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Inflammatory-related Risk Factors and the Abundance of Immune Cells in the Tumor Microenvironment among Black and White Women with High-grade Serous Ovarian Cancer

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By

Mengying Xia

Bachelor of Medicine
Sun Yat-sen University
2020

Thesis Advisor: Joellen M. Schildkraut, PhD, MPH
Field Advisor: Lauren C. Peres, PhD, MPH

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Abstract

Inflammatory-related Risk Factors and the Abundance of Immune Cells in the Tumor Microenvironment among Black and White Women with High-grade Serous Ovarian Cancer
By Mengying Xia

Background

Ovarian cancer is a lethal gynecologic malignancy, ranking fifth in cancer deaths among women. Inflammatory-related risk factors and immune cell abundance in tumor immune microenvironment (TIME) were associated with survival of high-grade serous ovarian cancer (HGSOC), respectively. The effects of inflammatory-related risk factors on HGSOC were hypothesized to be mediated through TIME. Black women have a poorer survival compared to White women. Survival differences may be explained by the different associations of inflammatory-related risk factors and TIME.

Methods

121 Black women and 121 White women with HGSOC were selected from North Carolina Ovarian Cancer Study (NCOCS) and African American Cancer Epidemiology Study (AACES). Inflammatory-related factors were determined using survey data and the inflammation-related risk score (IRRS) was calculated. The abundance of tumor infiltrating lymphocytes (TILs), cytotoxic T-cells, regulatory T-cells (Tregs), myeloid cells, and neutrophils in TIME were measured by multiplex immunofluorescence. The immunoscore, representing the density and location of TILs and cytotoxic T-cells, was calculated. Unconditional logistic regression and polytomous logistic regression were conducted to determine the relationships of inflammatory-related risk factors and IRRS with immune cell abundance and immunoscore in the overall population and stratified by race, respectively.

Results

In the overall population, significant associations between the inflammatory-related exposures and immune cell abundance in TIME include talc use and higher total TILs (OR=1.74, 95% CI: 1.03-2.95), fibroids and higher tumoral cytotoxic T-cells (OR=2.17, 95% CI: 1.16-4.07), acetaminophen use and higher total myeloid cells (OR=4.52, 95%CI: 1.01-20.27), and higher IRRS and lower total neutrophils (OR=0.55, 95% CI: 0.31-0.98). Other non-significant patterns were observed, such as higher BMI in young adulthood or measured within 5 years prior to diagnosis and higher immune cell abundance. The descriptive analysis and regression analysis indicated racial differences in the prevalence of exposures and their associations with immune cell abundance in TIME.

Conclusion

In this exploratory analysis, the effect of inflammatory-related risk factors on survival of HGSOC may be mediated by immune cell abundance in TIME in the overall population, but this association differed according to race.

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LIST OF TABLES

TABLE OF CONTENTS

BACKGROUND AND SIGNIFICANCE

Occurrence of ovarian cancer

Ovarian cancer is a lethal gynecologic malignancy. It ranks fifth in cancer deaths among women, affecting approximately 300,000 women worldwide annually [1]. It is estimated that 21,410 new cases will be diagnosed and ovarian cancer will cause more deaths than any other gynecologic cancers in the United States in 2021 [2]. According to data from the Surveillance, Epidemiology, and End Results (SEER) Program (2011-2017), the 5-year relative survival rate in the US is approximately 49.1% [3]. The frontline treatment of ovarian cancer encompasses surgical resection and a combination of platinum and taxane chemotherapy. It remains a challenging disease with a poor prognosis, causing the most deaths among women with gynecological cancers.

Data from national databases indicate racial differences in epithelial ovarian cancer risk and survival, with white women having a higher incidence but black women having a lower survival rate than other racial groups [4]. Based on SEER Cancer Statistics Review (1975-2018) [5], the age-adjusted incidence rate was 9.0 per 100,000 in Black women and 11.3 per 100,000 in White women; the age-adjusted mortality rate was 5.9 per 100,000 in Black women and 6.9 per 100,000 in White women from 2014 to 2018 in the US population. Racial disparities in mortality-incidence ratios for ovarian cancer were also found and reported that Black women with ovarian cancer have a worse survival outcome compared to White women: the five-year survival rates (SEER 18 Registries, 2011-2017) are 43.0 (±1.1) % for the Black and 49.4 (±0.4) % for the White. Black women experienced the poorest relative survival (36%) regardless of disease stage [4]. Despite the fact that White women have a greater incidence of OC in the

United States, Black women have a disproportionately higher incidence of OC-related death [6]. However, what drives theses racial and ethnic differences is unclear.

Some reports using population-based databases have demonstrated racial, ethnic, and socioeconomic differences in access to care and treatment among women with ovarian cancer, which support discrepancies in treatment among Black women and women of lower socioeconomic position (SES) [7, 8]. A previous study of SEER data between 1988 and 2001 suggests that race can act as an independent prognostic factor for survival in epithelial ovarian cancer (EOC) [9]. In another study using SEER data linked to Medicare claims for 1997 to 2007, Black women (54%) were less likely to receive guideline-adherent care than White women (68%) and the hazard of death in Black women was 1.27 times the hazard in White women. It also indicates that the difference in rates of recommended treatment and care are associated with racial/ethnic disparities of mortality among women [10]. A study of cancer registry data in California, including a sample size of 11,865 women with ovarian cancer, concluded that Black, low SES, and underqualified treatment are statistically and clinically significant independent predictors of receiving frontline treatment [11, 12]. Using data from 1307 White and 106 Black ovarian cancer patients from the Kaiser Permanente-Research on Ovarian Cancer Survival (KP-ROCS) Cohort Study, Bandera, et al. observed that White women were 1.5 times more likely to receive surgery-chemotherapy sequence than Black women with higher age-adjusted Charlson comorbidity index (AAGI), but the hazard of death was greater for Black women than White women among patients who all had higher AAGI and received frontline treatment [13]. Therefore, while research suggests that socioeconomic variables and access to the health care play a role in the gap in survival among Black women with ovarian cancer, there are likely other factors at play that have yet to be discovered.

Inflammatory-Related Risk Factors

Inflammation shares signaling pathways with cancer initiation and progression. Immune cells maturation, antigen presentation, and the adaptive immune system activation triggered by inflammation can activate the anti-tumor immune response. However, the stimuli of inflammatory cells can in turn suppress cell death and stimulate cell proliferation and thereby tumor growth. [14-18] Previous studies have provided evidence to support the hypothesis that ovarian cancer risk is mediated by inflammation. [19-21] Inflammation resulting from inflammatory-related risk factors can communicate with tumor immune microenvironment (TIME) shaped by networks of innate and adaptive immune cells, metabolic pathways, intracellular signaling molecules, and a wide range of soluble factors to affect cancer survival [22], and racial disparity in the inflammatory and immune response may explain difference in cancer risk and survival. Common inflammatory-related risk factors in women's life are categorized into different groups, including menstrual history, body mass index (BMI) in young adulthood and within 5 years prior to diagnosis, smoking, talc use, analgesic medication use, and benign gynecological conditions. Here, we review the potential mechanisms that influence inflammation and immunity, inflammation-related exposure associations with risk and survival of ovarian cancer (**Table 1**), and the racial disparity in exposure and treatment to them.

Ovarian cancers vary in histological characteristics and immunological parameters. High-grade serous ovarian cancer (HGSOC) is the most common type, characterized by severe nuclear atypia, a high nuclear-to-cytoplasmic ratio, and an abundance of mitoses. Age is identified as an important risk factor of developing ovarian cancer. More than 90% of tumors in people over the age of 40 are epithelial tumors, and the risk increases with age, peaking in their late 70s [23].

Aging impacts on immune system. The age-related alterations in both innate and adaptive immune cells and molecules result in the limitations in the immunity [24, 25]. Stage at diagnosis is one of the most important predictors of overall survival, as stage is linked to the severity and toxicity of cancers. A study with 28,118 incident EOC cases from SEER diagnosed in 2004-2014 indicated that localized/regional tumor is associated with a more favorable outcome [26]. Therefore, we matched on these two variables when selecting subjects with HGSOC for survival analysis.

Menopausal status

The end of a woman's reproductive period is marked by menopause, the permanent cessation of both the menstrual cycle and the ovarian function. It can be affected by the reproductive history such as parity and age at menarche. A plausible biologic mechanism linking ovulation to risk of ovarian cancer may be that over a woman's reproductive years, repeated exposure to the acute proinflammatory milieu that follows ovulation at the ovarian surface and distal fallopian tube may raise her risk of ovarian cancer. There is another hypothesis that the longer a woman is exposed to estrogen, the higher her risk of ovarian cancer is thought to be. Because large quantities of estrogen are only present during a woman's reproductive years, the longer she menstruates, the greater her risk. The association of immune function and menopause may be mediated by the sex hormone and the dramatic cascade hormone changes in female body resulting from menopause make it an important predictor of health outcomes [27]. Moreover, menopausal status is associated with age. Ovarian cancers is more common in postmenopausal women [28]. Women with ovarian cancer are more likely to have gone through menopause, although such difference is not significant [29]. Besides, menopause status was reported to interact with other factors to affect the risk of ovarian cancer. For an example, leisure-time

physical activity was associated with increased risk of ovarian cancer among premenopausal women, but no association among postmenopausal women [30]. With data from 96 patients in a retrospective clinical analysis with secondary ovarian carcinoma in New York, premenopausal patients exhibited a significantly shorter survival time than analogous postmenopausal patients (1.3 vs. 4.2 years, $p = 0.04$) [31].

Body mass index

Body mass index (BMI) is a quantitative trait with substantial genetic bases. Obesity influences pro-inflammatory cytokines in HGSOC, as different inter-cytokine correlations were detected based on BMI, potentially due to cytokine dysregulation in the setting of obesity [32]. Additionally, the presence of a high number of adipocytes in the human body causes adipose tissue deterioration, which can lead to immunological and hormonal changes in the microenvironment. Genetically predicted higher BMI was reported to be significantly associated with risk of non-HGSOC (OR = 1.29, 95% CI 1.03-1.61 per 5 units BMI) through mendelian randomization [33]. Data from the Ovarian Cancer Cohort Consortium (OC3) suggested that high BMI (≥35 vs. 20 to < 25 kg/m2, RR = 1.93, 95% CI: 1.46-2.56) was associated with increased risk of highly aggressive disease (death in < 1 year) [34]. BMI interacts with other exposures, such as hormone therapy and menopausal status [35-37], to affect such risk. From a meta-analysis including 13 case-control studies and 13 cohort studies, overweight and obesity were associated with increased risk of ovarian cancer in the premenopausal period (overweight vs. normal weight, RR = 1.07, 95% confidence interval: 1.02-1.12; obesity vs. normal weight, RR = 1.28, 95% CI: 1.16-1.41). A meta-analysis of 17 cohort studies suggests that obesity in the young adulthood and 5 years preceding the onset of ovarian cancer are associated with poor survival of EOC (early adulthood: pooled HR = 1.67, 95% CI: 1.29-2.16; 5 years before ovarian

cancer diagnosis: pooled HR = 1.35; 95% CI: 1.03-1.76). [38] Another meta-analysis of 14 studies with BMI measured recently (at diagnosis, and 1-5 year before) in Ovarian Cancer Association Consortium (OCAC) suggested that higher recent BMI was associated with adverse survival among the majority of women with ovarian cancer. [39]

Smoking history

Smoking constitutes a risk factor for adverse survival among women with ovarian cancer. Nicotine can suppress the function of immune system [40]. Smoking tends to alter immunological responses by weakening Th1-type responses and boosting Th2-dependent responses, primarily via upgrading the immune abundance, modifying the immune activities of a bunch of immune cells, and exacerbating allergic inflammation [41]. The exposure to smoke increases the level of interleukin (IL)-17A released from natural killer (NK), natural killer T (NKT) and γδ T-cells [42]. With data from a pooled analysis of 21 case-control studies [43], hazardous effects of smoking were observed: former smoking increased the risk of borderline serous ovarian tumors (OR = 1.30, 95 % CI: 1.12-1.50) and current smoking increased the risk of mucinous (OR = 1.31, 95 % CI: 1.03-1.65) and borderline mucinous ovarian tumors (OR = 1.83, 95 % CI: 1.39-2.41). Using data from 19 case-control studies in OCAC, Praestegaard, et al. showed a significant association of smoking status and survival among women with high-grade tumors (former smokers vs. never smokers, HR = 1.10, 95% CI: 1.02-1.18; current smokers vs. never smokers, HR = 1.11, 95% CI: 0.99-1.23) [44].

Talc use

Talc is the main ingredient of body powder. It is a magnesium silicate hydroxide, characterized by water molecules trapped between silicate sheets. An increased expression of ANTI-MUC1 antibodies was observed to correlated with talc use to genital area and other parts

of the body [45]. Talc can regulate the heat shock proteins to raise immunoglobulin protein levels in the blood [46]. Talc use was hypothesized to be associated with chronic pelvic inflammation status [21], and the perineal talc use may initiate an inflammatory response as foreign bodies [47]. The use of talc was significantly associated with an increased risk of invasive EOC in the population-based case-control study, African American Cancer Epidemiology Study (AACES) (OR = 1.39, 95% CI: 1.10-1.76). A stronger effect was observed in use around genital area and risk of ovarian cancer (OR=1.44, 95% CI: 1.11-1.86) [48]. A consistent result was found with data from OCAC, the odds ratio (OR) for the association of ever genital use of talc with incident EOC was 1.24 (1.15-1.33) compared to never use and elevated risk was also observed in invasive serous type (OR=1.20, 95% CI: 1.09-1.32) [49]. The association of talc use with ovarian cancer survival has not been investigated.

