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Dose-Response Association of CD8+ Tumor-Infiltrating Lymphocytes and Survival Time in High-Grade Serous Ovarian Cancer

Ovarian Tumor Tissue Analysis (OTTA) Consortium

IMPORTANCE Cytotoxic CD8+ tumor-infiltrating lymphocytes (TILs) participate in immune control of epithelial ovarian cancer; however, little is known about prognostic patterns of CD8+ TILs by histotype and in relation to other clinical factors.

OBJECTIVE To define the prognostic role of CD8+ TILs in epithelial ovarian cancer.

DESIGN, SETTING, AND PARTICIPANTS This was a multicenter observational, prospective survival cohort study of the Ovarian Tumor Tissue Analysis Consortium. More than 5500 patients, including 3196 with high-grade serous ovarian carcinomas (HGSOCs), were followed prospectively for over 24 650 person-years.

EXPOSURES Following immunohistochemical analysis, CD8+ TILs were identified within the epithelial components of tumor islets. Patients were grouped based on the estimated number of CD8+ TILs per high-powered field: negative (none), low (1-2), moderate (3-19), and high (≥20). CD8+ TILs in a subset of patients were also assessed in a quantitative, uncategorized manner, and the functional form of associations with survival was assessed using penalized B-splines.

MAIN OUTCOMES AND MEASURES Overall survival time.

RESULTS The final sample included 5577 women; mean age at diagnosis was 58.4 years (median, 58.2 years). Among the 5 major invasive histotypes, HGSOCs showed the most infiltration. CD8+ TILs in HGSOCs were significantly associated with longer overall survival; median survival was 2.8 years for patients with no CD8+ TILs and 3.0 years, 3.8 years, and 5.1 years for patients with low, moderate, or high levels of CD8+ TILs, respectively (*P* value for trend = 4.2×10^{-16}). A survival benefit was also observed among women with endometrioid and mucinous carcinomas, but not for those with the other histotypes. Among HGSOCs, CD8+ TILs were favorable regardless of extent of residual disease following cytoreduction, known standard treatment, and germline *BRCA1* pathogenic mutation, but were not prognostic for *BRCA2* mutation carriers. Evaluation of uncategorized CD8+ TIL counts showed a near-log-linear functional form.

CONCLUSIONS AND RELEVANCE This study demonstrates the histotype-specific nature of immune infiltration and provides definitive evidence for a dose-response relationship between CD8+ TILs and HGSOC survival. That the extent of infiltration is prognostic, not merely its presence or absence, suggests that understanding factors that drive infiltration will be the key to unraveling outcome heterogeneity in this cancer.

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Supplemental content

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Epithelial ovarian cancer (OC) is the most lethal gynecologic cancer and is responsible for approximately 14 000 deaths annually in the United States.[1] While initial remission is often achieved, most patients relapse and die from their disease. Immune checkpoint inhibitors have demonstrated clinical activity in a small subset of patients with OC.[2,3] Understanding the endogenous immune response to OC—including the frequency of CD8+ tumor-infiltrating lymphocytes (TILs) and their impact on prognosis—has biological and clinical relevance.

Earlier studies[4-8] demonstrated that OC prognosis is associated with TILs at the time of primary cytoreductive surgery. CD8+ T cells are stimulated by peptides from degraded proteins bound to human leukocyte antigen class I molecules.[9] This can trigger CD8+ T cells to kill tumor cells and secrete proinflammatory cytokines. While the presence of CD8+ TILs within the epithelial component of OCs has been associated with favorable prognosis,[2,6-8,10-12] most prior analyses used simple dichotomous classification of CD8+ TILs and neglected to specify the inclusion or exclusion of stromal tissue. Prior analyses have been inadequately powered to evaluate histotype-specific survival associations. This is critical, as the invasive histotypes (high-grade serous OC [HGSOC], the most common and most lethal[13]; endometrioid OC [ENOC][14]; clear cell OC [CCOC][14,15]; mucinous OC [MOC][16]; and low-grade serous OC [LGSOC][17-20]) represent distinct biological processes, with distinct proposed cells of origin, clinical courses, and responses to chemotherapy.[21-23]

We conducted a large-scale assessment of intraepithelial CD8+ TILs in more than 5000 prospectively followed patients with OC. Our goals were to clarify the associations and evaluate the functional form of CD8+ TILs with overall survival in HGSOCs, and to explore association of CD8+ TIL levels with overall survival in patients with other histotypes.

