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ARTICLE

Association of inflammation-related exposures and ovarian cancer survival in a multi-site cohort study of Black women

Courtney E. Johnson[1], Anthony J. Alberg[2], Elisa V. Bandera[3], Lauren C. Peres[4], Maxwell Akonde[2], Lindsay J. Collin[5], Michele L. Cote[6], Theresa A. Hastert[7], James R. Hébert[2], Edward S. Peters[8], Bonnie Qin[3], Paul Terry[9], Ann G. Schwartz[10], Melissa Bondy[11], Michael P. Epstein[12], Hannah B. Mandle[1], Jeffrey R. Marks[13], Andrew B. Lawson[14,15] and Joellen M. Schildkraut[1]✉

BACKGROUND: An association was observed between an inflammation-related risk score (IRRS) and worse overall survival (OS) among a cohort of mostly White women with invasive epithelial ovarian cancer (EOC). Herein, we evaluated the association between the IRRS and OS among Black women with EOC, a population with higher frequencies of pro-inflammatory exposures and worse survival.

METHODS: The analysis included 592 Black women diagnosed with EOC from the African American Cancer Epidemiology Study (AACES). Cox proportional hazards models were used to compute hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of the IRRS and OS, adjusting for relevant covariates. Additional inflammation-related exposures, including the energy-adjusted Dietary Inflammatory Index (E-DII^{TM}), were evaluated.

RESULTS: A dose–response trend was observed showing higher IRRS was associated with worse OS (per quartile HR: 1.11, 95% CI: 1.01–1.22). Adding the E-DII to the model attenuated the association of IRRS with OS, and increasing E-DII, indicating a more pro-inflammatory diet, was associated with shorter OS (per quartile HR: 1.12, 95% CI: 1.02–1.24). Scoring high on both indices was associated with shorter OS (HR: 1.54, 95% CI: 1.16–2.06).

CONCLUSION: Higher levels of inflammation-related exposures were associated with decreased EOC OS among Black women.

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BACKGROUND

Invasive epithelial ovarian cancer (EOC) is the most lethal gynaecologic cancer, with a five-year cause specific survival of 47% [1]. Although incidence of EOC is lower in Black women compared with White women (9.8 cases/100,000 compared to 13/100,000 respectively), Black women with EOC have worse 5-year survival compared with White women [2] (41% vs 48%, respectively) [3] across cancer stage and histologic subtypes [1]. It has been reported that Black women are less likely to receive appropriate treatment [4–7], and the age- and stage-adjusted hazard ratio (HR) for ovarian cancer mortality is higher in Black women compared with White women (HR = 1.41) [8].

Chronic inflammation, involving an immune response, likely influences ovarian carcinogenesis [9]. Some have proposed that the response to inflammation-related exposures may affect the immune landscape of the tumour [10, 11]. In support of the importance of the potential effects of inflammation on poor cancer survival, it has been shown that there are differences in the immune response between racial and ethnic groups that could result from nutritional and environmental influences as well as from having a genetic autoimmune component [12]. Black women have a higher prevalence of some pro-inflammatory-related exposures, such as use of body powder and a higher body mass index (BMI) [12], and we posit that these exposures may be drivers contributing to poor survival among Black women with EOC. However, some inflammation-related factors women are commonly exposed to are anti-inflammatory, such as menopausal hormonal therapy (MHT), which has been reported to be inversely related to survival [13].

Brieger et al. [14] developed a weighted inflammation-related risk score (IRRS) using 12 inflammation-related exposures and evaluated associations with EOC survival in an analysis of over 8000 women from 11 studies participating in the Ovarian Cancer Association Consortium (OCAC). In this report, a higher pre-

[1]Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, GA, USA. [2]Department of Epidemiology and Biostatistics, University of South Carolina Arnold School of Public Health, Columbia, SC, USA. [3]Cancer and Epidemiology and Health Outcomes, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA. [4]Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA. [5]Department of Population Health Sciences, University of Utah Huntsman Cancer Institute, Salt Lake City, UT, USA. [6]Melvin and Bren Simon Comprehensive Cancer Center, Indiana University, Bloomington, IN, USA. [7]Department of Oncology, Wayne State University School of Medicine, Detroit, MI, USA. [8]Department of Epidemiology, University of Nebraska Medical Center College of Public Health, Omaha, NE, USA. [9]Department of Medicine, University of Tennessee Medical Center-Knoxville, Knoxville, TN, USA. [10]Department of Oncology, Wayne State University School of Medicine Karmanos Cancer Institute, Detroit, MI, USA. [11]Department of Epidemiology and Population Health, Stanford University School of Medicine, Stanford, CA, USA. [12]Department of Human Genetics, Emory University School of Medicine, Atlanta, GA, USA. [13]Department of Surgery, Duke University School of Medicine, Durham, NC, USA. [14]Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC, USA. [15]Usher Institute, School of Medicine, University of Edinburgh, Edinburgh, Scotland.
✉email: joellen.m.schildkraut@emory.edu