Analgesic medication use

Non-steroidal anti-inflammatory drugs (NSAIDs) are common for analgesic and antipyretic use. NSAIDs achieve its anti-inflammatory and antineoplastic effects by inhibiting cyclooxygenase (COX)-2 enzymes in the biosynthesis of prostaglandin and macrophage infiltration in tumor. Similarly, acetaminophen is analgesic and antipyretic, but has weak anti-inflammatory properties [50, 51]. Data from 13 studies in including 758,892 women suggest a daily intake of aspirin is significantly associated with a decreased risk of ovarian cancer (0.90, 95% CI: 0.82-1.00). Moreover, frequent aspirin (≥4 days/week) otherwise presented no protective effect in the study, which suggested a threshold effect for aspirin use. This study additionally showed that daily acetaminophen use is associated with increased ovarian cancer risk (RR=1.28, 95% CI 1.00-1.65) while no significant association was observed for non-aspirin NSAIDs (RR=1.00, 95% CI 0.90-1.11) [52]. Using data from a pooled analysis of 12 population-

based case-control studies in OCAC, the association of aspirin use was consistent in OC3 (OR = 0.91, 95% CI: 0.84-0.99), and strongest association was observed among daily users and users with low-dose (OR = 0.80, 95% CI: 0.67-0.96; OR = 0.66, 95% CI: 0.53-0.83, respectively) [53]. The inhibition of platelet activation was hypothesized to mediate the cancer-preventive effects of low-dose aspirin [54]. Similar but not significant results was observed among non-aspirin NSAIDs users (OR = 0.90, 95% CI: 0.77-1.05). No association was observed in acetaminophen use (OR = 0.99, 95% CI: 0.88-1.12) [53]. With data from the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII) in the United States, recent post-diagnosis use of aspirin and non-aspirin NSAIDs were associated with increased ovarian cancer survival (HR = 0.68, 95% CI: 0.52-0.89; HR = 0.67, 95% CI: 0.51-0.87, respectively) but no association with survival was observed for pre-diagnosis use [55]. With pooled data from 12 studies in OCAC, regular analgesic use was not associated with ovarian cancer survival (aspirin: HR = 0.96, 95% CI: 0.88-1.04; non-aspirin NSAIDs, HR = 0.97, 95% CI: 0.89-1.05; acetaminophen, HR = 1.01, 95% CI: 0.93-1.10) [56].

History of benign gynecologic conditions

Endometriosis is the condition that occurs when endometrial tissue appears outside the uterus and causes pelvic pain. There is a hypothesis that endometrial fragments result in immune system dysfunction when they make their way to the pelvic cavity, and neutrophils, which contribute to the resolution of inflammatory response, play a role in this process. Endometriosis patients have reduced number of mature dendritic cells (DC) compared to healthy women, which can adversely affect the activation of naïve T-cells into CD8+ cytotoxic or T helper state and hence a decreased self-immunity [57]. Data from AACES suggested that a history of endometriosis was significantly associated with increased risk of ovarian cancer overall (OR =

1.78, 95% CI: 1.09-2.90) [58]. With data from 13 case-control studies in OCAC, the history of endometriosis was reported to be strongly associated with a significantly increased risk of clear-cell, low-grade serous, and endometrioid invasive ovarian cancers (OR = 3.05, 95% CI: 2.43-3.84; OR = 2.11, 95% CI: 1.39-3.20; OR = 2.04, 95% CI: 1.67-2.48). Moreover, an increased risk was found between endometriosis and risk of HGSOC in the histological subtypes stratified analyses, albeit not significant (RR = 1.13, 95% CI: 0.97-1.32) [59]. With data from the Division of Pathology and the Division of Gynecologic Oncology in Wayne State University, the median survival (199 vs. 62 months) and the 5-year survival (62% vs. 51%) were better for patients with endometriosis-associated ovarian cancer compared to patients with ovarian cancer ($p = 0.038$) [60]. A consistent result was observed from patients diagnosed with clear cell carcinoma at Massachusetts General Hospital between 1975 and 2002. Median survival was 196 (28-363) months for patients with endometriosis and 34 (13-55) months for patients without endometriosis ($p = 0.01$) [61].

Uterine fibroids is a benign gynecologic tumor affecting 70% of women of reproductive age [62]. The extracellular matrix (ECM) proteins have an excessive expression during the pathology of fibroids that can trigger the abnormal inflammation response. Macrophage, marked by CD68 when activated and mature, plays a dominating role in the regulation of inflammation status by fibrosis [63]. Data from AACES suggested that the history of fibroid was associated with an increased but not significant risk of non-serous ovarian cancer (OR = 1.22, 95% CI: 0.85-1.75) [58]. No clear relationship with survival has been observed for fibroids [23].

Other benign conditions, including pelvic inflammatory disease (PID) and polycystic ovary syndrome (PCOS), also have been found to increase the risk and decrease the survival rate

of ovarian cancer [64, 65], but the current study cannot address this due to sample size constraints of women with PID and PCOS in NCOCS and AACES.

The inflammatory-related risk factors listed above may differ in prevalence or molecular mechanism of action by race and ethnicity. For example, patients from different racial/ethnic groups can undergo inconsistent physiological characteristics and clinical symptoms of menopause [66]. Black individuals are exposed to a larger intensity of smoke and intake more nicotine per cigarette compared with White individuals [67]. Although the strength of association between talc use and ovarian cancer was similar across race, genital talc use was more prevalent among Black women [68]. Racial/ethnic minorities receive less pain treatment then White individuals [69], which may result in differences in the prevalence of analgesic use by race. Previous studies also revealed racial/ethnic differences in gynecological diseases. Black women are more likely to develop uterine fibroids than White women [70, 71]. Moreover, the racial/ethnic difference was not only indicated in metabolic and immune response towards benign conditions such as PID, PCOS [72, 73], but also in the access to surgery with minimal invasion for fibroids and endometriosis [74, 75].

Ovarian Tumor Immune Microenvironment

Tumor immune microenvironment (TIME) refers to the niche where tumor cells interact with the host stroma including immune cells, endothelial cells, fibroblasts, and metabolites [76]. EOC is an immunogenic tumor with a wide variety of immune cells in its TIME [77]. The immune cell abundance and spatial pattern in TIME can indicate the anti-tumor function and contribute to prognosis. An immunosuppressive TIME is characterized by less enriched cytotoxic T-cells, reduced cytolytic activity, lower level of cytokines and tumor inflammatory

markers. The poor immune activity is associated with a worse survival outcome [78]. Understanding the function of immune cells in TIME is critical, as immunocompetent cells are substantial for establishing effective antitumor responses.

In ovarian cancer, an increase abundance in TILs and cytotoxic lymphocytes are generally related to a better survival outcome, while the abundance in Tregs, tumor-associated myeloid cells, and tumor-associated macrophages were associated with a worse survival outcome [79-81]. A recent manuscript by Peres, et al. [82] examined the association between immune cell abundance and survival of HGSOC by race. Immune cell abundance of tumor-infiltrating lymphocytes (TILs), cytotoxic T-cells, regulatory T-cells (Tregs), myeloid cells, and neutrophils from matched Black and White participants was measured by multiplex immunofluorescence. The presence of CD3+ TILs and cytotoxic T-cells in tumor islets was associated with better survival of HGSOC (HR = 0.68, 95% CI: 0.53-0.88; HR = 0.69, 95% CI: 0.52-0.92). Better survival outcomes were observed for higher levels of Tregs, but such association was in a site-specific manner. No association with survival was observed for Tregs overall and in the tumor in the intratumoral area; higher numbers of Tregs in the stroma, on the other hand, were associated with increased survival (HR = 0.69, 95% CI: 0.49-0.96). Presence of myeloid cells and neutrophils were both associated with better outcomes regardless of site. These associations were present in White women but attenuated and not statistically significant in Black women.

As in the report by Peres, et al. the immune cells we assess include TILs, cytotoxic T-cells, Tregs, myeloid cells, and neutrophils. Tumor-infiltrating lymphocytes, identified by CD3, play an active role for chemokines inside tumors and thereby accompanied by the expression of interferon-γ and IL-2. The presence of TILs is often observed in EOC and there is evidence that its abundance is a predictor of better prognosis. [83] Cytotoxic T-cells, identified by double

positive CD3 and CD8, are deemed as the most effective effectors in the antitumor immune reaction [84]. Tregs, identified by double positive CD3 and FoxP3, are vital to maintain the T-cell tolerance for self-antigens, however, they can negatively affect antitumor immunity to tumor antigen and result in immune escape [85]. Myeloid cells, identified by positive CD11b, are also known as granulocytes and monocytes. They are differentiated progeny of common progenitors produced from bone marrow hematopoietic stem cells. Different transcription factors control commitment to either lineage of myeloid cells, which is followed by final differentiation in response to certain colony-stimulating factors. Activated myeloid cells play a critical role in phagocytosis and inflammatory cytokines release [86]. When NF-κB is activated in myeloid cells, it results in transcription of genes that codes for growth and survival factors, which can help tumor cells proliferate[17]. Neutrophils, identified by double positive CD11b and CD15, conduct a variety of effector mechanisms and contribute to the host defense against infection [87].

In summary

Exposure to inflammatory-related risk factors is associated with ovarian cancer risk and survival. Inflammatory-related exposures may contribute to tumor formation and development via inflammatory signaling pathways, and TIME composition was found to be significantly associated with survival outcome. There was a racial/ethnic differential in survival and the strength of association between TIME and survival. As a result, we propose that inflammatory-related risk factors are associated with TIME, with the strength of association varying by race.

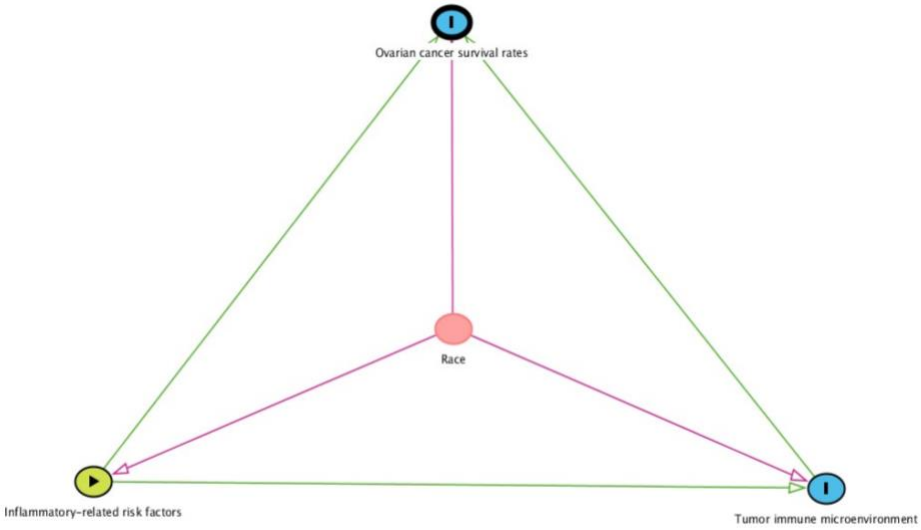

Figure 1. Directed acyclic graph showing correlations between exposure (inflammatory-related risk factor) and outcome (tumor immune microenvironment, TIME). Model drawn according to www.dagitty.net. Red lines: biasing path, green lines: causal path, red circles: ancestor of exposure and outcome.

METHODS

Data sources

The North Carolina Ovarian Cancer Study (NCOCS) [88] and the African American Cancer Epidemiology Study (AACES) [89] are two population-based case-control studies included in this study. NCOCS is a study of women with incident invasive or borderline EOC between 1999 and 2008. Cases were identified from the cancer registry and resided in 48 counties in North Carolina and were 20-74 years of age. Baseline questionnaire and inflammatory-related exposure information were collected by an in-person interview with trained nurse interviewers. The facility where the primary debulking operation was performed provided formalin-fixed paraffin embedded (FFPE) tumor blocks. Study pathologists performed a standardized pathologic and histologic review on all cases.

AACES is an ongoing, multi-state, multi-center study of self-identified African-American women with incident invasive EOC diagnosed between 2010 and 2015 and age- and

location-matched controls. The geographic locations are concentrated in Eastern US, including Alabama, Georgia, Illinois, Louisiana, Michigan, New Jersey, North Carolina, Ohio, South Carolina, Tennessee, and Texas. It is aimed to study ovarian cancer in AA women and explore the racial disparity in ovarian cancer etiology and survival. Cases were identified via state cancer registries, SEER registries, or gynecologic oncology departments, and were aged 20-79 years old. Demographic characteristics and inflammatory-related exposure information were collected by telephone interview. FFPE tissue specimens were acquired, and a centralized pathology evaluation was undertaken, same as in NCOCS.

Study population

Using the study population of AACES and NCOCS, 121 Black women with HGSOC tumors were matched to 121 White women with HGSOC by five-year age group and stage at diagnosis for the present study. As potential heterogeneity may exist by histotype, this study was restricted to women with HGSOC. The study was also limited to women who had not received any treatment prior to debulking surgery, as chemotherapy has been found to alter TIME[90].

Covariates

Age and stage at diagnosis were the matching variables for the selection and were included in all regression models. Age at diagnosis was considered a continuous variable and stage was classified as localized, regional, and distant. Localized refers to that there is no evidence that the malignancy has spread beyond the ovaries, regional refers to that the cancer has progressed to neighboring structures or lymph nodes outside of the ovaries, and distant refers to

that cancer has spread to other regions of the body. It was re-categorized into two strata in this analysis, localized and regional as early stage and distant as late stage.

Exposure classification

The inflammatory-related exposures include menopausal status (pre/postmenopausal), ever regular use of talc (yes/no), ever use of talc to genital areas (yes/no), use of aspirin (yes/no), use of non-aspirin NSAIDs (yes/no), use of acetaminophen (yes/no), history of endometriosis (yes/no), history of fibroids (yes/no), BMI in young adulthood (age 18 years), recent BMI 1-5 years prior to diagnosis., and smoking history. BMI in young adulthood (at age 18 years) was categorized based on BMI-for-age percentiles for girls' growth from Centers for Disease Control and Prevention (CDC)[91]. The corresponding categories used in this analysis were "<17.5 kg/m^2" for underweight, "17.5-25.7 kg/m^2" for healthy weight, and "≥25.7 kg/m^2" for overweight and obese. For recent BMI, the corresponding categories are "<25 kg/m^2" for underweight and healthy weight, "25-30 kg/m^2" for overweight, and "≥30.0 kg/m^2" for obese. Smoking history was categorized as "Non-smokers", "<5 pack years", "5-10 pack years", and "≥10 pack years". Given few patients had a history of PID and PCOS and the population size was limited for frequency and duration of talc use and the age diagnosed with endometriosis and fibroids, it is hard to produce convincing power after stratification, therefore, all of these variables were excluded from future analyses.