Key Points

Question To what extent are CD8+ tumor-infiltrating lymphocytes (TILs) prognostic in epithelial ovarian cancer?

Findings This cohort study of more than 24 000 person-years of follow-up on more than 5500 patients shows improved survival with increasing CD8+ TIL counts in high-grade serous, endometrioid, and mucinous ovarian cancers (*P* value for trends were 4.2×10^{-16}; .008, and .04, respectively). Among high-grade serous ovarian cancers, this nearly log-linear relationship was present regardless of extent of residual disease following cytoreduction, receipt of standard treatment, and germline *BRCA1* mutation.

Meaning CD8+ TILs are a key prognostic factor in certain ovarian cancer histotypes and warrant additional study in the context of immunotherapy.

Methods

Study Design and Participants

We assembled a prospective cohort of 7377 women with a primary diagnosis of epithelial ovarian, peritoneal, or fallopian tube cancer, with a final sample size of 5577. Patients were followed from enrollment in an institutional review board-approved protocol until death from any cause (see eTable 1 in Supplement 1).[24-26] We requested and received institutional review board/ethics board approval from more than 20 institutions participating in the Ovarian Tumor Tissue Analysis Consortium. None of the studies provided compensation for participants (Supplement 2). Tumor specimens were obtained at initial debulking surgery, formalin fixed, paraffin embedded, and arrayed on tissue microarrays (TMAs). Clinical covariates and vital status underwent standardized quality control measures. We excluded 288 patients owing to loss to follow-up, 11 with missing age at diagnosis, 65 with nonepithelial disease, and 1436 owing to inadequate quality or amount of arrayed tumor tissue. The final sample size of 5577 included 5078 women with tumors of the 5 major invasive histotypes (HGSOC, ENOC, CCOC, MOC, and LGSOC) (see eTable 2 in Supplement 1). The median time from diagnosis to enrollment was zero days (interquartile range, 0-63 days); however, 38% of patients were enrolled more than 1 month after diagnosis. Because some HGSOC may be mistaken as ENOC,[27] we used WT1 and TP53 immunohistochemical staining from 17 studies to reclassify 82 ENOC cases as HGSOC; overall survival of these reclassified patients was consistent with HGSOC (see eFigure 1 in Supplement 1).

Immunohistochemical Analysis and Scoring

For most patients (4669 [84%]), staining was performed at the Mayo Clinic using the Leica Bond RX stainer; however, for patients enrolled at the Study of Epidemiology and Risk Factors and Cancer Heredity (SEA) and Mayo Clinic Ovarian Cancer Study (MAY1) study sites (476 [8%] and 432 [9%], respectively), previously stained slides were used. Immunohistochemical methods are provided in the eMethods in Supplement 1. Scoring was conducted at the University of Calgary; each core was screened for a hotspot of CD8+ TILs using a Nikon eclipse 80i microscope at original magnification ×200. Within each hotspot, 1 high-power field at original magnification ×400 with a 0.55-mm field diameter was evaluated, ensuring comparable area despite different core sizes across studies. Only CD8+ TILs within the epithelial component of the tumor (tumor islets) were considered, and CD8+ cells in the stroma or abutting tumor cells were disregarded (as seen, eg, in eFigure 2 in Supplement 1 classified as negative). A 4-point ordinal score was defined a priori based on CD8+ TIL counts per high-powered field: negative (none), low (1-2 TILs), moderate (3-19 TILs), and high (≥20 TILs), similar to the validated method of Zhang and colleagues,[4] except that we decreased the low to moderate cutoff from 6 TILs to 3 TILs. We did this to increase ease and consistency of scoring, as a cutoff of 3 or more TILs is routinely used in colorectal carcinoma reporting to assess Lynch syndrome.[28] Multiple cores from 156 cases were evaluated blindly by 2 gynecologic pathologists (W.C. and M.K.), and a weighted κ statistic was estimated. Differences in interpretation were discussed at a multiheaded microscope, and the 2 pathologists scored 24% and 76% of the remaining cohort, respectively. The TMAs included an average of 2.4 cores per

patient; for cases with more than 1 scored core, the maximum score was used, consistent with the scoring of hotspot regions.