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diagnostic IRRS was associated with a higher risk of mortality after an EOC diagnosis. However, fewer than 3% of the women included in the analysis were Black, a vulnerable population given their generally higher inflammatory profile [12] and worse EOC survival [8].

Here we calculate the IRRS among self-identified Black women with EOC enrolled in the African American Cancer Epidemiology Study (AACES), the largest cohort of Black women diagnosed with EOC [15], to see if the IRRS predicts survival in this population. To expand our exploration of the relationship between inflammation-related exposures and survival in the AACES, we also evaluate other inflammation-related exposures, including an inflammation-related dietary index and the number of lifetime ovulatory cycles, previously shown to be associated with EOC risk and/or survival in Black women [10, 16–18], for potential confounding and possible interaction with the IRRS. We aim to learn if the IRRS, developed by Brieger [14], is generalisable to Black women with EOC.

METHODS

Study population

The AACES, a cohort of newly diagnosed EOC, has been described in detail elsewhere [15]. In brief, AACES is the largest population-based study of EOC in Black women. Here we included 592 participants with EOC who were diagnosed between 2010 and 2015 and were residents of one of 11 geographic locations (described below) in the United States. Using rapid-case ascertainment, we identified women eligible to participate in AACES who were newly diagnosed with EOC, who self-identified as Black or African American and were diagnosed between the ages of 20 and 79 years.

Measures

Eligible women were contacted by trained interviewers who conducted a baseline telephone survey that included confirmed and suspected risk factors for EOC [15]. Diet was self-assessed using the Block 2005 food frequency questionnaire (FFQ) [19]. If requested, the interviewers assisted the participant in its completion.

Vital status was ascertained using databases such as the National Death Index (NDI) and LexisNexis. Follow-up time was measured as the number of years of overall survival (OS) from the date of diagnosis to the date of death or last contact as of March 2022 for Detroit, and October 2022 for all other locations.

The IRRS, a sum of weights for 12 pre-diagnostic measures thought to be either pro- or anti-inflammatory, was developed from an analysis performed within a training subset of women in the Ovarian Cancer Association Consortium (OCAC) by fitting a Cox proportional hazards (PH) model of these measures, while controlling for a priori clinical factors and study features [14]. The coefficients for each inflammatory variable were then used as weights, and these weights derived in the Brieger study were applied to the participants in AACES. An individual's IRRS was defined as the sum of the weights multiplied by each participant's exposure level. A higher IRRS can be interpreted as having higher levels of inflammation, and a lower IRRS as lower levels of inflammation. Because the weights were specific to the way each variable was defined in the Brieger study, we were unable to include alcohol use in the calculation of the IRRS in AACES. The FFQ used in AACES does not collect information on timing of alcohol use as defined in the IRRS by Brieger (current, former, never), and thus we did not apply the alcohol recency weights in our study. Within AACES, the only similar categorisation was a binary "any vs no" consumption of alcohol in the year prior to diagnosis. Notably, based on the Brieger weights, the only detectable effect of alcohol use was within the former use category (HR = 1.11), and not the current use category (HR = 1.00).

We incorporated 11 of the 12 pre-diagnostic factors that comprised the IRRS: regular aspirin use (yes, no), regular other nonsteroidal anti-inflammatory drug (NSAID) use (yes, no), body mass index in the year before diagnosis (BMI) (kg/m^2, continuous), secondhand smoke exposure in the home as an adult (yes, no), history of pelvic inflammatory disease (PID) (yes, no), history of polycystic ovary syndrome (PCOS) (yes, no), history of endometriosis (yes, no), MHT use (never, <5 years, 5+ years), physical inactivity in the year before diagnosis as defined by the 2008 Physical Activity Guidelines for Americans (PAGA) (<75 weekly minutes of strenuous physical activity, <150 weekly minutes of moderate activity, or an equivalent combination of the two [20]; yes, no), smoking status (never, former, current), and regular talc use (never, use on non-genital areas, use on genital areas).