A weighted inflammation-related risk score (IRRS) developed by Brieger, et al. [92] was applied to Black and White cases from AACES and NCOCS. The variables that make up this composite variable are: alcohol use (yes/no), aspirin use (yes/no), other NSAID use (yes/no), body mass index (BMI), smoke exposure in the adult home (yes/no), PID (yes/no), PCOS

(yes/no), endometriosis (yes/no), menopausal hormone therapy use (never/<5 years/5+ years), physical inactivity (less than 2 hours physical activity per week/2+ hours physical activity per week), smoking status (current/former/never), talc use (never/yes, genital/yes, non-genital). Confounders included race (Black/White) (in overall analysis of both racial groups), menopausal status (pre/post), histotype (high-grade serous/non-high-grade serous), stage (localized/regional/distant), education (less than high school/high school equivalent/some college/college graduate), and age at diagnosis. To account for missing data, 50 multiply imputed datasets were created with the R package mice [93]. Using these imputed datasets, a Cox proportional hazards model was fit with the noted inflammatory variables, while adjusting for age at diagnosis, stage, and education, and stratifying by race, site, histotype, and menopausal status. Pooled coefficients for the inflammatory variables were obtained using Rubin's rules. In order to use these coefficients to get an individual level risk score, the missing values in the original dataset were replaced by the mode values generated from the 50 imputed datasets. Then, using this coalesced dataset, the pooled coefficients were multiplied by each participant's exposure level, and these products were summed to create the IRRS. This risk score was then brought into the subset of participants in this analysis of 242 women with HGSOC. IRRS is dichotomized by its median, 0.138, for future analysis.

Outcome classification

Multiplex immunofluorescence, which is a technique widely used for simultaneous detection of multiple biomarkers on a single tissue section [94], was applied to measure the abundance of immune cells in the primary tumors of 242 women with HGSOC. Three intratumoral regions of interest were selected from each section, composed of 80-90% tumor

cells by morphology and Pancytokeratin expression. CD3+ is used to denote TILs, and T-cell subsets, including cytotoxic T-cells which are marked by CD8, and Tregs by FoxP3. Myeloid cells are marked by CD11b, and neutrophils by CD11b and CD15. For each case, the abundance of immune cells was averaged across the three ROIs, and the abundance of each immune cell type overall (tumor and stroma) and in the tumor was dichotomized based on their percent. The cut-off point was 1% (<1%, ≥1%) for CD3+ and CD3+CD8+, while the cut-off point was presence (=0, >0) for CD3FoxP3+, CD11b+, and CD11b+CD15+. Tumors were also classified using a summary measure developed by Angell, et al. first in colorectal cancer [95]. The immunoscore is calculated by measuring the density and spatial location of CD3+ and CD8 + cells. The densities are scored on a scale of 0 to 4 (0: ≤10%, 1: 10-25%, 2: 25-70%, 3: 70-95%, and 4: 95-100%). Finally, the score is divided three groups, low (0 and 1), intermediate (2), and high (3) [7]. Better overall and progression-free survival was reported to associate with higher immunoscore [96].

Statistical analysis

A variety of descriptive statistical analyses were performed to explore the distribution of inflammatory-related risk factors, IRRS, and immune cell abundance.

The difference between Black and White women of each variable were tested by t-test for continuous variables normally distributed by race, Kruskal-Wallis rank sum test for continuous variables not normally distributed, and Chi-square test for categorical variables.

Unconditional logistic regression was employed to analyze the relationship between each inflammatory-related factor, including IRRS, and abundance for each immune cell type. Polytomous logistic regression was utilized to analyze the relationship between inflammatory-

related factors, including IRRS, and immunoscore. Firstly, the regressions ran in the overall population, adjusting for age at diagnosis, stage (early, late), and race (Black, White) to determine the overall association. Moreover, as the sample size was too small to generate robust power for interaction by race, we stratified the population based on race and the regressions ran in the race-stratified population respectively, adjusting for age at diagnosis and stage (early, late) to obtain the stratified associations. We compared the stratified associations between Black and White women to observe the trends and evaluate the potential racial disparities in TIME which may lead to different survival rates between races.

All analyses were performed using R, version 4.1.2.

RESULTS

Descriptive characteristics

Descriptive characteristics of the study population by categories of exposure, together with immune cell abundance and immunoscore, are presented in **Table 2**. The median age at diagnosis was 57.8 years old and 78.1% of the patients had late-stage disease. We observed no significant differences by race for menopausal status, the use of aspirin, history of endometriosis, but young adulthood BMI and recent BMI in Black women was significantly higher than White women, 22.0 vs. 20.4 kg/m2 ($p=0.001$), 31.7 vs. 26.5 kg/m2 ($p<0.001$). Blacks had a higher IRRS compared to Whites (0.145 vs. 0.109, $p=0.022$), but were less likely to engage in heavy smoking compared to Whites ($p<0.001$). Black women were more likely to use non-aspirin NSAIDs, acetaminophen, body power, and apply body power to genital area than White women ($p<0.001$, $p=0.036$, $p=0.012$, $p=0.009$, respectively).

Association of inflammatory-related exposures and immune cell abundance

Overall population

Among 242 participants, Tregs, myeloid cells, and TILs are the more prevalent while cytotoxic T-cells and neutrophils are less prevalent.

The results based on the regression was presented in **Table 3, Table 4, Table 5, Table 6,** and **Table 7**. Adjusting for age at diagnosis, stage at diagnosis, and race, being premenopausal at diagnosis was associated with less immune cells regardless of whether in tumor or in total (how is this defined?) compared to be women who were postmenopausal at diagnosis. For example, premenopausal women had a lower abundance of cytotoxic T-cells overall compared to postmenopausal women (OR=0.31, 95% CI: 0.12-0.82).

Higher young adult BMI was associated with larger abundance of overall TILs and Tregs and a potential dose response was observed. Women with a young adult BMI ≥ 25.7 had 2.39 (0.78-7.35) times the odds of ≥1% TIL abundance compared to women with a young adult BMI <17.5. As for overall Tregs, the OR for a young adult BMI of 17.5-25.7 vs. <17.5 was 1.03 (0.33, 3.27) and for ≥25.7 vs. <17.5, the OR was 2.69 (0.43, 16.72). The association of young adult BMI with cytotoxic T-cells was mostly null, and for neutrophils and myeloid cells, the association was null or slightly inverse with wide confidence intervals. Higher recent BMI was detected with less immune cell abundance overall and in tumor. No obvious dose response was observed.

Smoking was detected with less cell abundance of TILs, cytotoxic T-cells, neutrophils compared to non-smokers, but such association was close to null or has a positive effect among groups with ⩾10 pack years. Smokers were associated with larger cell abundance of myeloid cell compared to non-smokers. Moreover, association for Tregs was null.

Ever regular use of talc was associated with larger cell abundance regardless of the cell type and position. For example, women who used talc had a higher abundance of TILs overall (OR = 1.74, 95% CI: 1.03, 2.95) compared to non-users. Ever talc uses to genital area was also associated with larger cell abundance of TILs and cytotoxic T-cells, but null association was observed for Tregs, myeloid cells, and neutrophils.

Use of aspirin was associated with larger cell abundance of TILs, myeloid cells, and neutrophils. Null or a weak inverse association was observed in cytotoxic T-cells and Tregs. Use of non-aspirin NSAIDs was associated with less cell abundance for cytotoxic T-cells, Tregs, and neutrophils. The association with TILs was observed to be null. Albeit insignificant, the women with non-aspirin NSAIDs use had a higher abundance in myeloid cells in tumor but less overall (OR = 1.29, 95% CI: 0.65-2.56; OR = 0.74, 95% CI: 0.35-1.56). Use of acetaminophen was significantly associated with higher abundance of myeloid cells overall (OR = 4.52, 95% CI: 1.01-20.27). It was associated with lower abundance of neutrophils. As for TILs, cytotoxic T-cells, and Tregs, the associations were close to null.

The history of endometriosis was associated with less cell abundance of TILs and Tregs, and higher abundance of cytotoxic T-cells. Moreover, a null association was observed in myeloid cells and neutrophils.

Women with the history of fibroids had 2.17 (1.16, 4.07) times the odds of ≥1% cytotoxic T-cell abundance compared to women without the history of fibroids. In addition, it was associated with less abundance of myeloid cells and neutrophils and its association with Tregs was barely null.

Higher IRRS was associated with less cell abundance of TILs, cytotoxic T-cells, and neutrophils. For example, higher IRRS was significantly associated with less abundance of

neutrophil overall (OR = 0.55, 95% CI: 0.31-0.98). As for Tregs and myeloid cells, the association was null.

Race-stratified population

We generally observed a similar prevalence of the immune cells by race. Like the overall population that combined both racial groups, TILs, Tregs, and myeloid were more prevalent while cytotoxic T-cells and neutrophils were less prevalent.

The direction of the associations of menopausal status and IRRS with immune cell abundance was consistent by race. For example, premenopausal women had lower abundance of cytotoxic T-cells overall as in total population (OR = 0.12, 95% CI: 0.02-0.68); patients with higher IRRS were more likely to have less cell abundance TIME.

The association of young adulthood BMI suggested racial differences. The association of higher young adulthood BMI with higher cell abundance of TILs, cytotoxic T-cells, and Tregs but less abundance of myeloid cells overall and neutrophils in Blacks. However, the association of young adult BMI and immune cell abundance appeared to be null across all cell types in Whites. For example, the OR of women with young adult BMI ≥25.7 vs. <17.5 was 4.07 (0.92, 17.92) in Blacks and was 0.78 (0.11, 5.35) in Whites.

Racial differences were also observed in the association of recent BMI with immune cell abundance. Higher recent BMI was associated with more abundant TIME of TILs, and myeloid cells in Blacks but less abundant in Whites, although they were insignificant. Take myeloid cell abundance for example, the OR of women with recent BMI 25-30 vs. < 25 was 1.78 (0.41, 7.78) in Blacks but was 0.47 (0.15, 1.52) in Whites. That the higher recent BMI was associated with less abundance of neutrophils was consistent for Blacks and Whites. Association with cytotoxic T-cells or Tregs was mostly null for both racial groups.

Heavier smoking defined by pack years was associated with less cell abundance of TILs, cytotoxic T-cells, Tregs and higher abundance of myeloid in Blacks while heavier smoking amount was associated with more cell abundance in Whites. For cytotoxic T-cells, the OR of women smoking 0-5 pack years vs. non-smokers was 0.33 (0.11, 1.04) in Black but 3.25 (0.81, 13.12) in Whites. The association with neutrophils was null.

The associations of regular use of talc with higher abundance of TILs, cytotoxic T-cells, Tregs were consistent across race. However, there appeared to be racial difference in association with myeloid cells and neutrophils. Use of talc was associated with higher abundance in Whites, while the association was null in Blacks. For example, women with regular use of talc had 2.95 (1.13, 7.68) times odds of myeloid cells compared to women without talc use in Whites, but the association in Black was 0.69 (0.28, 1.71).

For TILs and cytotoxic T-cells, the talc use to genital area was associated with higher abundance in Blacks while the association was null in Whites. In particular, the OR for the association of talc use to genital area with overall TILs was 2.39 (1.10, 5.18) and the OR with cytotoxic T-cells in tumor was 2.35 (1.03, 5.36) in Blacks, but was 1.09 (0.46, 2.56) and 1.08 (0.42, 2.75) in Whites. The association was close to null for Tregs, myeloid cells, and neutrophils across race.

An obvious racial difference was present by the different association of aspirin use and immune cell abundance. Generally, compared to non-users, aspirin use was associated with increased abundance for all types of immune cells in Blacks, but such association was null or moderately inverse in Whites. For example, the OR of aspirin use among presence of myeloid cell was 5.62 (0.64, 49.41) in Blacks but 0.71 (0.19, 2.62) in Whites.

The associations of non-aspirin NSAIDs use with cell abundance of TILs in tumor, cytotoxic T-cells, Tregs, myeloid cells, and neutrophils were consistent in Blacks and Whites. However, for overall TILs and overall cytotoxic T-cells, the effects went different direction, albeit insignificant. The ORs for the association of non-aspirin NSAIDs us with TILs ≥1% were 1.60 (0.64, 3.97) in Blacks and 0.88(0.41, 1.87) in Whites, while the ORs for the association of non-aspirin NSAIDs us with cytotoxic T-cells ≥1% were 0.59 (0.21, 1.65) in Blacks and 1.20 (0.54, 2.71) in Whites.

Use of acetaminophen was associated with less cell abundance for TILs, cytotoxic T-cells, and Tregs in Black but higher abundance in Whites. The women with acetaminophen use had significantly less abundance of Tregs inn tumor (OR = 0.23, 95% CI: 0.06-0.88) compared to women without acetaminophen use in Blacks. Despite wide and insignificant CIs, the effect in Whites went opposite direction (OR = 4.77, 95% CI: 0.57-39.87) compared to Blacks. Acetaminophen use was associated with higher abundance of myeloid cells but less neutrophils, which was consistent across race.

Although associations were insignificant for all cell types, the history of endometriosis was linked to higher abundance in Blacks and less abundance in Whites, compared to those without endometriosis. For cytotoxic T-cells, the OR of women with endometriosis was 2.82 (0.78, 10.15) in Blacks and 0.72 (0.21, 2.47) in Whites.

There was racial difference among the associations of fibroids and cell abundance for Tregs, myeloid cells, and neutrophil; compared to those without fibroids, Blacks with fibroids had less immune cell abundance while Whites had higher immune cell abundance, albeit insignificant. For example, the OR of fibroids was 0.59 (0.21, 1.66) among presence of Tregs and 3.34 (0.41, 27.40) among presence of Tregs in Whites. Both Black and White women with

fibroids were associated with higher abundance of TILs and cytotoxic T-cells. Particularly, the OR for the association of history of fibroids with cytotoxic T-cells was 2.61 (1.13, 6.03) in Blacks.

Association of inflammatory-related exposures and the immunoscore

Among all 238 subjects in this study with known immunoscore, there were 62 (26.1%) with a low, 50 (21.0%) with an intermediate, and 126 (52.9%) with a high immunoscore. The prevalence of immune cells in race stratified population was similar to the overall population.

The results are shown in **Table 8**. Generally, being premenopausal at diagnosis was associated with lower immunoscore across races and in the overall population. Overall, premenopausal women had lower odds of high vs. low immunoscore (OR = 0.15, 95% CI: 0.03-0.66) compared to postmenopausal women. As there were no premenopausal women at diagnosis with high immunoscore in White population, the model did not converge to get the stratified association with high immunoscore in Whites.