Statistical Analysis

χ^2 Tests compared CD8+ TIL categories across clinical factors. Kaplan-Meier curves visually compared survival across categories. Cox proportional hazards regression estimated hazard ratios (HRs) and 95% CIs. Primary analyses were based on tests for trend, modeling the ordered CD8+ TIL categories as a 1 *df* linear term. Regression models included age at diagnosis (continuous), stage (I/II, III/IV, unknown), and study site as covariates; we also ran sensitivity analyses adjusting for extent of residual disease and postsurgical treatment. Separate analyses were conducted by histotype and among histopathological groupings (eg, combining LGSOC with their suspected precursor, serous borderline tumors), and by relevant clinical factors. This report meets reporting recommendations for tumor marker prognostic studies (REMARK)[29]; additional statistical methods are provided in Supplement 1.

CD8+ TIL Cut Point Analysis

Because categorical CD8+ TIL cut points may artificially restrict variability in the data and can be somewhat arbitrary, the pathologist (M.K.) rescored all cores from a subset of 2175 patients (1449 with HGSOC), recording CD8+ TIL count as a numeric marker. Each core was given a value of 0 to 20 or greater, using a threshold of 20 for counts that exceeded that number. As before, the maximum score was used for cases with more than 1 scored core. Among patients with HGSOC, we compared survival distributions of those with rescored levels to those without using Cox proportional hazards regression. Among HGSOC cases with rescored CD8+ TIL levels, we ran 5 additional sets of Cox regression analyses. We first categorized the levels using our original thresholds (0, 1-2, 3-19, and ≥20 CD8+ TILs) to confirm that our original results using all HGSOC cases did not differ from the subset who were rescored. Second, we categorized the levels using the thresholds of Zhang and colleagues[4] to determine the robustness of our original results to these cut points. Third, we assessed the functional form of the association between CD8+ TIL levels and survival using penalized B-splines.[30] Fourth, we fitted the numerically valued CD8+ TIL levels as a 1 *df* linear term. Finally, we carried out a formal cut point analysis similar to that described by Budczies and colleagues.[31] Briefly, this approach examines all possible contiguous dichotomizations of TIL levels (ie, 0 vs ≥1, 0-1 vs ≥2, 0-2 vs ≥3) using Cox proportional hazards regression to identify the threshold that best discriminates survivors from nonsurvivors based on evidence of association.

Results

Distribution of CD8+ TILs by Histotype

The final sample included 5577 women; mean age at diagnosis was 58.4 years (median, 58.2 years). Epithelial CD8+ TILs were assessed using a 4-tiered scoring system (interobserver agreement, 81.8%; weighted κ, 0.846; 95% CI, 0.804-0.888). We observed intratumoral heterogeneity in CD8+ TILs across cores per patient (intraclass correlation coefficient, 0.56; 95% CI, 0.54-0.57). CD8+ TILs varied across the major invasive OC histotypes (HGSOC, ENOC, CCOC, MOC, and LGSOC; χ^2 $P = 2.8 \times 10^{-103}$; see eFigure 3 in Supplement 1). Most HGSOC cases (83%) had evidence of CD8+ TILs, with a lower proportion seen in LGSOC and ENOC cases (73% and 72%, respectively) and CCOC and MOC cases (52% and 51%, respectively). Most borderline tumors showed evidence of CD8+ TILs (serous, 84%; mucinous. 70%; see eTable 3 in Supplement 1).

Associations of CD8+ TILs With Overall Survival by Histotype

We observed a striking association for longer survival time with increasing levels of CD8+ TILs in HGSOC cases (*P* value for trend adjusted for study, age, and stage = 4.2×10^{-16}) (**Table**; **Figure**). Median survival was 2.8 years for women negative for CD8+ TILs, and 3.0 years, 3.8 years, and 5.1 years for low, moderate, or high levels, respectively. At the extremes, women with high levels of CD8+ TILs (≥20 per field) had a 43% reduced risk of death compared with women with no evidence of CD8+ TILs (HR, 0.57; 95% CI, 0.49-0.65) (Table). Associations were similar after adjustment for residual disease (see eTable 4 in Supplement 1).

