No evidence that genetic variation in the myeloid-derived suppressor cell pathway influences ovarian cancer survival

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ABSTRACT

Background: The precise mechanism by which the immune system is adversely affected in cancer patients remains poorly understood, but the accumulation of immune suppressive/pro-tumorigenic myeloid-derived suppressor cells (MDSCs) is thought to be one prominent mechanism contributing to immunologic tolerance of malignant cells in epithelial ovarian cancer (EOC). To this end, we hypothesized genetic variation in MDSC pathway genes would be associated with survival after EOC diagnoses.

Methods: We measured the hazard of death due to EOC within 10 years of diagnosis, overall and by invasive subtype, attributable to SNPs in 24 genes relevant in the MDSC pathway in 10,751 women diagnosed with invasive EOC. Versatile Gene-based Association study (VEGAS) and the Admixture Likelihood method (AML), were used to test gene and pathway associations with survival.

Results: We did not identify individual SNPs that were significantly associated with survival after correction for multiple testing ($p<3.5 \times 10^{-5}$), nor did we identify significant associations between the MDSC pathway overall, or the 24 individual genes and EOC survival.

Conclusions: In this well-powered analysis, we observed no evidence that inherited variations in MDSC-associated SNPs, individual genes, or the collective genetic pathway contributed to EOC survival outcomes.

Impact: Common inherited variation in genes relevant to MDSCs were not associated with survival in women diagnosed with invasive EOC.

INTRODUCTION

Survival after a diagnosis of epithelial ovarian cancer (EOC) has seen only modest improvements in recent decades, making the identification of novel mechanisms and pathways associated with EOC prognosis imperative. EOC is associated with immunosuppressive pathways including regulatory T cells and myeloid derived suppressor cells (MDSC) that can be barriers to anti-tumor immunity and adversely affect clinical outcomes. To this end, MDSCs suppress the antigen-specific T cell response by both CD4+ and CD8+ T cells, and elevated concentrations of MDSCs have been detected in the peripheral blood of cancer patients when compared with normal controls [1, 2] . We hypothesized that common inherited genetic variation in genes involved in the MDSC pathway is associated with survival following ovarian cancer diagnosis.

MATERIALS AND METHODS

We conducted a pooled analysis utilizing individual-level data from 28 studies in the Ovarian Cancer Association Consortium (OCAC) to assess the association of genes in the MDSC associated pathway with EOC survival. Participants included 11,034 women aged 18 years and older with a histologically confirmed primary diagnosis of invasive EOC, fallopian tube cancer, or primary peritoneal cancer who were genotyped on the Ilumina iSelect array designed for the Collaborative Oncological Gene-environment Study (COGS) [3]. Clinical, epidemiological, and follow-up data were made available for all analyses.

To assess the association between invasive EOC outcome and inherited variation in the MDSC pathway, we conducted SNP, gene, and pathway-based analyses of 24 candidate genes relevant to the biology of MDSCs, as established from an extensive literature review utilizing the PubMed database (*ARG1, CD274, CSF2, CSF3, EIF2AK4, FLT3, IL10RA, IL13RA2, IL4, IL4R, IL5RA, IL6R, IDO, IRF8, KITLG, MMP1, MMP12, MMP3, MMP9, NOS2A, PSME4, STAT1, STAT3, VEGFA*). SNP selection and quality control were performed as previously described, yielding a total of 736 SNPs for analyses [4]. We calculated the effective number of independent SNPs tested; this value was used in a Bonferroni correction to determine single SNP significance [4]. We utilized Cox proportional hazards regression models adjusted for age, tumor stage and grade to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) representing SNP associations with EOC overall and by invasive histotype. Survival time was defined as the time from diagnosis of invasive EOC until death from

any cause or time of last follow-up. Analyses accommodated left truncation to account for prevalent cases where appropriate and right censoring was done at > 10 years follow-up time. Analyses and graphics were done using R (https://www.r-project.org). Gene- and pathway-based tests of association with hazard of death were performed using Versatile Gene-based Association Study (VEGAS) and the Admixture Likelihood Method (AML), respectively [5] [6].

RESULTS

The clinical characteristics of the study population are presented in Table 1. As expected, the majority of patients were diagnosed with serous EOCs, had poorly differentiated tumors, and were diagnosed with distant disease.