Young adult BMI ≥25.7 was associated with intermediate and high immunoscore in the overall population and in Blacks. In particular, such association with an intermediate immunoscore was significant (OR = 7.88, 95% CI: 1.44-43.10) in the overall population. For high immunoscore, the OR of young adult BMI ≥25.7 vs. <17.5 was 5.83 (0.79, 42.88) in the overall population, insignificant but informative. Since no White women were categorized into the group of young adult BMI ≥25.7, the association did not converge for Whites. We cannot evaluate whether there was a racial difference.

The odds of higher recent BMI were linked to intermediate immunoscore rather than low immunoscore in the overall population. The association was in the same direction with overall

and slightly stronger in Blacks but null in Whites (BMI 25-30 vs. <25: Black, OR = 3.32, 95% CI: 0.95-11.55; Whites, OR = 0.96, 95% CI: 0.33-2.82). In contrast, the odds of higher recent BMI were linked to low immunoscore instead of high immunoscore in overall population. The association was in the same direction with overall population and stronger in Whites and null or slightly inverse in Black this time (BMI ≥30 vs. <25: Whites, OR = 0.37, 95% CI: 0.08-1.76; Black, OR = 1.57, 95% CI: 0.45-5.50).

The association of smoking and intermediate immunoscore was null in overall population and across race except for the comparison between 0-5 pack years and non-smokers for high immunoscore (overall: OR = 1.67, 95% CI: 0.57-4.88; Blacks: OR = 0.65, 95% CI: 0.15-2.77; Whites: OR = 10.83, 95% CI: 1.09-107.84).

Talc use to genital area was suggestively related to low immunoscore in Whites (OR = 0.52, 95% CI: 0.19-1.44). Other association of talc use with intermediate or high immunoscore in overall population or across race was null.

Use of aspirin was associated with intermediate and high immunoscore in Blacks but low immunoscore in the overall population and in Whites. Women with use of acetaminophen had higher immunoscore in the overall population. However, the association was different across race, as the use of acetaminophen was associated with low immunoscore in Blacks but higher immunoscore in Whites. The OR of acetaminophen use and high immunoscore vs. low was 7.34 (1.31, 41.05) among White women, but was 0.74 (0.12, 4.46) among Black women.

The history of endometriosis was associated with lower immunoscore in overall population. The stratified associations were consistent for intermediate immunoscore. However, there was racial difference for odds of endometriosis among high immunoscore in Blacks (High

vs. low, OR = 1.98, 95% CI: 0.46-8.59) and in Whites (High vs. low, OR = 0.37, 95% CI: 0.07-2.08).

No obvious difference in the associations with immunoscore across race was observed in regular use of talc, non-aspirin NSAIDs use, history of fibroids, and IRRS. The stratified association was consistent with overall. They were insignificant but informative: the association of talc use and intermediate immunoscore was null and the odds of women with talc use vs. non-users were higher in magnitude for those with a high immunoscore compared to low immunoscore; the odds of women with non-NSAIDs use vs. non-users were larger among both intermediate and high immunoscore compared to low immunoscore; the odds of women with history of fibroids was smaller in intermediate immunoscore compared to low immunoscore, but was larger in high immunoscore compared to low immunoscore; the odds of women with higher IRRS was larger in intermediate immunoscore compared to low immunoscore, but was smaller in high immunoscore compared to low immunoscore.

DISCUSSION

The present study of Black and White women with HGSOC was an exploratory analysis to investigate the association of inflammatory-related risk factors with immune cell abundance in TIME. Despite the small sample size and wide CIs, many associations between inflammatory-related risk factors with immune cell abundance in TIME overall or by race were suggestive. The total immune cell abundance was a combination of immune cells in tumor and in stroma, with cells in tumor accounting for 80%~90% of total immune cells. Thus, the direction of associations was fairly consistent in the tumor and in total.

In the overall population, having higher BMI in young adulthood, use of regular talc, use of talc to genital area, use of aspirin, and a history of fibroids were related to a more abundant TIME, particularly a higher abundance of TILs, cytotoxic T-cells, and Tregs. Being premenopausal at diagnosis, having higher BMI measured within 5 years prior to diagnosis, smoking, use of non-aspirin NSAIDs, and having higher IRRS were linked to a TIME with low immune cell abundance. Although acetaminophen use was significantly associated with higher abundance of myeloid cells, its effect on the whole dynamic TIME remains unknown.

There was no obvious pattern in most of the inflammatory-related risk factors and the immunoscore, except for the trends of being premenopausal at diagnosis with low immunoscore and higher young adulthood BMI with intermediate immunoscore. Due to the low prevalence of females in young adulthood BMI categories as having an overweight/obese BMI, there was no sufficient statistical power for us to detect a robust association.

In the present study, we observed a significantly lower overall cytotoxic T-cell abundance in TIME among premenopausal women at diagnosis. Our result is consistent with a recent study that observed a significantly increased CD8+ T-cells in postmenopausal women with HGSOC compared to premenopausal patients[97]. Previous studies demonstrated cytotoxic killing by CD8+T-cells was significantly higher in postmenopausal women compared to premenopausal women irrespective of menstrual cycle stage [98] and an increase in CD8+ T-cells with direct cytotoxic activity was observed in endometrium after menopause [99], which can potentially be explained by the reduced sensitivity of transforming growth factor β (TGF-β) suppression to cytotoxic activity after menopause [99]. A recent study about TIME and breast cancer bone metastases showed that pre-menopausal patients had an alteration in immunological signaling pathways and cell patterns when compared to post-menopausal individuals [100]. Sex

hormone level change in pre- and post-menopause may contribute to this alteration. As stated in the introduction section, both being menopausal at diagnosis and the reduced cell abundance in TIME was linked to a poor survival, with the result that being premenopausal was linked to lower abundance in TIME, we hypothesize that the effect of being premenopausal on survival may be mediated by TIME.

Our data show a significant association of regular use of aspirin with higher overall TIL abundance and an obvious increasing trend in abundance of myeloid cells and neutrophils. Aspirin has been reported to disrupt the angiogenic of breast cancer cells and its inflammatory cytokines interplay with macrophages [101] and alter the enrichment in dominant CD8+ T-cell to myeloid-derived suppressor cells [102]. Few studies revealed the relationship between aspirin and TILs in TIME. Instead, previous studies suggested consistently that aspirin has a suppressive effect on macrophage recruitment by inhibiting COX-1/thromboxane A2 pathway and change the ratio of M1/M2 macrophage phenotype by inducing the polarization to achieve antitumor function. [103-105] Mechanisms how aspirin affects TIL are uncertain currently, however, the effect of aspirin on survival could potentially be mediated by TIME involving other types of immune cells. It may be worthwhile to investigate macrophages as a future direction.

A significant association of fibroids with higher cytotoxic T-cell abundance in tumor was observed in this analysis. Uterine fibroids involve in PD-L1 expression and cytotoxic T-cell infiltration, and immune system behavior differs among uterine smooth muscle tumors. The number of tumor-associated CD8+ cells was reported to be greatest in leiomyosarcomas.[106, 107] Therefore, fibroids can associate with cell abundance in TIME through plausible mechanism and we can hypothesize that fibroids have potential positive effect on survival with TIME mediation. As **Table 1** shows, endometriosis was reported to be associated with better

survival. Among Black women, cytotoxic T-cells was suggestive in terms of endometriosis being positively associated with a higher abundance of those immune cells.

Higher IRRS was observed to be associated with a low immune cell abundance in TIME, with significant reduced overall neutrophils abundance. To date, no study has evaluated how IRRS impacted the cell abundance in TIME. Brieger, et al. developed the score and reported that higher prediagnosis IRRS was linked to an increased mortality risk following the ovarian cancer diagnosis[92]. Therefore, cell abundance in TIME may be a mediator of IRRS's effect on ovarian cancer survival. Limitations in the reports of associations with IRRS and survival mainly lie in that the population included in the published paper was mostly white hence a limited generalizability to the Black population.

Suggestive patterns were observed in the relationship of BMI in young adulthood and recent BMI measured within 5 years prior to diagnosis with cell abundance in TIME. However, they interestingly indicated opposite effects: higher young adult BMI was associated with increased cell abundance of TIME while higher recent BMI with decreased cell abundance of TIME. Adipose tissue is a vital organ for endocrine function, which can secret the growth hormones, insulin, adipokines, chemokines regulating inflammation and anti-tumor immunity [108]. Obesity is reported to increase the tumor burden by suppressing the antitumor immunity and shaping immune cell metabolism in TIME [109]. Data from murine model suggested stunted CD8+ T-cell infiltration and effector function [110]. Macrophage proliferation was also observed within adipose tissue, stimulated by MCP-1. After successive reactions involving a range of proinflammatory mediators, a chronic inflammation status was maintained and was linked to the tumor growth. An elevated level of C-reactive protein and IL 6 was observed in obese women [18, 111] while IL6 can participate in the down-regulation of CD8+ T-cells and up-regulation of

FoxP3+ T-cells in TIME in cancer-associated fibroblasts [112]. The result of higher recent BMI was fairly consistent with the biological mechanism; however, the reason why higher young adult BMI was linked to an abundant TIME was not clear. Moreover, for recent BMI, it may affect ovarian cancer survival through TIME, but for young adult BMI, there must be other causal pathways at play regarding long term effect of obesity in young adulthood. A potential explanation could be that BMI likely represents different body compositions in different age groups.

As for smoking, although ever smoking was more likely to be associated with lower cell abundance in general, women in the heaviest smoking group were associated with lowest magnitude. In a prospective study of colorectal cancer, Ugai, et al. followed up 131,144 participants and found that macrophage density and polarization differed by the patients' smoking experience. The hazard of mortality was higher for patients with heavier smoking habits, but the association was not statistically significant for tumors with higher macrophage abundance. These findings indicate an interplay of smoking and macrophage density in colorectal carcinogenesis, which have an impact on survival outcome. [113] This could be explained by the potential relationship between the higher abundance of TIME in those with a heavy smoking load compared to light smokers.

The prevalence of inflammatory-related exposure was significantly different among Black and White women with HGSOC for most of the inflammatory-related risk factors. In the stratified population, racial differences were observed in the associations of all inflammatory-related risk factors except for menstrual history, although the majority of them were insignificant. In general, Black women with the exposures were linked to higher immune cell

abundance of TILs and cytotoxic T-cells, less myeloid cells and neutrophils compared to White women, and the direction of the associations with Tregs varies by exposures across race.

Significant associations of acetaminophen use with less Tregs in Blacks and regular use of talc with more myeloid cells in Whites were observed. However, associations were inconsistent and in the opposite direction in Whites compared to Blacks. This may be a possible contributor to the racial disparity in survival. Moreover, in Black women, the significant associations of fibroids with higher cytotoxic T-cell abundance in tumor, talc use to genital area with higher overall TIL abundance and higher Treg abundance in tumor were observed, while their counterparts in Whites were null. The association of being premenopausal with less cytotoxic T-cells was significant in Whites but insignificant in Blacks. The presence and abundance of cytotoxic T-cells, TILs, and Tregs in TIME promise an improved overall survival of HGSOC, under this circumstance, Black women are expected to have similar survival as Whites. However, Peres, et al. reported the survival benefit of a strong immune infiltration attenuated among Black women with HGSOC [7], which was strengthen by this result. A plausible explanation was a higher proportion of exhausted T-cells in TIME observed in Black women with breast cancer compared to White women [114].

The strengths of this study include the incorporation of data and biospecimens from the robust population-based studies and the validated, high-quality multiplex immunofluorescence assay to the ascertain outcome of immune cell types. However, there are still limitations for our analysis. The sample size was too small to generate sufficient statistical power, especially after stratification and models failed to converge for many associations. Self-reported bias of smoking may lead to the misclassification of current smokers; therefore, we use pack years instead, but this increased the number of categories and can also reduce power. Moreover, population from

two studies were recruited from different time periods and different regions which may involve unmeasured confounders. Current studies include only a fraction of the immune cells in TIME, other important modulator like macrophages were not analyzed and the subgroups of T-cell differentiation were not sufficiently identified. Low exposure prevalence of medication uses and benign gynecological conditions would lower the statistical power for the analysis of dose, frequency, and duration, so we did not conduct those analyses. The generalizability was limited as the study was restricted to women with HGSOC.

To the best of our knowledge, this study is the first to explore the racial differences in inflammatory-related risk factors and tumor immune microenvironment in women with HGSOC. We have compared our result to previous studies regarding tumor immunity and survival. Previous studies suggest that the effect of inflammatory-related risk factors on survival of HGSOC can be mediated through TIME, however, this association differed according to race. For further investigation, we recommend replicating the study in a larger dataset with the identification of more immune cell types and emphasize on the relationship of TIME and inflammatory-related risk factors with significant association in our analysis.

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Table 1. Direction of the effects based on literature review.

Inflammatory-related exposures	Direction of effect[a]	
	Risk of OC	**Survival of OC**
Menopausal status		
postmenopausal	increased	better
premenopausal	decreased	poorer
BMI (kg/m^2)		
higher young adult BMI	increased	poorer
higher recent BMI	increased	poorer
Behavior		
ever smoker	increased	poorer
Talc use[b]		
ever regular use of talc	increased	Unknown
ever talc uses to genital area	increased	Unknown
Analgesic medication use		
aspirin	decreased with regular use	better with regular use
non-aspirin NSAIDs	decreased with intensive use	better with regular use
acetaminophen	increased with daily use	no association
Benign gyn conditions		
endometriosis	increased	better
fibroids[c]	increased	Unknown

[a]This table describes a potential direction of each inflammatory-related risk factor, but the effect can be insignificant.
[b]No available relationship of talc use and ovarian cancer mortality and survival rate from previous studies.
[c]No available relationship of history of fibroids and ovarian cancer mortality and survival rate from previous studies.

Table 2. Characteristics of patients with high-grade serous ovarian cancers overall and by race/ethnicity.