Additional variables considered in the analysis as potential inflammation-related exposures or confounders included alcohol consumption in the year before diagnosis (any vs none), lifetime ovulatory cycles in months (LOC) [16], summarised into quartiles, annual household income (<$10,000, $10,000– < $50,000, $50,000+), and a validated energy-adjusted dietary inflammatory index (E-DII) based on food and supplements [21, 22]. In previous analyses conducted within AACES, the E-DII including supplements showed a stronger association with all-cause mortality than the E-DII excluding supplements, and thus was the form of the E-DII selected in this analysis [17]. For this study, the components of the E-DII included each participant's recorded intake of carbohydrates, protein, fat, alcohol, fibre, cholesterol, saturated, monounsaturated and polyunsaturated fatty acids, omega3 and omega6 polyunsaturated fatty acids, trans-fat, niacin, vitamins A, B1, B2, B6, B12, C, D, and E, iron, magnesium, zinc, selenium, folic acid, beta carotene, and isoflavones as calculated from the Block FFQ. LOC were previously found to be related to an increased risk of EOC within AACES [16], and the E-DII was previously found to be related to an increased risk of ovarian cancer and of all-cause mortality among women with EOC in AACES [17, 18].

Other variables included in the model as adjustment or stratification variables were histotype (high-grade serous, all other histotypes), debulking status after cytoreductive surgery (optimal: <1 cm residual tumour diameter or post-treatment levels of CA125 < 35 units/mL, suboptimal: ≥1 cm residual tumour or CA125 ≥ 35 units/mL or no surgery performed), residential location (North: Illinois, Detroit, Ohio, New Jersey; Southeast: Georgia, North Carolina, South Carolina, Tennessee; Southwest: Texas, Alabama, Louisiana), International Federation of Gynecology and Obstetrics (FIGO) stage (early: I/II, late: III/IV), age at diagnosis (continuous), highest education level achieved (less than high school, high school graduate or GED, some college, college graduate), and menopausal status (pre, post).

Statistical analysis

Descriptive statistics were generated for all components of the IRRS and additional covariates. The IRRS, the E-DII, and LOC were divided into quartiles for the primary analyses; as described below the categories were dichotomised into low (bottom two quartiles) vs high (upper two quartiles) to assess the potential interaction between IRRS and the E-DII. Categorical variables were summarised by frequencies and percentages, and continuous variables were summarised by the mean and standard deviation. Bar charts and error plots were generated to compare the distributions of categorical and continuous variables, respectively, between the AACES results and those reported by Brieger et al. [14].

Debulking status was missing at a much higher rate than the other variables in the data set (35%) and thus was only included in sensitivity analyses. The highest rate of missing data included in the main analyses were exposures calculated from the FFQ (the E-DII and alcohol use) at ≤18%, while data among the components of the IRRS and the other covariates were individually missing at rates ≤10%. Restricting to a complete case analysis produces a sample of only 422 participants with full information on every variable, so to preserve the sample size and power, multiple imputation by chained equations (MICE) was employed to create 50 datasets prior to calculating the IRRS and fitting models to the data, and pooled afterwards to generate estimates [23]. For each of the 11 available inflammation-related risk factors, the coefficients derived by Brieger et al. [14] were applied to each participant within each imputed dataset.

Associations of the IRRS and the E-DII with OS were analysed [1] categorically, based on quartiles and [2] continuously to obtain a per-quartile effect estimate. First, both forms of the IRRS were fit in Cox PH models while adjusting for FIGO stage and age at diagnosis, and allowing the baseline hazard to vary by histology, menopausal status, and geographical region. As in the analysis by Brieger et al. [14], our covariates were selected a priori. Each variable was assessed for violations of the PH assumption, and were shifted to stratification levels as necessary. HRs and 95% CIs were calculated, as well as the p values from Wald statistics for each coefficient. We also estimated the association with the addition of other covariates: alcohol consumption, income, LOC, and E-DII. A second Cox PH model was fit with the IRRS, the E-DII, age at diagnosis, and FIGO stage, and the baseline hazard varied by histology, menopausal status, and residential region. Quartile-specific and per-quartile HRs, 95% CIs, and Wald p values were calculated for the main associations of the IRRS and the E-DII

within this model. To check the validity of the multiple imputation results, we performed a sensitivity analysis restricting to the complete case study population (i.e., excluding observations with missing data).

