = MALOVA

Figure 2.

Odds ratios and 95% confidence intervals by OCAC site for rs12951053 for the mixed effects (solid squares) and fixed effect (open diamonds) models and overall odds ratio and confidence interval with (dotted line) and without (dashed line) the discovery datasets; NCO = NCOCS, MAY = MAYO, POC = POCS, MAL = MALOVA

Table 1
Replication analyses for five SNPs (rs2287498, rs12951053, rs9894946, rs1625895, rs1042522) in the *TP53* region in white non-Hispanic serous invasive ovarian cancer cases ^{*,†}

Site	All Sites					All sites except Discovery sites		
	HWE	MAF	N cases	N controls	Posterior Median OR	95% Credible Intervals	Posterior Median OR	95% Probability Intervals)
rs2287498								
HAW	0.019	0.076	36	157	1.26	(0.84 – 1.84)	1.19	(0.74 – 1.79)
MALOVA	0.991	0.086	267	1209	1.24	(0.96 – 1.57)	1.21	(0.93 – 1.55)
MAYO	0.480	0.053	193	441	1.42	(1.05 - 1.98)	Omitted	
NCOCs	0.973	0.062	391	786	1.41	(1.11 – 1.83)	Omitted	
POCS	0.396	0.084	118	618	1.26	(0.91 – 1.70)	Omitted	
SEA	0.064	0.072	324	1213	1.16	(0.88 – 1.49)	1.14	(0.86 – 1.49)
STA	0.163	0.069	154	356	1.27	(0.91 – 1.74)	1.22	(0.85 – 1.71)
UKO	0.524	0.072	121	578	1.26	(0.90 – 1.72)	1.21	(0.84 – 1.68)
USC	0.574	0.062	255	569	1.46	(1.12 – 1.98)	1.44	(1.07 – 2.00)
Overall			1,859	5,927	1.30	(1.07 – 1.58)	1.23	(0.94 – 1.58)
Bayes Factor								
rs12951053								
AUS	0.332	0.069	443	1060	1.29	(1.03 – 1.62)	1.27	(1.00 – 1.62)
HAW	0.853	0.073	36	157	1.16	(0.79 – 1.63)	1.11	(0.72 – 1.61)
MALOVA	0.148	0.094	156	1018	1.19	(0.92 – 1.64)	1.16	(0.88 – 1.53)
MAYO	0.434	0.066	193	456	1.23	(0.92 - 1.64)	Omitted	
NCOCs	0.230	0.061	391	786	1.34	(1.06 – 1.75)	Omitted	
NEC	0.030	0.066	287	910	1.21	(0.93 – 1.56)	1.18	(0.90 - 1.55)
NHS	0.094	0.059	60	355	1.05	(0.67 – 1.44)	0.99	(0.59 – 1.40)
POCS	0.236	0.094	118	624	1.16	(0.86 – 1.53)	Omitted	
SEA	0.450	0.082	321	1195	1.06	(0.81 – 1.34)	1.03	(0.78 – 1.32)
STA	0.163	0.069	149	356	1.18	(0.86 – 1.60)	1.14	(0.82 – 1.58)
UCI	0.487	0.080	148	458	1.16	(0.86 – 1.54)	1.12	(0.82 – 1.53)
UKO	0.060	0.073	117	563	1.24	(0.92 – 1.66)	1.21	(0.88 – 1.67)
USC	0.614	0.075	255	570	1.22	(0.94 – 1.58)	1.19	(0.91 – 1.58)
Overall			2,585	8,508	1.19	(1.01 – 1.38)	1.14	(0.93 – 1.36)

Site	All Sites					All sites except Discovery sites		
	HWE	MAF	N cases	N controls	Posterior Median OR	95% Credible Intervals	Posterior Median OR	95% Probability Intervals
Bayes Factor								
rs9894946								
AUS	0.970	0.164	297	665	47.8	(0.75 – 1.24)	9.2	(0.73 – 1.20)
HAW	0.280	0.170	29	144	0.98	(0.57 – 1.52)	0.93	(0.54 – 1.39)
MAYO	0.009	0.182	189	444	0.96	(0.73 – 1.25)	0.89	(0.70 – 1.20)
POCS	0.053	0.130	117	621	1.41	(1.01 – 2.06)	Omitted	
Overall			832	1,874	1.06	(0.74 – 1.55)	0.91	(0.62 – 1.33)
Bayes Factor								
rs1625895								
AUS	0.689	0.128	298	666	0.98	(0.76 – 1.23)	0.96	(0.75 – 1.20)
HAW	0.978	0.145	30	145	0.98	(0.65 – 1.39)	0.94	(0.62 – 1.36)
MAL	0.044	0.100	236	873	1.08	(0.84 – 1.38)	1.05	(0.81 – 1.35)
MAY	0.023	0.135	192	455	1.06	(0.83 – 1.37)	1.03	(0.81 – 1.35)
NCOCs	0.906	0.151	331	637	0.96	(0.76 – 1.19)	0.94	(0.75 – 1.17)
POCS	0.975	0.098	117	617	1.23	(0.92 – 1.75)	Omitted	
SEA	0.509	0.129	212	834	1.07	(0.83 – 1.37)	1.04	(0.81 – 1.34)
STA	0.036	0.136	158	359	1.01	(0.74 – 1.34)	0.98	(0.73 – 1.30)
Overall			1,574	4,586	1.04	(0.86 – 1.25)	0.99	(0.81 – 1.20)
Bates Factor								
rs1042522								
AUS	0.002	0.239	194	360	0.99	(0.79 – 1.22)	0.97	(0.77 – 1.21)
HAW	0.978	0.145	30	145	1.00	(0.69 – 1.36)	0.97	(0.66 – 1.34)
MAL	0.044	0.100	236	873	1.10	(0.92 – 1.32)	1.09	(0.90 – 1.31)
MAYO	0.057	0.254	192	455	1.14	(0.93 – 1.42)	1.13	(0.91 – 1.41)
NCOCs	0.122	0.263	252	437	1.05	(0.85 – 1.29)	1.04	(0.84 – 1.27)
POCS	0.038	0.240	118	620	1.21	(0.97 – 1.57)	Omitted	
SEA	0.796	0.259	212	842	1.04	(0.85 – 1.26)	1.03	(0.83 – 1.25)
STA	0.087	0.247	157	363	1.05	(0.82 – 1.34)	1.03	(0.81 – 1.32)
Overall			926	4,236	1.07	(0.91 – 1.26)	1.03	(0.86 – 1.23)
Bayes Factor								
					4.0		1.9	