Patient Characteristics	Overall (N=242)	Black (N=121)	White (N=121)	p-value[h]
	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)	
Age at diagnosis				
Continuous, years	57.8 (8.90)	57.7 (9.08)	57.9 (8.75)	0.891
<50 years	44 (18.2)	22 (18.2)	22 (18.2)	0.999
50-59 years	101 (41.7)	51 (42.1)	50 (41.3)	
60-69 years	69 (28.5)	34 (28.1)	35 (28.9)	
≥70 years	28 (11.6)	14 (11.6)	14 (11.6)	
Tumor stage[a]				
Early stage	53 (21.9)	27 (22.3)	26 (21.5)	1
Late stage	189 (78.1)	94 (77.7)	95 (78.5)	
Menopausal status at diagnosis				
Postmenopausal	193 (79.8)	94 (77.7)	99 (81.8)	0.522
Premenopausal	49 (20.2)	27 (22.3)	22 (18.2)	
Young adult BMI[b]				
Continuous, kg/m^2	21.2 (3.81)	22.0 (4.33)	20.4 (3.03)	0.001
<17.5 kg/m^2	28 (11.8)	13 (11.1)	15 (12.5)	0.007
17.5-25.7 kg/m^2	182 (76.8)	83 (70.9)	99 (82.5)	
≥25.7 kg/m^2	27 (11.4)	21 (17.9)	6 (5.0)	
Unknown	5	4	1	
Recent BMI[b]				
Continuous, kg/m^2	29.1 (8.03)	31.7 (8.96)	26.5 (5.96)	<0.001
<25 kg/m^2	88 (36.7)	26 (21.7)	62 (51.7)	<0.001
25-30 kg/m^2	64 (26.7)	32 (26.7)	32 (26.7)	
≥30 kg/m^2	88 (36.7)	62 (51.7)	26 (21.7)	
Unknown	2	1	1	
IRRS[c]				
Continuous	0.127 (0.147)	0.145 (0.142)	0.109 (0.150)	0.022[e]
<0.1377349	121 (50.0)	49 (40.5)	72 (59.5)	0.005
≥0.1377349	121 (50.0)	72 (59.5)	49 (40.5)	
Smoking history				
Non-smoker	120 (50.0)	56 (46.3)	64 (53.8)	<0.001
<5 packyear	37 (15.4)	27 (22.3)	10 (8.4)	
5-10 packyear	22 (9.2)	16 (13.2)	6 (5.0)	
≥10 packyear	61 (25.4)	22 (18.2)	39 (32.8)	
Unknown	2	0	2	
Ever use of aspirin[g]				
Yes	28 (14.3)	15 (14.4)	13 (14.1)	1
No	168 (85.7)	89 (85.6)	79 (85.9)	
Unknown	46	17	29	
Ever use of non-aspirin NSAIDs				

Patient Characteristics	Overall (N=242)	Black (N=121)	White (N=121)	p-value[h]
	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)	
Yes	83 (35.2)	26 (22.6)	57 (47.1)	<0.001
No	153 (64.8)	89 (77.4)	64 (52.9)	
Unknown	6	6	0	
Ever use of acetaminophen				
Yes	34 (17.4)	12 (11.5)	22 (23.9)	0.036
No	162 (82.7)	92 (88.5)	70 (76.1)	
Unknown	46	17	29	
Ever regular use of talc				
Yes	125 (51.9)	73 (60.3)	52 (43.3)	0.012
No	116 (48.1)	48 (39.7)	68 (56.7)	
Unknown	1	0	1	
Ever apply talc to genital areas				
Yes	78 (32.2)	49 (40.5)	29 (24.0)	0.009
No	164 (67.8)	72 (59.5)	92 (76.0)	
Talc application to genital areas (times/month)[d]	20.1 (11.3)	22.0 (11.0)	16.9 (11.4)	0.059[e]
Unknown	1	0	1	
Talc application to genital areas (yrs)[c]	19.8 (19.3)	20.7 (20.5)	17.3 (15.2)	0.755[e]
Unknown	5	0	5	
Ever diagnosed with endometriosis				
Yes	27 (11.2)	11 (9.2)	16 (13.2)	0.441
No	213 (88.8)	108 (90.8)	105 (86.8)	
Unknown	2	2	0	
Age diagnosed with endometriosis[d]	32.0 (5.86)	33.8 (5.83)	30.8 (5.73)	0.190
Ever diagnosed with uterine fibroids				
Yes	71 (30.0)	49 (40.5)	22 (19.0)	<0.001
No	166 (70.0)	72 (59.5)	94 (81.0)	
Unknown	5	0	5	
Age diagnosed with uterine fibroids[d]	39.0 (9.53)	39.0 (10.6)	38.8 (6.67)	0.91
Unknown	3	1	2	
Ever diagnosed with PID				
Yes	14 (5.8)	10 (8.3)	4 (3.3)	0.167[f]
No	228 (94.2)	111 (91.7)	117 (96.7)	
Age diagnosed with PID[d]	26.4 (8.30)	25.7 (8.69)	28.0 (8.16)	0.657
Ever diagnosed with PCOS				
Yes	2 (0.8)	0 (0)	2 (1.7)	0.247[f]
No	239 (99.2)	121 (100)	118 (98.3)	
Unknown	1	0	1	
CD3+ in tumor				
<1%	117 (48.3)	60 (49.6)	57 (47.1)	0.797
≥1%	125 (51.7)	61 (50.4)	64 (52.9)	

Patient Characteristics	Overall (N=242)	Black (N=121)	White (N=121)	p-value[h]
	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)	
CD3+ in total				
<1%	107 (44.2)	55 (45.5)	52 (43.0)	0.796
≥1%	135 (55.8)	66 (54.5)	69 (57.0)	
CD3+CD8+ in tumor				
<1%	173 (71.5)	86 (71.1)	87 (71.9)	1
≥1%	69 (28.5)	35 (28.9)	34 (28.1)	
CD3+CD8+ in total				
<1%	163 (67.4)	82 (67.8)	81 (66.9)	1
≥1%	79 (32.6)	39 (32.2)	40 (33.1)	
CD3+FoxP3+ in tumor				
<1%	42 (17.4)	24 (19.8)	18 (14.9)	0.396
≥1%	200 (82.6)	97 (80.2)	103 (85.1)	
CD3+FoxP3+ in total				
<1%	34 (14.0)	18 (14.9)	16 (13.2)	0.853
≥1%	208 (86.0)	103 (85.1)	105 (86.8)	
CD11b+ in tumor				
<1%	55 (22.7)	27 (22.3)	28 (23.1)	1
≥1%	187 (77.3)	94 (77.7)	93 (76.9)	
CD11b+ in total				
<1%	41 (16.9)	21 (17.4)	20 (16.5)	1
≥1%	201 (83.1)	100 (82.6)	101 (83.5)	
CD11b+CD15+ in tumor				
<1%	177 (73.1)	84 (69.4)	93 (76.9)	0.246
≥1%	65 (26.9)	37 (30.6)	28 (23.1)	
CD11b+CD15+ in total				
<1%	166 (68.6)	80 (66.1)	86 (71.1)	0.489
≥1%	76 (31.4)	41 (33.9)	35 (28.9)	
Immunoscore				
Low	62 (26.1)	33 (27.7)	29 (24.4)	0.831
Intermediate	50 (21.0)	24 (20.2)	26 (21.8)	
High	126 (52.9)	62 (52.1)	64 (53.8)	
Unknown	4	2	2	

SD: standard deviation
BMI: body mass index
IRRS: inflammation risk score
PID: pelvic inflammatory disease
PCOS: polycystic ovarian syndrome
[a]Localized and regional tumors are categorized as early stage while distant tumors are categorized as late stage.
[b]For young adult BMI, it is categorized based on BMI-for-age percentiles. BMI percentiles for 18-year-olds are used in this study. After looking into the table published by CDC, the corresponding categories are "<17.5 kg/m^2" for underweight, "17.5-25.7 kg/m^2" for healthy weight, and "≥25.7 kg/m^2" for overweight and obese; for recent BMI, the corresponding categories are "<25 kg/m^2" for underweight and healthy weight, "25-30 kg/m^2" for overweight, and "≥30.0 kg/m^2" for obese.
[c]IRRS is dichotomized with its median, 0.1377349.
[d]Some participants had not ever applied talc to genital areas or been diagnosed with comorbidities and hence structural missing values for frequency and duration of talc use and ages at diagnosis for them, and the missing values presented in the table only reflect the missing pattern of those who applied talc to genital area or were diagnosed of diseases. There were 164 structural missing values for frequency of talc application,

164 for duration of talc application, 215 for age diagnosed with endometriosis, 171 for age diagnosed with uterine fibroids, and 228 for age diagnosed with PID.

Basically, missing values were excluded when testing. The statistical difference between black and white of each variable were tested by t-test for continuous variables and Chi-square test for categorical variables, except for:
[e]The frequency and duration of talc application to genital areas and IRRS were tested by Kruskal-Wallis rank sum test, as they cannot be regarded as normally distributed by race.
[f]Ever diagnosed with PID, and ever diagnosis with PCOS were tested by Fisher's Exact Test, as they have cells under 5.
[g]NCOCS did not collect data on aspirin use for the first two years of the study but did so in subsequent years.
[h]p-value is for the difference in prevalence of inflammatory-related risk factors or immune cell abundance between Blacks and Whites.

Table 3. Numbers of participants with abundant CD3 in tumor and in total, and odds ratios and 95% confidence intervals for the association of inflammatory-related exposures and of CD3 abundance in tumor and in total in the total study population overall and by race/ethnicity.

Inflammatory-related exposures	CD3+ in tumor						CD3+ in total					
	Overall		Black		White		Overall		Black		White	
	≥1% N[a]	OR (95% CI)[b]	≥1% N[a]	OR (95% CI)[c]	≥1% N[a]	OR (95% CI)[c]	≥1% N[a]	OR (95% CI)[b]	≥1% N[a]	OR (95% CI)[c]	≥1% N[a]	OR (95% CI)[c]
Menopausal Status												
postmenopausal	101	1.00 (Referent)	47	1.00 (Referent)	54	1.00 (Referent)	108	1.00 (Referent)	51	1.00 (Referent)	57	1.00 (Referent)
premenopausal	24	0.71 (0.30, 1.67)	14	0.88 (0.26, 2.98)	10	0.54 (0.16, 1.86)	27	0.68 (0.28, 1.61)	15	0.80 (0.24, 2.71)	12	0.58 (0.17, 1.99)
BMI (kg/m^2)												
young adult BMI												
<17.5	12	1.00 (Referent)	5	1.00 (Referent)	7	1.00 (Referent)	13	1.00 (Referent)	5	1.00 (Referent)	8	1.00 (Referent)
17.5-25.7	93	1.47 (0.65, 3.31)	40	1.51 (0.45, 5.02)	53	1.48 (0.48, 4.54)	100	1.43 (0.64, 3.20)	43	1.75 (0.53, 5.83)	57	1.20 (0.39, 3.63)
≥25.7	17	2.49 (0.82, 7.59)	14	3.26 (0.76, 13.97)	3	1.17 (0.17, 8.06)	18	2.39 (0.78, 7.35)	15	4.07 (0.92, 17.92)	3	0.78 (0.11, 5.35)
recent BMI												
<25	47	1.00 (Referent)	11	1.00 (Referent)	36	1.00 (Referent)	53	1.00 (Referent)	14	1.00 (Referent)	39	1.00 (Referent)
25-30	31	0.84 (0.43, 1.63)	17	1.59 (0.56, 4.56)	14	0.56 (0.23, 1.34)	34	0.77 (0.39, 1.50)	18	1.14 (0.40, 3.24)	16	0.61 (0.25, 1.45)
≥30	46	0.98 (0.52, 1.85)	33	1.54 (0.61, 3.90)	13	0.75 (0.30, 1.90)	47	0.75 (0.40, 1.42)	34	1.03 (0.41, 2.60)	13	0.59 (0.23, 1.48)
Behavior, smoking history (packyear)												
Non-smoker	64	1.00 (Referent)	32	1.00 (Referent)	32	1.00 (Referent)	70	1.00 (Referent)	35	1.00 (Referent)	35	1.00 (Referent)
<5	15	0.60 (0.28, 1.29)	9	0.38 (0.14, 1.01)	6	1.36 (0.34, 5.39)	17	0.61 (0.28, 1.29)	11	0.42 (0.16, 1.09)	6	1.24 (0.31, 4.90)
5-10	10	0.71 (0.28, 1.81)	8	0.73 (0.24, 2.26)	2	0.46 (0.08, 2.75)	10	0.57 (0.23, 1.45)	8	0.58 (0.19, 1.80)	2	0.41 (0.07, 2.45)
≥10	35	1.19 (0.64, 2.22)	12	0.93 (0.34, 2.53)	23	1.40 (0.63, 3.16)	37	1.11 (0.59, 2.08)	12	0.74 (0.27, 2.03)	25	1.46 (0.64, 3.32)
Talc use												
ever regular use of talc												
no	53	1.00 (Referent)	19	1.00 (Referent)	34	1.00 (Referent)	57	1.00 (Referent)	21	1.00 (Referent)	36	1.00 (Referent)
yes	71	1.60 (0.95, 2.69)	42	2.06 (0.96, 4.39)	29	1.30 (0.62, 2.70)	77	1.74 (1.03, 2.95)	45	2.07 (0.97, 4.40)	32	1.47 (0.70, 3.10)
ever talc uses to genital area												
no	78	1.00 (Referent)	30	1.00 (Referent)	48	1.00 (Referent)	85	1.00 (Referent)	33	1.00 (Referent)	52	1.00 (Referent)
yes	47	1.66 (0.95, 2.93)	31	2.36 (1.10, 5.07)	16	1.07 (0.46, 2.50)	50	1.70 (0.96, 3.01)	33	2.39 (1.10, 5.18)	17	1.09 (0.46, 2.56)
Analgesic medication use												
aspirin												
no	82	1.00 (Referent)	40	1.00 (Referent)	42	1.00 (Referent)	90	1.00 (Referent)	45	1.00 (Referent)	45	1.00 (Referent)
yes	17	1.78 (0.77, 4.14)	10	3.23 (0.95, 10.97)	7	1.01 (0.30, 3.36)	17	1.50 (0.65, 3.49)	10	2.53 (0.75, 8.53)	7	0.90 (0.27, 2.98)
non-aspirin NSAIDs												
no	76	1.00 (Referent)	43	1.00 (Referent)	33	1.00 (Referent)	83	1.00 (Referent)	46	1.00 (Referent)	37	1.00 (Referent)
yes	45	1.11 (0.63, 1.94)	14	1.32 (0.54, 3.21)	31	1.03 (0.49, 2.19)	48	1.09 (0.62, 1.91)	16	1.60 (0.64, 3.97)	32	0.88 (0.41, 1.87)
acetaminophen												
no	81	1.00 (Referent)	46	1.00 (Referent)	35	1.00 (Referent)	89	1.00 (Referent)	51	1.00 (Referent)	38	1.00 (Referent)
yes	18	1.09 (0.51, 2.32)	4	0.56 (0.15, 2.03)	14	1.77 (0.65, 4.82)	18	0.90 (0.42, 1.93)	4	0.45 (0.12, 1.62)	14	1.46 (0.54, 3.94)
Benign gyn conditions												
endometriosis												
no	111	1.00 (Referent)	53	1.00 (Referent)	58	1.00 (Referent)	119	1.00 (Referent)	57	1.00 (Referent)	62	1.00 (Referent)
yes	12	0.69 (0.31, 1.57)	6	1.19 (0.34, 4.20)	6	0.48 (0.16, 1.45)	14	0.80 (0.35, 1.80)	7	1.51 (0.41, 5.52)	7	0.49 (0.17, 1.46)
fibroids												
no	81	1.00 (Referent)	32	1.00 (Referent)	49	1.00 (Referent)	88	1.00 (Referent)	36	1.00 (Referent)	52	1.00 (Referent)
yes	43	1.78 (0.99, 3.20)	29	1.91 (0.90, 4.03)	14	1.58 (0.60, 4.14)	45	1.68 (0.93, 3.04)	30	1.66 (0.79, 3.50)	15	1.78 (0.66, 4.79)
Composite inflammation risk score, IRRS												
<median	65	1.00 (Referent)	27	1.00 (Referent)	38	1.00 (Referent)	71	1.00 (Referent)	29	1.00 (Referent)	42	1.00 (Referent)
≥median	60	0.83 (0.49, 1.41)	34	0.70 (0.33, 1.46)	26	1.00 (0.47, 2.14)	64	0.75 (0.44, 1.27)	37	0.69 (0.33, 1.46)	27	0.81 (0.38, 1.74)