We further assessed interaction between the IRRS and E-DII by calculating interaction on additive and multiplicative scales, using the relative excess risk due to interaction (RERI) and multiplicative interaction (INT_M), respectively, between the two scores, both simplified to binary variables split at the median using the extension to the Cox PH model described by Li and Chambless [24] and explored by VanderWeele [24, 25]. The RERI is interpreted by positivity: a value greater than 0 indicates a positive additive interaction, with a significant 95% CI not crossing 0. INT_M can be understood in the same way as an HR, i.e., greater than or less than 1, with a significant 95% CI not crossing 1. A positive RERI indicates that the joint effect of the E-DII and the IRRS on OS is greater than the sum of their individual effects, while a positive INT_M indicates that the joint of the effects of the E-DII and the IRRS on OS is greater than the product of their individual effects. Both interaction measures were also calculated with a complete case sensitivity analysis. The correlation between the IRRS and the E-DII was also calculated.

We performed a complete case sensitivity analysis among women who had known treatment data, as debulking status was missing at a much higher rate than other variables (35%). For this we fit Cox PH models with the IRRS, the E-DII, and debulking status, while adjusting for FIGO stage and age at diagnosis, and allowing the baseline hazard to vary by menopause, histotype, and residential region. HRs, 95% CIs, and *p* values from Wald statistics for the IRRS, the E-DII, and debulking status were calculated.

RESULTS

Distributions in study population

Data from 592 women enrolled in AACES from 2010 to 2015 with pathologically confirmed EOC were included in the current analysis. The majority of these women had tumours classified as high-grade serous (67.7%), were diagnosed at a late stage (66.8%), were post-menopausal at the time of their diagnosis (75.0%), or had an elevated BMI (mean = 32.7 kg/m^2, SD = 8.28) (Tables 1 and 2). Among the EOC cases, 43% and 16% of women in AACES were classified as obese (BMI ≥ 30 kg/m^2 but <40 kg/m^2) or severely obese (BMI ≥ 40 kg/m^2), respectively. Additionally, the majority of women with EOC in AACES were physically inactive as defined by the 2008 PAGA guidelines in the year prior to diagnosis (75.4%), did not use aspirin or other NSAIDs regularly (83.1% and 78.1%, respectively), had never used menopausal hormone therapy (83.0%), had not been diagnosed with PCOS, PID, or endometriosis (98.6%, 92.1%, and 83.0%, respectively), and reported adulthood secondhand smoke exposure (72.0%) (Table 2). Slightly more than half of the women enrolled in AACES had at least some college education (55.2%), slightly more than half reported never smoking (55.2%), and just under half reported talc use on genital areas (44.0%) or ever alcohol use (48.6%) (Tables 1 and 2).

As of October 2022, only 215 (36%) of the study population were still alive. Among women who were deceased, OS time ranged from 0.45 years to 11.16 years with an average of 3.31 years (SD = 1.94), and among surviving women, OS time ranged from 6.25 to 11.86 years, with an average of 9.30 years (SD = 1.31) from the date of EOC diagnosis (Table 1).

IRRS and OS

After multiple imputation, the IRRS within AACES ranges from −0.184 to 0.833, with a median of 0.368. The overall median of the IRRS was higher in the AACES population compared with those in the Brieger study (0.368 vs 0.252, respectively) [14]. The determinants of the higher median score were illustrated by the striking differences in the underlying distributions of the inflammatory factors in AACES as compared with Brieger et al., primarily among physical inactivity (75.4% vs 21.6%), BMI (32.7 kg/m^2 vs 26.9 kg/m^2), hormone therapy duration (<5 years: 10.4% vs 14.6%; 5+ years: 6.6% vs 16.3%), and talc use on genital areas (44.0% vs 31.4%) (Supplemental Figs. 1 and 2). The percentage of women in AACES

Table 1. Demographic and clinical information among women with epithelial ovarian cancer in AACES.