Increasing levels of CD8+ TILs were also associated with longer survival time among women with ENOC (*P* value for trend = .008) (Table; Figure). This association was also apparent in separate analyses of grade 1 ENOC and grades 2 and 3 ENOC, although these were limited in sample size (see eTable 5 in Supplement 1). While there was a statistically significant dose-response similar to HGSOC, it is noteworthy that ENOCs with moderate levels (3-19 per field) showed the greatest improvement in survival time compared with women with ENOC and no detectable CD8+ TILs (HR, 0.50; 95% CI, 0.34-0.74).

A similar association was observed for women with MOC (*P* = .04) (Table; Figure), although, as the histotype with the lowest overall levels of CD8+ TILs, only 13 women (4%) had high TIL levels. Kaplan-Meier plots indicate a dose-response relationship, at least for negative to moderate levels (Figure). In contrast, CCOCs and LGSOCs showed no apparent association between CD8+ TILs and survival time (Table; see eFigure 4 in Supplement 1). Because LGSOC is the rarest of the invasive histotypes, the null association in this group should be interpreted with caution. As some prior studies combined LGSOC and HGSOC, we also analyzed invasive serous cases as a group, including those with missing grade. We found that the striking HGSOC results were attenuated (see eTable 5 in Supplement 1), suggesting that the relevance of CD8+ TILs among serous cases may be limited to HGSOC and confirming that immunohistochemistry-aided histotype classification is a critical first step to improving the classification of OC cases.[27,32] No other patterns were observed in analyses of histopathological groups (see eTable 5 in Supplement 1).

Among the 5 major invasive histotypes, time to disease progression was known for 52% of cases (n = 2681). Progression-free survival results were remarkably similar to overall survival results (see eTable 6 in Supplement 1).

Table. Multivariable-Adjusted Association of CD8+ Tumor-Infiltrating Lymphocytes (TIL) and Overall Survival Among 5078 Patients With the 5 Most Common Invasive Epithelial Ovarian Cancer Histotype[a]

Histotype	CD8+ TILs	No.	Person-years	Events, %	HR (95% CI)	*P* Value for Trend	*P* Value for 3 *df* Test
High-grade serous	Negative	546	1709.75	76.2	1 [Reference]	4.2×10^{-16}	7.2×10^{-15}
	Low	546	1908.39	72.3	0.86 (0.75-0.99)		
	Moderate	1,394	5264.82	69.0	0.77 (0.69-0.87)		
	High	710	3110.87	56.5	0.57 (0.49-0.65)		
Endometrioid	Negative	206	1118.53	33.5	1 [Reference]	.008	.006
	Low	130	675.44	34.6	0.80 (0.54-1.18)		
	Moderate	283	1844.53	18.0	0.50 (0.34-0.74)		
	High	110	657.59	22.7	0.76 (0.47-1.23)		
Clear cell	Negative	309	1640.28	41.1	1 [Reference]	.50	.52
	Low	141	658.25	45.4	1.16 (0.84-1.60)		
	Moderate	118	618.79	41.5	0.88 (0.62-1.24)		
	High	80	412.44	40.0	0.92 (0.61-1.39)		
Mucinous	Negative	168	750.75	44.0	1 [Reference]	.04	.16
	Low	77	375.26	31.2	0.91 (0.55-1.51)		
	Moderate	85	470.62	27.1	0.56 (0.34-0.93)		
	High	13	72.35	23.1	0.79 (0.23-2.68)		
Low-grade serous	Negative	43	198.06	48.8	1 [Reference]	.91	>.99
	Low	44	184.89	65.9	0.94 (0.50-1.74)		
	Moderate	63	272.13	47.6	0.98 (0.52-1.83)		
	High	12	49.53	41.7	0.92 (0.33-2.59)		

Abbreviation: TIL, tumor-infiltrating lymphocytes.