OR: odds ratio, CI: confidence interval, CD: cell differentiation.

Total CD is the combination of CD in tumor and in stroma.
[a]≥1%N is the number of participants with the percent of CD3 ≥1%.
[b]Estimated using a repeated measures framework where each inflammatory-related exposure is included in the models. Models are adjusted for age at diagnosis (years), stage (early, late), and race (Black, White).
[c]Estimated using a repeated measures framework where each inflammatory-related exposure is included in the models. Models are adjusted for age at diagnosis (years) and stage (early, late) in the race-stratified population respectively.

Table 4. Numbers of participants with abundant CD3CD8 in tumor and in total, and odds ratios and 95% confidence intervals for the association of inflammatory-related exposures and of CD3CD8 abundance in tumor and in total in the total study population overall and by race/ethnicity.

Inflammatory-related exposures	CD3+CD8+ in tumor						CD3+CD8+ in total					
	Overall		Black		White		Overall		Black		White	
	≥1% N[a]	OR (95% CI)[b]	≥1% N[a]	OR (95% CI)[c]	≥1% N[a]	OR (95% CI)[c]	≥1% N[a]	OR (95% CI)[b]	≥1% N[a]	OR (95% CI)[c]	≥1% N[a]	OR (95% CI)[c]
Menopausal status												
postmenopausal	59	1.00 (Referent)	27	1.00 (Referent)	32	1.00 (Referent)	68	1.00 (Referent)	30	1.00 (Referent)	38	1.00 (Referent)
premenopausal	10	0.40 (0.15, 1.08)	8	0.56 (0.15, 2.16)	2	0.18 (0.03, 1.01)	11	0.31 (0.12, 0.82)	9	0.47 (0.13, 1.76)	2	0.12 (0.02, 0.68)
BMI												
young adult BMI												
<17.5	9	1.00 (Referent)	3	1.00 (Referent)	6	1.00 (Referent)	9	1.00 (Referent)	3	1.00 (Referent)	6	1.00 (Referent)
17.5-25.7	48	0.84 (0.35, 2.03)	23	1.35 (0.33, 5.47)	25	0.61 (0.19, 1.97)	58	1.06 (0.45, 2.5)	27	1.66 (0.41, 6.62)	31	0.78 (0.25, 2.47)
≥25.7	9	1.16 (0.36, 3.75)	7	1.62 (0.32, 8.15)	2	0.93 (0.12, 7.33)	9	1.12 (0.35, 3.58)	7	1.52 (0.30, 7.59)	2	0.92 (0.12, 7.07)
recent BMI												
<25	27	1.00 (Referent)	7	1.00 (Referent)	20	1.00 (Referent)	33	1.00 (Referent)	9	1.00 (Referent)	24	1.00 (Referent)
25-30	17	0.80 (0.38, 1.68)	8	0.97 (0.29, 3.24)	9	0.76 (0.29, 2.01)	19	0.69 (0.34, 1.41)	9	0.80 (0.26, 2.50)	10	0.66 (0.26, 1.68)
≥30	24	0.79 (0.39, 1.61)	20	1.27 (0.45, 3.56)	4	0.42 (0.12, 1.39)	26	0.66 (0.34, 1.30)	21	0.96 (0.36, 2.55)	5	0.40 (0.13, 1.21)
Behavior, smoking history (packyear)												
Non-smoker	38	1.00 (Referent)	21	1.00 (Referent)	17	1.00 (Referent)	42	1.00 (Referent)	23	1.00 (Referent)	19	1.00 (Referent)
<5	8	0.59 (0.24, 1.44)	4	0.31 (0.09, 1.05)	4	1.53 (0.37, 6.36)	11	0.80 (0.35, 1.80)	5	0.33 (0.11, 1.04)	6	3.25 (0.81, 13.12)
5-10	5	0.60 (0.20, 1.80)	3	0.36 (0.09, 1.46)	2	1.20 (0.19, 7.42)	5	0.53 (0.18, 1.57)	3	0.29 (0.07, 1.19)	2	1.10 (0.18, 6.60)
≥10	17	0.86 (0.43, 1.71)	7	0.86 (0.30, 2.52)	10	0.92 (0.36, 2.32)	20	0.92 (0.47, 1.78)	8	0.89 (0.32, 2.54)	12	1.05 (0.44, 2.52)
Talc use												
ever regular use of talc												
no	27	1.00 (Referent)	10	1.00 (Referent)	17	1.00 (Referent)	33	1.00 (Referent)	12	1.00 (Referent)	21	1.00 (Referent)
yes	41	1.56 (0.87, 2.82)	25	1.86 (0.78, 4.46)	16	1.35 (0.59, 3.10)	45	1.41 (0.80, 2.46)	27	1.72 (0.75, 3.96)	18	1.17 (0.53, 2.55)
ever talc uses to genital area												
no	40	1.00 (Referent)	15	1.00 (Referent)	25	1.00 (Referent)	48	1.00 (Referent)	18	1.00 (Referent)	30	1.00 (Referent)
yes	29	1.68 (0.92, 3.09)	20	2.35 (1.03, 5.36)	9	1.08 (0.42, 2.75)	31	1.53 (0.85, 2.75)	21	2.07 (0.93, 4.60)	10	1.01 (0.41, 2.49)
Analgesic medication use												
aspirin												
no	48	1.00 (Referent)	26	1.00 (Referent)	22	1.00 (Referent)	56	1.00 (Referent)	29	1.00 (Referent)	27	1.00 (Referent)
yes	9	1.30 (0.53, 3.19)	5	1.50 (0.44, 5.12)	4	1.20 (0.32, 4.56)	9	1.00 (0.42, 2.43)	5	1.32 (0.39, 4.46)	4	0.81 (0.22, 2.98)
non-aspirin NSAIDs												
no	46	1.00 (Referent)	28	1.00 (Referent)	18	1.00 (Referent)	51	1.00 (Referent)	31	1.00 (Referent)	20	1.00 (Referent)
yes	21	0.68 (0.36, 1.30)	5	0.53 (0.18, 1.59)	16	0.90 (0.38, 2.13)	26	0.82 (0.45, 1.51)	6	0.59 (0.21, 1.65)	20	1.20 (0.54, 2.71)
acetaminophen												
no	46	1.00 (Referent)	29	1.00 (Referent)	17	1.00 (Referent)	53	1.00 (Referent)	32	1.00 (Referent)	21	1.00 (Referent)
yes	11	1.25 (0.55, 2.87)	2	0.49 (0.10, 2.48)	9	2.30 (0.78, 6.80)	12	1.12 (0.50, 2.50)	2	0.43 (0.09, 2.16)	10	2.06 (0.74, 5.80
Benign gyn conditions												
endometriosis												
no	58	1.00 (Referent)	28	1.00 (Referent)	30	1.00 (Referent)	67	1.00 (Referent)	31	1.00 (Referent)	36	1.00 (Referent)
yes	9	1.28 (0.54, 3.07)	5	2.17 (0.60, 7.86)	4	0.96 (0.28, 3.35)	10	1.23 (0.53, 2.86)	6	2.82 (0.78, 10.15)	4	0.72 (0.21, 2.47)
fibroids												
no	41	1.00 (Referent)	16	1.00 (Referent)	25	1.00 (Referent)	49	1.00 (Referent)	20	1.00 (Referent)	29	1.00 (Referent)
yes	28	2.17 (1.16, 4.07)	19	2.61 (1.13, 6.03)	9	1.76 (0.66, 4.71)	29	1.78 (0.97, 3.26)	19	1.87 (0.84, 4.15)	10	1.74 (0.67, 4.53)
Composite inflammation risk score, IRRS												
<median	39	1.00 (Referent)	15	1.00 (Referent)	24	1.00 (Referent)	44	1.00 (Referent)	18	1.00 (Referent)	26	1.00 (Referent)
≥median	30	0.65 (0.36, 1.18)	20	0.79 (0.35, 1.80)	10	0.53 (0.22, 1.30)	35	0.68 (0.39, 1.20)	21	0.62 (0.28, 1.39)	14	0.78 (0.34, 1.76)

OR: odds ratio, CI: confidence interval, CD: cell differentiation.

Total CD is the combination of CD in tumor and in stroma.

[a]≥1%N is the number of participants with the percent of CD3CD8 ≥1%.

[b]Estimated using a repeated measures framework where each inflammatory-related exposure is included in the models. Models are adjusted for age at diagnosis (years), stage (early, late), and race (Black, White).
[c]Estimated using a repeated measures framework where each inflammatory-related exposure is included in the models. Models are adjusted for age at diagnosis (years) and stage (early, late) in the race-stratified population respectively.

Table 5. Numbers of participants with abundant CD3FoxP3 in tumor and in total, and odds ratios and 95% confidence intervals for the association of inflammatory-related exposures and of CD3FoxP3 abundance in tumor and in total in the total study population overall and by race/ethnicity.