Site	All Sites				All sites except Discovery sites		
	HWE	MAF	N cases	N controls	Posterior Median OR	95% Credible Intervals	Posterior Median OR (95% Probability Intervals)

* Results in bold type have probability intervals that excludes 1.0

† Analyses are adjusted for age and prior breast cancer

Overall per allele median ORs and 95% probability intervals (PIs) for the association between two SNPs in the *TP53* region and invasive ovarian cancer in non-Hispanic whites, by histologic subtype, adjusted for age and study site^{*,†}

Polymorphism	Histology	N cases	N controls	Posterior Median OR	(95% Probability Intervals)	Bayes Factor	P(OR > 1 Data)
rs2287498 [‡]	Serous	1,859	5,927	1.30	(1.07 – 1.57)	165.7	0.99
	Mucinous	301	5,927	1.07	(0.74 – 1.54)	1.8	0.64
	Endometrioid	555	5,927	1.25	(0.94 – 1.65)	14.0	0.93
rs12951053 [‡]	Clear Cell	288	5,927	0.95	(0.62 – 1.39)	0.7	0.41
	Serous	2,585	8,508	1.19	(1.01 – 1.38)	47.8	0.98
	Mucinous	354	8,508	1.06	(0.76 – 1.43)	1.8	0.64
	Endometrioid	782	8,508	1.31	(1.05 – 1.62)	109.6	0.99
	Clear Cell	410	8,508	1.00	(0.73 – 1.34)	1.0	0.50

* Results in bold type have probability intervals that excludes 1.0

[‡] Includes the following OCAC sites: HAW, MALOVA, MAYO, NCOCS, POCS, SEA, STA, UKO, USC

[‡] Includes the following OCAC sites: AUS, HAW, MALOVA, MAYO, NCOCS, NEC, NHS, POCS, SEA, STA, UCI, UKO, USC

⁺ Analyses are adjusted for age and prior breast cancer

Table 3

Overall per allele median ORs and 95% probability intervals (PIs) for the association between two SNPs in the *TP53* region and serous invasive ovarian cancer in women of African Ancestry, adjusted for age and study site^{*,†,‡}

Polymorphism	N cases	N controls	Posterior Median OR	(95% Probability Intervals)	Bayes factor	P(OR > 1 Data)
<i>rs2287498</i>						
HAW	2	0	0.71	(0.36 – 1.38)		
MAY	1	1	0.71	(0.35 – 1.40)		
NCO	60	160	0.70	(0.41 – 1.16)		
SEA	3	0	0.72	(0.37 – 1.43)		
UKO	1	0	0.71	(0.36 – 1.42)		
USC	5	9	0.72	(0.37 – 1.39)		
Overall	69	173	0.71	(0.40 – 1.27)	0.1	0.12
<i>rs12951053</i>						
HAW	0	2	1.80	(0.88 – 3.55)		
MAY	1	2	1.79	(0.88 – 3.60)		
NCO	60	160	1.81	(1.04 – 3.08)		
NEC	4	10	1.85	(0.93 – 3.64)		
NHS	0	3	1.79	(0.87 – 3.56)		
SEA	3	0	1.80	(0.88 – 3.59)		
UCI	0	2	1.79	(0.88 – 3.57)		
UKO	0	1	1.79	(0.88 – 3.57)		
USC	5	9	1.76	(0.86 – 3.43)		
Overall	73	189	1.79	(0.96 – 3.25)	29.4	0.97

* Results in bold type have probability intervals that excludes 1.0

† MAY = MAYO, NCO = NCOCS

‡ Analyses are adjusted for age and prior breast cancer