[a] Adjusted for study, age (continuous), and stage (I/II, III/IV, unknown); levels based on counts of TIL per high-powered field (HPF): negative, no CD8+ TILs; low, 1-2 CD8+ TILs; moderate, 3-19 CD8+ TILs; high, 20 or more CD8+ TILs per HPF; adjusted for study, age (continuous), and stage (I/II, III/IV, unknown); HR, hazard ratio; *P* value trend, from a 1 *df* trend test; *P* value for 3 *df* test, from an unordered test comparing risk across the 4 CD8+ TIL groups.

Associations of CD8+ TILs With Clinical Features in HGSOC

The extent of residual disease following primary cytoreductive surgery was available for 2173 HGSOC cases. Our results showed that a greater proportion of tumors without macroscopic residual disease had high CD8+ TIL levels than those with macroscopic disease (26% vs 20%; *P* = .006; see eFigure 3 in Supplement 1). Increasing CD8+ TILs were associated with improved survival in a dose-response manner in both surgical outcome groups, indicating that immune response improves prognosis regardless of the remaining residual disease after surgery (see eTable 7 in Supplement 1).

Our study included 133 *BRCA1* and 66 *BRCA2* mutation carriers and 844 tested noncarriers. The extent of CD8+ TILs differed by mutation status (*P* = .02), as 29% of *BRCA1* mutation carriers had high TIL counts, yet only 18% of noncarriers and 15% of *BRCA2* mutation carriers did (see eFigure 3 in Supplement 1). The survival benefit associated with CD8+ TILs was also found to differ by mutation status (*P* value for interaction = .006). Increased CD8+ TILs were associated with favorable survival among cases without mutations ($P = 5.1 \times 10^{-7}$) and among cases with a *BRCA1* mutation (*P* = .003) (see eTable 7 in Supplement 1). Among *BRCA2* mutation carriers, there was no evidence of association between CD8+ TILs and survival (*P* = .62).

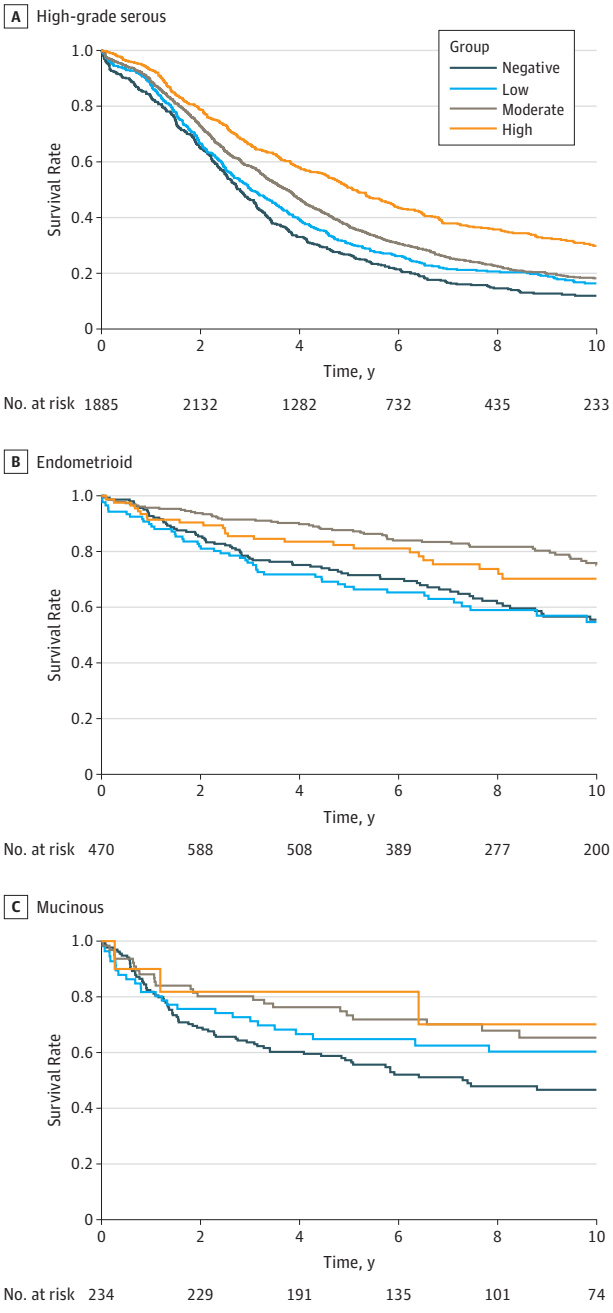
Treatment details were documented for 501 patients with HGSOC who received standard first-line chemotherapy, including 295 who received the standard dose (carboplatin area under the curve, 5 or 6, and paclitaxel, 135 mg/m^2 or 175 mg/m^2). Association with CD8+ TIL level and overall survival was also observed within this group (*P* value for trend = .003) (see eTable 7 in Supplement 1).