Inflammatory-related exposures	CD3+FoxP3+ in tumor						CD3+FoxP3+ in total					
	Overall		Black		White		Overall		Black		White	
	present N[a]	OR (95% CI)[b]	present N[a]	OR (95% CI)[c]	present N[a]	OR (95% CI)[c]	present N[a]	OR (95% CI)[b]	present N[a]	OR (95% CI)[c]	present N[a]	OR (95% CI)[c]
Menopausal status												
postmenopausal	163	1.00 (Referent)	79	1.00 (Referent)	84	1.00 (Referent)	169	1.00 (Referent)	83	1.00 (Referent)	86	1.00 (Referent)
premenopausal	37	0.69 (0.23, 2.07)	18	0.48 (0.11, 2.10)	19	1.20 (0.21, 7.03)	39	0.49 (0.15, 1.64)	20	0.40 (0.08, 2.10)	19	0.68 (0.11, 4.35)
BMI												
young adult BMI												
<17.5	22	1.00 (Referent)	9	1.00 (Referent)	13	1.00 (Referent)	24	1.00 (Referent)	11	1.00 (Referent)	13	1.00 (Referent)
17.5-25.7	150	1.42 (0.52, 3.88)	66	1.83 (0.49, 6.86)	84	1.13 (0.22, 5.79)	154	1.03 (0.33, 3.27)	69	0.97 (0.19, 4.96)	85	1.20 (0.23, 6.22)
≥25.7	23	2.18 (0.52, 9.22)	18	3.62 (0.62, 21.11)	5	0.80 (0.05, 11.93)	25	2.69 (0.43, 16.72)	19	2.27 (0.27, 19.46)	6	--[d]
recent BMI												
<25	75	1.00 (Referent)	21	1.00 (Referent)	54	1.00 (Referent)	78	1.00 (Referent)	23	1.00 (Referent)	55	1.00 (Referent)
25-30	50	0.62 (0.26, 1.48)	25	0.74 (0.20, 2.77)	25	0.53 (0.17, 1.67)	52	0.55 (0.21, 1.40)	27	0.63 (0.13, 3.00)	25	0.46 (0.14, 1.50)
≥30	73	0.96 (0.40, 2.27)	50	0.95 (0.29, 3.08)	23	1.26 (0.30, 5.24)	76	0.84 (0.32, 2.17)	52	0.64 (0.16, 2.57)	24	1.68 (0.32, 8.80)
Behavior, smoking history (packyear)												
Non-smoker	99	1.00 (Referent)	47	1.00 (Referent)	52	1.00 (Referent)	101	1.00 (Referent)	48	1.00 (Referent)	53	1.00 (Referent)
<5	30	1.01 (0.38, 2.69)	20	0.54 (0.17, 1.72)	10	--[e]	32	1.30 (0.43, 3.89)	22	0.79 (0.23, 2.79)	10	--[f]
5-10	17	0.82 (0.26, 2.56)	12	0.65 (0.17, 2.57)	5	0.97 (0.10, 9.61)	19	1.29 (0.34, 4.95)	14	1.40 (0.26, 7.65)	5	0.89 (0.09, 8.85)
≥10	52	1.21 (0.51, 2.86)	18	0.81 (0.22, 3.03)	34	1.47 (0.47, 4.63)	54	1.47 (0.58, 3.74)	19	1.05 (0.25, 4.49)	35	1.69 (0.49, 5.82)
Talc use												
ever regular use of talc												
no	92	1.00 (Referent)	37	1.00 (Referent)	55	1.00 (Referent)	98	1.00 (Referent)	41	1.00 (Referent)	57	1.00 (Referent)
yes	107	1.57 (0.79, 3.14)	60	1.32 (0.52, 3.36)	47	2.44 (0.79, 7.51)	109	1.21 (0.58, 2.55)	62	0.86 (0.30, 2.49)	47	2.00 (0.64, 6.31)
ever talc uses to genital area												
no	134	1.00 (Referent)	57	1.00 (Referent)	77	1.00 (Referent)	141	1.00 (Referent)	62	1.00 (Referent)	79	1.00 (Referent)
yes	66	1.25 (0.58, 2.66)	40	1.23 (0.47, 3.18)	26	1.48 (0.39, 5.65)	67	0.92 (0.41, 2.05)	41	0.80 (0.28, 2.25)	26	1.26 (0.33, 4.86)
Analgesic medication use												
aspirin												
no	139	1.00 (Referent)	70	1.00 (Referent)	69	1.00 (Referent)	145	1.00 (Referent)	75	1.00 (Referent)	70	1.00 (Referent)
yes	23	0.94 (0.32, 2.76)	14	3.48 (0.42, 28.84)	9	0.34 (0.08, 1.46)	23	0.74 (0.25, 2.21)	14	2.47 (0.29, 20.96)	9	0.31 (0.07, 1.36)
non-aspirin NSAIDs												
no	127	1.00 (Referent)	72	1.00 (Referent)	55	1.00 (Referent)	132	1.00 (Referent)	76	1.00 (Referent)	56	1.00 (Referent)
yes	68	0.78 (0.37, 1.63)	20	0.71 (0.24, 2.09)	48	0.67 (0.23, 1.92)	70	0.74 (0.34, 1.63)	21	0.66 (0.21, 2.09)	49	0.65 (0.21, 1.98)
acetaminophen												
no	134	1.00 (Referent)	77	1.00 (Referent)	57	1.00 (Referent)	138	1.00 (Referent)	80	1.00 (Referent)	58	1.00 (Referent)
yes	28	0.91 (0.33, 2.45)	7	0.23 (0.06, 0.88)	21	4.77 (0.57, 39.87)	30	1.31 (0.41, 4.14)	9	0.41 (0.09, 1.81)	21	4.23(0.50, 35.51)
Benign gyn conditions												
endometriosis												
no	177	1.00 (Referent)	86	1.00 (Referent)	91	1.00 (Referent)	185	1.00 (Referent)	92	1.00 (Referent)	93	1.00 (Referent)
yes	21	0.69 (0.26, 1.88)	9	1.16 (0.23, 5.90)	12	0.44 (0.12, 1.66)	21	0.51 (0.18, 1.40)	9	0.74 (0.14, 3.86)	12	0.35 (0.09, 1.34)
fibroids												
no	139	1.00 (Referent)	59	1.00 (Referent)	80	1.00 (Referent)	144	1.00 (Referent)	63	1.00 (Referent)	81	1.00 (Referent)
yes	58	0.93 (0.43, 1.99)	38	0.69 (0.27, 1.74)	20	1.68 (0.34, 8.15)	61	0.98 (0.42, 2.26)	40	0.59 (0.21, 1.66)	21	3.34 (0.41, 27.40)
Composite inflammation risk score, IRRS												
<median	102	1.00 (Referent)	41	1.00 (Referent)	61	1.00 (Referent)	105	1.00 (Referent)	43	1.00 (Referent)	62	1.00 (Referent)
≥median	98	0.91 (0.45, 1.84)	56	0.77 (0.30, 2.02)	42	1.05 (0.35, 3.09)	103	0.93 (0.43, 1.99)	60	0.77 (0.26, 2.27)	43	1.07 (0.34, 3.34)

OR: odds ratio, CI: confidence interval, CD: cell differentiation.

Total CD is the combination of CD in tumor and in stroma.

[a]≥1%N is the number of participants with the percent of CD3FoxP3 ≥1%.

[b]Estimated using a repeated measures framework where each inflammatory-related exposure is included in the models. Models are adjusted for age at diagnosis (years), stage (early, late), and race (Black, White).
[c]Estimated using a repeated measures framework where each inflammatory-related exposure is included in the models. Models are adjusted for age at diagnosis (years) and stage (early, late) in the race-stratified population respectively.
[d]Failing to converge due to that no total CD3FoxP3 absence for patients with BMI ≥25.7 in White population.
[e]Failing to converge due to that no CD3FoxP3 absence in tumor for patients with 0-5 packyears smoking history in White population.
[f]Failing to converge due to that no total CD3FoxP3 absence for patients with 0-5 packyears smoking history in White population.

Table 6. Numbers of participants with abundant CD11b in tumor and in total, and odds ratios and 95% confidence intervals for the association of inflammatory-related exposures and of CD11b abundance in tumor and in total in the total study population overall and by race/ethnicity.

Inflammatory-related exposures	CD11b+ in tumor						CD11b+ in total					
	Overall		Black		White		Overall		Black		White	
	present N[a]	OR (95% CI)[b]	present N[a]	OR (95% CI)[c]	present N[a]	OR (95% CI)[c]	present N[a]	OR (95% CI)[b]	present N[a]	OR (95% CI)[c]	present N[a]	OR (95% CI)[c]
Menopausl status												
postmenopausal	151	1.00 (Referent)	74	1.00 (Referent)	77	1.00 (Referent)	162	1.00 (Referent)	79	1.00 (Referent)	83	1.00 (Referent)
premenopausal	36	0.56 (0.20, 1.58)	20	0.46 (0.10, 2.12)	16	0.69 (0.16, 2.86)	39	0.38 (0.12, 1.25)	21	0.30 (0.05, 1.66)	18	0.50 (0.09, 2.70)
BMI												
young adult BMI												
<17.5	22	1.00 (Referent)	11	1.00 (Referent)	11	1.00 (Referent)	25	1.00 (Referent)	12	1.00 (Referent)	13	1.00 (Referent)
17.5-25.7	140	1.04 (0.39, 2.79)	62	0.59 (0.12, 3.05)	78	1.48 (0.42, 5.25)	151	0.68 (0.19, 2.43)	67	0.38 (0.04, 3.31)	84	0.96 (0.19, 4.86)
≥25.7	21	1.03 (0.28, 3.89)	18	1.25 (0.17, 9.24)	3	0.36 (0.05, 2.68)	21	0.44 (0.09, 2.06)	18	0.56 (0.05, 6.40)	3	0.12 (0.01, 1.18)
recent BMI												
<25	71	1.00 (Referent)	20	1.00 (Referent)	51	1.00 (Referent)	76	1.00 (Referent)	21	1.00 (Referent)	55	1.00 (Referent)
25-30	47	0.65 (0.29, 1.43)	26	1.36 (0.37, 5.06)	21	0.40 (0.15, 1.08)	53	0.78 (0.31, 1.95)	28	1.78 (0.41, 7.78)	25	0.47 (0.15, 1.52)
≥30	68	0.76 (0.35, 1.65)	48	0.94 (0.31, 2.89)	20	0.74 (0.24, 2.28)	71	0.62 (0.26, 1.48)	51	1.00 (0.30, 3.36)	20	0.43 (0.13, 1.46)
Behavior, smoking history (packyear)												
Non-smoker	90	1.00 (Referent)	42	1.00 (Referent)	48	1.00 (Referent)	98	1.00 (Referent)	46	1.00 (Referent)	52	1.00 (Referent)
<5	27	0.93 (0.39, 2.22)	20	1.27 (0.43, 3.79)	7	0.74 (0.17, 3.28)	30	1.07 (0.40, 2.87)	21	1.03 (0.32, 3.33)	9	1.96 (0.22, 17.29)
5-10	19	2.16 (0.58, 8.03)	13	1.67 (0.39, 7.10)	6	--[d]	20	2.39 (0.50, 11.34)	14	1.78 (0.33, 9.58)	6	--[e]
≥10	51	1.75 (0.78, 3.90)	19	2.69 (0.67, 10.89)	32	1.54 (0.57, 4.17)	53	1.51 (0.62, 3.66)	19	1.75 (0.42, 7.38)	34	1.54 (0.50, 4.80)
Talc use												
ever regular use of talc												
no	85	1.00 (Referent)	38	1.00 (Referent)	47	1.00 (Referent)	94	1.00 (Referent)	40	1.00 (Referent)	54	1.00 (Referent)
yes	101	1.49 (0.80, 2.78)	56	0.69 (0.28, 1.71)	45	2.95 (1.13, 7.68)	106	1.29 (0.64, 2.57)	60	0.72 (0.26, 1.94)	46	2.13 (0.75, 6.09)
ever talc uses to genital area												
no	125	1.00 (Referent)	55	1.00 (Referent)	70	1.00 (Referent)	135	1.00 (Referent)	58	1.00 (Referent)	77	1.00 (Referent)
yes	62	1.06 (0.54, 2.09)	39	0.92 (0.37, 2.32)	23	1.17 (0.42, 3.25)	66	1.01 (0.47, 2.17)	42	1.08 (0.39, 3.03)	24	0.88 (0.29, 2.72)
Analgesic medication use												
aspirin												
no	131	1.00 (Referent)	70	1.00 (Referent)	61	1.00 (Referent)	138	1.00 (Referent)	73	1.00 (Referent)	65	1.00 (Referent)
yes	23	1.56 (0.53, 4.55)	14	5.62 (0.64, 49.41)	9	0.71 (0.19, 2.62)	24	1.62 (0.50, 5.23)	15	--[f]	9	0.54 (0.14, 2.07)
non-aspirin NSAIDs												
no	115	1.00 (Referent)	68	1.00 (Referent)	47	1.00 (Referent)	128	1.00 (Referent)	74	1.00 (Referent)	54	1.00 (Referent)
yes	67	1.29 (0.65, 2.56)	21	1.35 (0.44, 4.20)	46	1.51 (0.61, 3.71)	68	0.74 (0.35, 1.56)	21	0.86 (0.27, 2.77)	47	0.73 (0.26, 2.00)
acetaminophen												
no	124	1.00 (Referent)	73	1.00 (Referent)	51	1.00 (Referent)	130	1.00 (Referent)	76	1.00 (Referent)	54	1.00 (Referent)
yes	30	2.57 (0.84, 7.91)	11	3.88 (0.45, 33.39)	19	2.31 (0.61, 8.75)	32	4.52 (1.01, 20.27)	12	--[g]	20	2.87 (0.60, 13.78)
Benign gyn conditions												
endometriosis												
no	165	1.00 (Referent)	85	1.00 (Referent)	80	1.00 (Referent)	177	1.00 (Referent)	90	1.00 (Referent)	87	1.00 (Referent)
yes	21	0.97 (0.36, 2.59)	8	0.53 (0.12, 2.41)	13	1.40 (0.36, 5.44)	23	1.06 (0.34, 3.34)	9	0.66 (0.12, 3.68)	14	1.37 (0.28, 6.75)
fibroids												
no	129	1.00 (Referent)	58	1.00 (Referent)	71	1.00 (Referent)	140	1.00 (Referent)	62	1.00 (Referent)	78	1.00 (Referent)
yes	54	0.92 (0.46, 1.82)	36	0.73 (0.30, 1.79)	18	1.44 (0.44, 4.72)	57	0.79 (0.37, 1.69)	38	0.61 (0.23, 1.63)	19	1.32 (0.35, 5.06)
Composite inflammation risk score, IRRS												
<median	91	1.00 (Referent)	36	1.00 (Referent)	55	1.00 (Referent)	100	1.00 (Referent)	39	1.00 (Referent)	61	1.00 (Referent)
≥median	96	1.25 (0.66, 2.36)	58	1.49 (0.60, 3.67)	38	1.09 (0.44, 2.67)	101	1.00 (0.49, 2.04)	61	1.40 (0.52, 3.77)	40	0.71 (0.26, 1.96)

OR: odds ratio, CI: confidence interval, CD: cell differentiation.

Total CD is the combination of CD in tumor and in stroma.

[a]≥1%N is the number of participants with the percent of CD11b ≥1%.

[b]Estimated using a repeated measures framework where each inflammatory-related exposure is included in the models. Models are adjusted for age at diagnosis (years), stage (early, late), and race (Black, White).
[c]Estimated using a repeated measures framework where each inflammatory-related exposure is included in the models. Models are adjusted for age at diagnosis (years) and stage (early, late) in the race-stratified population respectively.
[d]Failing to converge due to that no CD11b absence in tumor for patients with 5-10 packyears smoking history in White population.
[e]Failing to converge due to that no total CD11b absence for patients with 5-10 packyears smoking history in White population.
[f]Failing to converge due to that no total CD11b absence for participants using aspirin in Black population.
[g]Failing to converge due to that no total CD11b absence for participants using acetaminophen in Black population.

Table 7. Numbers of participants with abundant CD11bCD15 in tumor and in total, and odds ratios and 95% confidence intervals for the association of inflammatory-related exposures and of CD11bCD15 abundance in tumor and in total in the total study population overall and by race/ethnicity.