We considered $p<3.5 \times 10^{-5}$ as the threshold for significance, based on a Bonferroni correction for the estimated number of independent SNPs (n=288) across five histotypes. Single SNP associations for EOC overall and by invasive histotype are shown in circular Manhattan style plots in Figure 1 with SNPs showing p<0.01 highlighted in red. The most significant single SNP was the C allele of rs6492925 in *EIF2AK4* on chromosome 15, with a reduction in hazard of death in women with mucinous tumors (HR=0.57, 95% CI= 0.42, 0.78, $p=3.7 \times 10^{-4}$).

The most significant gene-based associations for all invasive ovarian cancer cases (*KITLG*, p=.07), high-grade serous (*VEGFA*, p=.11), mucinous (*EIF2AK4*, p=.015), endometrioid (*CSF*, p=.02) and clear cell (*CD274*, p=.037) did not the pass multiple test correction threshold set for testing the 24 genes. Taken together the 24 genes showed no significant association with any histotype; mucinous cell tumors showed the most significant MDSC pathway association with survival (p=0.11).

DISCUSSION

Assuming genotyping captures, on average, 70% of the variation in each gene for tests of association with overall EOC and given the proportion of events at 51%, our study had 80% power at $p<3.5 \times 10^{-5}$ to detect an HR of 1.11 to 1.24 for minor allele frequencies between 40% and 10%, respectively. We conducted a well-powered, hypothesis-driven study to evaluate a role for common inherited variation in MDSC pathway genes

with EOC survival; we observed no evidence of an association at the SNP, gene or pathway level with EOC survival. To date, neither genome wide analyses of single SNP association with progression free survival nor copy number variation with overall survival showed significant findings and did not report suggestive associations in these genes [7, 8]. It is possible that rare variation in MDSC- associated genes not captured by these analyses could be correlated with EOC outcomes or that the magnitude of effect sizes were below detection. Additionally, recent work has identified an expanding list of genes associated with MDSCs, thus future studies should consider the importance of this emerging knowledge of MDSC biology.

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Table 1. Clinical characteristics of invasive epithelial ovarian cancer cases from the Ovarian Cancer Association Consortium analyzed for association with MSDC genetic variation			
Patient Characteristics	**Vital Status at last follow up**		**Total invasive EOC cases N=10,751**
	Alive N=5243 (48.8%)	**Deceased N=5508 (51.2%)**	
Age at diagnosis			
<50 years	1627 (59.1%)	1125 (40.9%)	2752
50-69 years	3100 (47.4%)	3445 (52.6%)	6545
70+ years	516 (35.5%)	938 (64.5%)	1454
Histology			
Serous	2765 (39.7%)	4207 (60.3%)	6972
high grade serous	2210 (38.2%)	3568 (61.8%)	5578
Mucinous	504 (72.1%)	197 (27.9%)	701
Endometrioid	1058 (68.7%)	485 (31.3%)	1543
Clear Cell	529 (67.1%)	260 (32.9%)	789
Mixed Cell	215 (56.7%)	166 (43.3%)	381
Undifferentiated/Poorly differentiated	92 (42.6%)	124 (57.4%)	216
Unknown Epithelial	70 (49.6%)	69 (50.3%)	139
Grade			
Well Differentiated	757 (70.5%)	316 (29.3%)	1073
Moderately Differentiated	1107 (50.6%)	1079 (49.4%)	2186
Poorly differentiated	2185 (42.4%)	2969 (57.6%)	5154
Undifferentiated	284 (46.8%)	323 (53.2%)	607
Unknown	583 (58.1%)	419 (41.9%)	1002
Stage			
Localized	1393 (81.3%)	320 (18.7%)	1713
Regional	1314 (66.4%)	665 (33.6%)	1979
Distant	2109 (34.3%)	4034(65.7%)	6134
Unknown	178 (55.5%)	143 (44.5%)	321

Figure legend

Figure 1. These five concentric circles are circular standard Manhattan plots. The chromosome is on the outer circle, –log10 p-values are on the (vertical) y-axis with each circle representing the p-value from single SNP tests of association with overall survival adjusted for age, stage and grade. The Manhattan plots are as follows: A) all ovarian cancer cases B) high grade serous C) mucinous cell D) endometrioid and E) clear cell. The red dashed line designates p=.01 , –log10(p-value)=2, with all red-colored SNPs above that line reflecting SNPs p<.01.

Fig. 1