Among HGSOC cases, CD8+ TIL level was associated with earlier stage ($P = 4.3 \times 10^{-4}$) and younger age at diagnosis ($P = 1.6 \times 10^{-4}$). In stratified analyses CD8+ TIL level was consistently prognostic in stage and age subgroups (see eTable 5 in Supplement 1). We also observed that patients born more recently showed higher levels (n = 2734, *P* = .001); we also adjusted all analyses for year of birth, and results were similar. CD8+ TIL level was not associated with year of diagnosis (*P* = .71), self-reported racial group (*P* = .74), or pretreatment or posttreatment level of protein CA 125 (*P* = .42 and .89, respectively).

Analysis of CD8+ TIL Cut Points in HGSOC

Of the 3196 HGSOC cases, 1449 (45%) were rescored using a numeric count. There were no differences in survival between women who were rescored and those who were not (*P* = .12; κ values comparing original values to rescored values, 0.91 (95% CI, 0.89-0.92). eTable 8 in Supplement 1 displays associations of categorized CD8+ TIL levels and survival in women with rescored tumors. After adjustment for age and stage, strong dose-response associations were observed using both the original threshold values (0, 1-2, 3-19, and ≥20 CD8+ TILs) and those used by Zhang and colleagues[4] (0, 1-5, 6-19, ≥20 CD8+ TILs) ($P < 10^{-5}$ for each). As before, associations were slightly attenuated but remained significant after

Figure. Kaplan-Meier Overall Survival Plots by CD8+ Tumor-Infiltrating Lymphocyte (TIL) Levels for the High-Grade Serous, Endometrioid, and Mucinous Ovarian Cancer



Negative, no CD8+ TILs; low, 1-2 CD8+ TILs; moderate, 3-19 CD8+ TILs; high, 20 or more CD8+ TILs per high-powered field. The numbers just below the x-axis represent the number of women at risk in 2-year time intervals. Number at risk on date of diagnosis may be smaller than number at risk later owing to left truncation of follow-up resulting from delayed study enrollment.

adjustment for extent of residual disease and postsurgical treatment ($P < 10^{-4}$ for each).

Assessment of the functional form of the association between numeric CD8+ TIL levels and survival using penalized B-splines, after adjustment for age and stage, is shown in eFigure 5 in Supplement 1. We observed a strong negative association with survival, indicating that increasing CD8+ TIL levels are progressively protective across this spectrum of values. The results of fitting CD8+ TIL levels as a 1 *df* linear term are also shown in eFigure 5 in Supplement 1 and track very closely to those using penalized B-splines, indicating that the association between CD8+ TIL levels and survival in women with HGSOC is virtually log-linear in nature.

Results of a formal cut point analysis examining all possible sets of contiguous dichotomizations of TIL levels can be found in eTable 9 in Supplement 1. The best discrimination of survivors from nonsurvivors occurred when comparing those with 0 to 13 TILs with those with 14 or more (HR, 0.75; 95% CI, 0.65-0.86; $P = 1.5 \times 10^{-5}$). However, each of the 19 dichotomizations yielded highly significant results (P values for all comparisons, $\leq 1.1 \times 10^{-3}$), with HRs consistently ranging from 0.75 to 0.83, again indicating that greater TIL levels are protective across the entire spectrum of values examined.