Inflammatory-related exposures	CD11b+CD15+ in tumor						CD11b+CD15+ in total					
	Overall		Black		White		Overall		Black		White	
	present N[a]	OR (95% CI)[b]	present N[a]	OR (95% CI)[c]	prese N[a]	OR (95% CI)[c]	present N[a]	OR (95% CI)[b]	present N[a]	OR (95% CI)[c]	present N[a]	OR (95% CI)[c]
Menopausal status												
postmenopausal	54	1.00 (Referent)	28	1.00 (Referent)	26	1.00 (Referent)	64	1.00 (Referent)	32	1.00 (Referent)	32	1.00 (Referent)
premenopausal	11	0.75 (0.28, 2.04)	9	0.79 (0.21, 2.96)	2	0.49 (0.08, 3.02)	12	0.62 (0.24, 1.62)	9	0.63 (0.17, 2.29)	3	0.50 (0.10, 2.43)
BMI												
young adult BMI												
<17.5	10	1.00 (Referent)	7	1.00 (Referent)	3	1.00 (Referent)	11	1.00 (Referent)	8	1.00 (Referent)	3	1.00 (Referent)
17.5-25.7	48	0.67 (0.29, 1.58)	25	0.38 (0.11, 1.30)	23	1.13 (0.28, 4.61)	58	0.75 (0.33, 1.72)	28	0.33 (0.09, 1.13)	30	1.63 (0.41, 6.47)
≥25.7	6	0.46 (0.14, 1.59)	5	0.24 (0.05, 1.13)	1	1.13 (0.09, 14.80)	6	0.41 (0.12, 1.39)	5	0.17 (0.04, 0.84)	1	1.06 (0.08, 13.58)
recent BMI												
<25	28	1.00 (Referent)	10	1.00 (Referent)	18	1.00 (Referent)	33	1.00 (Referent)	10	1.00 (Referent)	23	1.00 (Referent)
25-30	13	0.46 (0.21, 1.02)	7	0.47 (0.14, 1.51)	6	0.46 (0.16, 1.37)	17	0.53 (0.26, 1.09)	10	0.76 (0.25, 2.30)	7	0.39 (0.14, 1.09)
≥30	24	0.64 (0.32, 1.30)	20	0.73 (0.27, 1.92)	4	0.42 (0.12, 1.44)	26	0.59 (0.30, 1.17)	21	0.78 (0.30, 2.05)	5	0.37 (0.12, 1.16)
Behavior, smoking history (packyear)												
Non-smoker	36	1.00 (Referent)	18	1.00 (Referent)	18	1.00 (Referent)	40	1.00 (Referent)	20	1.00 (Referent)	20	1.00 (Referent)
<5	9	0.68 (0.29, 1.61)	6	0.70 (0.23, 2.09)	3	1.28 (0.28, 5.80)	11	0.80 (0.35, 1.80)	8	0.88 (0.32, 2.45)	3	1.10 (0.25, 4.93)
5-10	5	0.63 (0.21, 1.88)	4	0.70 (0.19, 2.56)	1	0.52 (0.05, 5.09)	6	0.72 (0.26, 2.02)	4	0.61 (0.17, 2.19)	2	1.20 (0.19, 7.64)
≥10	15	0.80 (0.39, 1.62)	9	1.71 (0.60, 4.90)	6	0.51 (0.18, 1.45)	19	0.93 (0.48, 1.82)	9	1.43 (0.51, 4.05)	10	0.84 (0.33, 2.09)
Talc use												
ever regular use of talc												
no	26	1.00 (Referent)	14	1.00 (Referent)	12	1.00 (Referent)	32	1.00 (Referent)	17	1.00 (Referent)	15	1.00 (Referent)
yes	39	1.46 (0.81, 2.64)	23	0.99 (0.43, 2.26)	16	1.91 (0.79, 4.59)	44	1.36 (0.78, 2.38)	24	0.78 (0.35, 1.73)	20	2.05 (0.90, 4.65)
ever talc uses to genital area												
no	43	1.00 (Referent)	22	1.00 (Referent)	21	1.00 (Referent)	52	1.00 (Referent)	25	1.00 (Referent)	27	1.00 (Referent)
yes	22	1.01 (0.54, 1.88)	15	0.82 (0.36, 1.89)	7	1.16 (0.42, 3.19)	24	0.90 (0.49, 1.64)	16	0.75 (0.33, 1.69)	8	0.98 (0.38, 2.56)
Analgesic medication use												
aspirin												
no	45	1.00 (Referent)	26	1.00 (Referent)	19	1.00 (Referent)	54	1.00 (Referent)	30	1.00 (Referent)	24	1.00 (Referent)
yes	10	1.59 (0.67, 3.80)	7	3.02 (0.90, 10.08)	3	0.75 (0.18, 3.15)	10	1.19 (0.50, 2.80)	7	2.25 (0.69, 7.28)	3	0.54 (0.13, 2.25)
non-aspirin NSAIDs												
no	46	1.00 (Referent)	28	1.00 (Referent)	18	1.00 (Referent)	54	1.00 (Referent)	32	1.00 (Referent)	22	1.00 (Referent)
yes	16	0.58 (0.30, 1.13)	6	0.69 (0.24, 1.93)	10	0.70 (0.28, 1.78)	19	0.55 (0.29, 1.04)	6	0.55 (0.20, 1.53)	13	0.72 (0.31, 1.68)
acetaminophen												
no	50	1.00 (Referent)	32	1.00 (Referent)	18	1.00 (Referent)	57	1.00 (Referent)	35	1.00 (Referent)	22	1.00 (Referent)
yes	5	0.41 (0.15, 1.14)	1	0.19 (0.02, 1.60)	4	0.68 (0.20, 2.32)	7	0.50 (0.20, 1.23)	2	0.37 (0.07, 1.81)	5	0.67 (0.22, 2.10)
Benign gyn conditions												
endometriosis												
no	59	1.00 (Referent)	32	1.00 (Referent)	27	1.00 (Referent)	66	1.00 (Referent)	35	1.00 (Referent)	31	1.00 (Referent)
yes	6	0.78 (0.30, 2.07)	5	1.74 (0.48, 6.33)	1	0.23 (0.03, 1.86)	9	1.17 (0.50, 2.77)	5	1.56 (0.43, 5.60)	4	0.96 (0.28, 3.35)
fibroids												
no	48	1.00 (Referent)	26	1.00 (Referent)	22	1.00 (Referent)	53	1.00 (Referent)	27	1.00 (Referent)	26	1.00 (Referent)
yes	16	0.62 (0.32, 1.23)	11	0.55 (0.24, 1.28)	5	0.91 (0.30, 2.82)	21	0.82 (0.44, 1.53)	14	0.72 (0.32, 1.59)	7	1.17 (0.42, 3.27)
Composite inflammation risk score, IRRS												
<median	38	1.00 (Referent)	17	1.00 (Referent)	21	1.00 (Referent)	45	1.00 (Referent)	19	1.00 (Referent)	26	1.00 (Referent)
≥median	27	0.57 (0.31, 1.05)	20	0.65 (0.29, 1.47)	7	0.49 (0.18, 1.31)	31	0.55 (0.31, 0.98)	22	0.64 (0.29, 1.41)	9	0.47 (0.19, 1.15)

OR: odds ratio, CI: confidence interval, CD: cell differentiation.

Total CD is the combination of CD in tumor and in stroma.

[a]≥1%N is the number of participants with the percent of CD11bCD15 ≥1%.

[b]Estimated using a repeated measures framework where each inflammatory-related exposure is included in the models. Models are adjusted for age at diagnosis (years), stage (early, late), and race (Black, White).
[c]Estimated using a repeated measures framework where each inflammatory-related exposure is included in the models. Models are adjusted for age at diagnosis (years) and stage (early, late) in the race-stratified population respectively.

Table 8. Numbers of participants with intermediate and high immunoscore in tumor and in total, and odds ratios and 95% confidence intervals for the association of inflammatory-related exposures and the immunoscore in total population and by race/ethnicity.

Inflammatory-related exposures	Overall				Black				White			
	N[a]		OR (95%)[b]		N[a]		OR (95%)[c]		N[a]		OR (95%)[c]	
	Intermediate	High	Intermediate	High	Intermediate	High	Intermediate	High	Intermediate	High	Intermediate	High
Menopausal status												
postmenopausal	95	46	1.00 (Referent)	1.00 (Referent)	46	20	1.00 (Referent)	1.00 (Referent)	49	26	1.00 (Referent)	1.00 (Referent)
premenopausal	31	4	0.60 (0.21, 1.68)	0.15 (0.03, 0.66)	16	4	0.72 (0.17, 3.08)	0.24 (0.04, 1.56)	15	0	0.52 (0.12, 2.2)	--[d]
BMI												
young adult BMI												
<17.5	13	5	1.00 (Referent)	1.00 (Referent)	7	1	1.00 (Referent)	1.00 (Referent)	6	4	1.00 (Referent)	1.00 (Referent)
17.5-25.7	91	38	1.39 (0.56, 3.45)	1.57 (0.49, 5.05)	39	17	1.11 (0.32, 3.92)	3.42 (0.36, 32.04)	52	21	1.72 (0.47, 6.32)	1.14 (0.26, 5.01)
≥25.7	20	5	7.88 (1.44, 43.10)	5.83 (0.79, 42.88)	14	5	4.71 (0.71, 31.19)	11.97 (0.79, 181.31)	6	0	--[e]	--[e]
recent BMI												
<25	41	22	1.00 (Referent)	1.00 (Referent)	10	6	1.00 (Referent)	1.00 (Referent)	31	16	1.00 (Referent)	1.00 (Referent)
25-30	37	11	1.63 (0.73, 3.67)	0.81 (0.30, 2.18)	21	4	3.32 (0.95, 11.55)	1.04 (0.21, 5.19)	16	7	0.96 (0.33, 2.82)	0.68 (0.19, 2.40)
≥30	47	17	1.37 (0.64, 2.94)	0.89 (0.36, 2.23)	31	14	2.11 (0.71, 6.21)	1.57 (0.45, 5.50)	16	3	1.01 (0.34, 3.03)	0.37 (0.08, 1.76)
Behavior, smoking history (packyear)												
Non-smoker	63	22	1.00 (Referent)	1.00 (Referent)	36	10	1.00 (Referent)	1.00 (Referent)	27	12	1.00 (Referent)	1.00 (Referent)
<5	18	10	1.00 (0.40, 2.54)	1.67 (0.57, 4.88)	3	6	1.07 (0.36, 3.19)	0.65 (0.15, 2.77)	15	4	1.40 (0.13, 14.76)	10.83 (1.09, 107.84)
5-10	9	5	0.52 (0.18, 1.53)	0.93 (0.26, 3.28)	2	2	0.58 (0.16, 2.12)	0.57 (0.11, 2.83)	7	3	0.46 (0.06, 3.61)	1.70 (0.20, 14.58)
≥10	35	12	1.23 (0.57, 2.63)	1.19 (0.46, 3.06)	22	7	1.95 (0.53, 7.18)	1.70 (0.36, 7.95)	13	5	0.97 (0.37, 2.53)	1.21 (0.34, 4.27)
Talc use												
ever regular use of talc												
no	64	19	1.00 (Referent)	1.00 (Referent)	26	8	1.00 (Referent)	1.00 (Referent)	38	11	1.00 (Referent)	1.00 (Referent)
yes	62	30	1.03 (0.55, 1.92)	1.63 (0.75, 3.54)	36	16	1.02 (0.43, 2.46)	1.47 (0.48, 4.50)	26	14	1.00 (0.41, 2.46)	1.72 (0.58, 5.12)
ever talc uses to genital area												
no	88	31	1.00 (Referent)	1.00 (Referent)	36	13	1.00 (Referent)	1.00 (Referent)	52	18	1.00 (Referent)	1.00 (Referent)
yes	38	19	0.85 (0.44, 1.67)	1.25 (0.56, 2.79)	26	11	1.21 (0.50, 2.96)	1.39 (0.46, 4.18)	12	8	0.52 (0.19, 1.44)	1.00 (0.31, 3.22)
Analgesic medication use												
aspirin												
no	89	34	1.00 (Referent)	1.00 (Referent)	47	16	1.00 (Referent)	1.00 (Referent)	42	18	1.00 (Referent)	1.00 (Referent)
yes	14	4	0.88 (0.34, 2.27)	0.59 (0.16, 2.13)	8	2	1.41 (0.36, 5.53)	1.08 (0.16, 7.04)	6	2	0.55 (0.14, 2.10)	0.35 (0.06, 2.15)
non-aspirin NSAIDs												
no	76	31	1.00 (Referent)	1.00 (Referent)	43	17	1.00 (Referent)	1.00 (Referent)	33	14	1.00 (Referent)	1.00 (Referent)
yes	46	17	1.42 (0.71, 2.83)	1.25 (0.54, 2.88)	15	5	1.78 (0.60, 5.27)	1.50 (0.39, 5.85)	31	12	1.32 (0.51, 3.39)	1.51 (0.48, 4.79)
acetaminophen												
no	86	28	1.00 (Referent)	1.00 (Referent)	50	16	1.00 (Referent)	1.00 (Referent)	36	12	1.00 (Referent)	1.00 (Referent)
yes	17	10	1.30 (0.49, 3.44)	2.23 (0.75, 6.65)	5	2	0.55 (0.14, 2.14)	0.74 (0.12, 4.46)	12	8	3.39 (0.69,16.78)	7.34 (1.31, 41.05)
Benign gyn conditions												
endometriosis												
no	115	42	1.00 (Referent)	1.00 (Referent)	59	18	1.00 (Referent)	1.00 (Referent)	56	24	1.00 (Referent)	1.00 (Referent)
yes	10	7	0.40 (0.15, 1.04)	0.85 (0.29, 2.45)	2	5	0.23 (0.04, 1.36)	1.98 (0.46, 8.59)	8	2	0.48 (0.15, 1.59)	0.37 (0.07, 2.08)
fibroids												
no	93	30	1.00 (Referent)	1.00 (Referent)	42	11	1.00 (Referent)	1.00 (Referent)	51	19	1.00 (Referent)	1.00 (Referent)
yes	30	20	0.70 (0.35, 1.41)	1.49 (0.66, 3.34)	20	13	0.59 (0.25, 1.43)	1.52 (0.52, 4.44)	10	7	0.97 (0.29, 3.20)	1.63 (0.44, 6.05)
Composite inflammation risk score, IRRS												
<median	54	32	1.00 (Referent)	1.00 (Referent)	18	14	1.00 (Referent)	1.00 (Referent)	36	18	1.00 (Referent)	1.00 (Referent)
≥median	72	18	1.38 (0.73, 2.61)	0.61 (0.27, 1.35)	44	10	1.90 (0.78, 4.64)	0.53 (0.18, 1.58)	28	8	1.00 (0.40, 2.51)	0.73 (0.23, 2.30)

OR: odds ratio, which is estimated by polytomous logistic regression with low immunoscore as the reference group.

[a]N is the number of participants under each inflammatory-related exposure category with intermediate or high immunoscore respectively.

[b]Estimated using a repeated measures framework where each inflammatory-related exposure is included in the models. Models are adjusted for age at diagnosis (years), stage (early, late), and race (Black, White).

[c]Estimated using a repeated measures framework where each inflammatory-related exposure is included in the models. Models are adjusted for age at diagnosis (years) and stage (early, late) in the race-stratified population respectively.
[d]Failing to converge due to that no high immunoscore for premenopausal patients in the White population.
[e]Failing to converge due to that no low immunoscore or high immunoscore for patients with BMI≥25.7 in the White population.