Discussion

To our knowledge, our study is the largest report on intraepithelial CD8+ TILs in OC to date and shows a robust dose-dependent increase in survival for increasing TIL levels in women with HGSOC. Analyses on a subset of individuals using numeric TIL counts confirmed a progressively protective, nearly log-linear survival effect as CD8+ TILs counts increased from 0 to 20 or more per high-powered field, suggesting that the quantity of CD8+ TILs, not merely their presence, is informative and that the most immune-rich HGSOCs are the most likely to have improved clinical outcome. This effect was not modified or confounded by the extent of residual disease after cytoreductive surgery. Because there are fewer than a handful of other validated prognostic biomarkers for HGSOC (eg, *BRCA1* and *BRCA2* status[33] and PR expression[26]), these results may provide increased prognostic prediction.

In addition, to our knowledge, this is the first CD8+ TIL study in histotypes other than HGSOC; we revealed a significant reduction in risk of death for patients diagnosed as having ENOC and MOC. In ENOC, patients with moderate CD8+ TIL levels had the most favorable survival, with no additional benefit observed beyond this threshold. Because prior reports suggest that ENOCs with high CD8+ TIL are more commonly mismatch repair deficient,[34] we speculate that, similar to endometrial cancers,[35,36] ENOC with high CD8+ TIL levels may be associated with an intermediate outcome owing to the association with mismatch repair deficiency. No survival associations were seen in CCOC.

Other investigations have noted higher response rates to immune checkpoint blockade among patients with a higher burden of neoantigens,[37,38] suggesting that increased neoantigens increases the likelihood that T lymphocytes recognize tumor as foreign and mount an immune response. It has also been demonstrated that *BRCA1*-mutated HGSOC tumors have a higher average neoantigen number than nonmutated tumors.[39] In this study, patients with HGSOC with germline *BRCA1* mutations demonstrated higher levels of CD8+ TILs than

patients with *BRCA2* mutations or those tested negative for mutation. While neoantigen load may explain higher levels of CD8+ TILs in *BRCA1*-mutated tumors, and their association with better outcome, it does not explain the better outcome of *BRCA2*-mutated tumors.[40,41]

Limitations

Given its robust prognostic ability, relative ease of testing, and low interobserver variability (percent agreement = 81.8%, weighted κ = 0.846), quantitation of CD8+ TILs should be considered for clinical evaluation as suggested for other cancers.[42-44] Unfortunately, as expected, we found intratumoral heterogeneity in CD8+ TILs across cores per patient (intraclass correlation coefficient = 0.56; 95% CI, 0.54-0.57). To account for this, we use the maximum score, which is akin to the hotspot assessment of proliferation in other cancers, and is more feasible for surgical specimens with many tumor-containing slides. We also propose that, similar to the system for patients with breast cancer, a practical and robust scoring system should be developed.[43] Additional issues requiring large-scale study that were not evaluated here include utility of image analysis; evaluation of stromal CD8+ TILs; consistency across multiple tumor sites per patient; impact of neoadjuvant chemotherapy[45-47]; relationships among CD8+ TIL levels, HGSOC molecular subtypes,[48-50] common genetic variation,[51] and epidemiologic risk factors[52]; and evaluation of other lymphocyte subsets, such as CD4+ TILs, CD20+ TILs (B cells), tertiary lymphoid structures, and plasma cells.[10,12-14,53] Clinically, it will be important to test whether CD8+ TILs predict response to certain therapies including standard chemotherapy and immune therapy, as, for example, CD8+ TILs predict chemoresponse in subtypes of breast cancer.[54] It will also be critical to study whether the immune response of CD8+ TILs can be activated by checkpoint blockade.

Conclusions

These large-scale analyses show that CD8+ TILs vary by histotype with HGSOC tumors having the highest levels and a strong association with survival, regardless of extent of residual disease or first-line chemotherapy treatment. Penalized B-splines revealed that this association was nearly log-linear in nature, indicating that progressively greater TIL counts yield progressively better prognoses for HGSOC tumors. We showed for the first time that CD8+ TILs in HGSOC cases with germline *BRCA2* mutations may not be associated with survival. Finally, we found that ENOC and MOC tumors show trends associating CD8+ TILs with survival time and that CCOC do not show these trends. A clinically applicable scoring system for CD8+ TILs should be developed to incorporate into clinical trials.

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