	***N* = 592** ***N* (%) or mean (SD)**
Vital status as of 2022[a]	
Alive	215 (36.3%)
Deceased	377 (63.7%)
Survival time in years	5.49 (3.37)
Among deceased	3.31 (1.94)
Among surviving	9.30 (1.31)
Histotype	
High-grade serous	397 (67.7%)
Low-grade serous	17 (2.9%)
Endometrioid	57 (9.7%)
Clear cell	23 (3.9%)
Mucinous	29 (4.9%)
Carcinosarcoma	18 (3.1%)
Other	45 (7.7%)
Unknown	6 (–)
Stage	
I/II (early)	183 (33.2%)
III/IV (late)	368 (66.8%)
Unknown	41 (–)
Debulking status	
Suboptimal	116 (30.3%)
Optimal	255 (66.6%)
No debulking surgery	12 (3.1%)
Unknown	209 (–)
Region	
North (IL, MI, OH, NJ)	138 (23.3%)
Southeast (GA, NC, SC, TN)	309 (52.2%)
Southwest (TX, AL, LA)	145 (24.5%)
Age at diagnosis	58.12 (10.85)
Menopausal status	
Premenopausal	148 (25.0%)
Postmenopausal	443 (75.0%)
Unknown	1 (–)
Education	
Less than high school	95 (16.0%)
High school or GED	170 (28.7%)
Some college	185 (31.2%)
College graduate	142 (24.0%)
Annual household income	
<$10,000	115 (21.5%)
$10,000–<$50,000	257 (48.4%)
$50,000+	159 (29.9%)
Unknown	61 (–)
E-DII[b]	
Quartile 1: [−5.22, −3.49)	123 (25.2%)
Quartile 2: [−3.49, −2.25)	121 (24.7%)
Quartile 3: [−2.25, 0.02)	122 (24.9%)
Quartile 4: [0.02, 3.11]	123 (25.2%)
Unknown	103 (–)

Table 1. continued

	N = 592 *N* (%) or mean (SD)
Lifetime ovulatory cycles (months)	
Quartile 1: <316	134 (25.0%)
Quartile 2: 316–396	134 (25.0%)
Quartile 3: 397–452	133 (24.8%)
Quartile 4: 453+	135 (25.2%)
Unknown	56 (–)

[a]MI participants were updated in March 2022, and all others were updated in October 2022.
[b]Energy-adjusted dietary inflammatory index with supplements.

who reported a history of PID was more than twice that of women in the Brieger study (7.8% vs 3.6%, respectively) (Supplemental Fig. 1).

Evaluation of the association of IRRS and other inflammation-related exposures with OS

A higher unadjusted IRRS score was associated with an increased risk of mortality (HR: 1.35, 95% CI: 1.01–1.80 for Q4 vs Q1) (Table 3, Model 1). After adjustment, this increased risk of mortality was sustained (HR: 1.37, 95% CI: 1.02–1.85 for Q4 vs Q1), with a statistically significant dose-response trend of 11 percent increased risk of mortality per quartile of IRRS (1.11, 95% CI: 1.01–1.22) (Table 3, Model 2).

Inclusion of alcohol consumption, LOC, and annual income were neither statistically significant in the models, nor did they alter the IRRS HRs ≥ 5%. There was a significant, but modest, positive correlation coefficient between the IRRS and the E-DII ($r^2 = 0.195$; $p < 0.001$). Inclusion of the E-DII attenuated the association between the IRRS and OS, but the IRRS was still weakly but positively associated with shorter OS (HR: 1.27, 95% CI: 0.93–1.73 for Q4 vs Q1), and still showed evidence of a dose-response trend although it was no longer statistically significant (HR: 1.09, 95% CI: 0.99–1.20) (Table 3, Model 3). Further, increasing quartiles of the E-DII were independently and positively associated with worse OS (HR: 1.42, 95% CI: 1.05–1.93 for Q4 vs Q1) with a statistically significant dose-response trend (HR: 1.12, 95% CI: 1.02–1.24) (Table 3, Model 3). The sensitivity analysis restricted to the complete case showed similar results (Supplemental Table 1).

To assess for the presence of interaction between IRRS and the E-DII, Table 4 summarises the results when the joint classification of IRRS (high/low) and E-DII (high/low) was analysed in relation to OS. Compared with women who were classified as low on both measures, those who were classified as high on only one measure did not experience a statistically significant difference in OS, whereas those who were classified as high on both measures experienced significantly worse OS (HR: 1.54, 95% CI: 1.16–2.06). With respect to formal tests for interaction, estimates of interaction were suggestive of a positive interaction between the E-DII and the IRRS on an additive scale (RERI = 0.41, 95% CI: −0.05–0.87 *p* value: 0.07) and less so on a multiplicative scale (INT_M:1.36, 95% CI 0.89–2.07, *p*-value 0.15) (Table 4). When restricting to the complete case analysis, interaction was significant on the additive scale, and suggestive on the multiplicative scale, while both had slightly higher magnitudes (RERI: 0.63, 95% CI: 0.09–1.16, *p*-value: 0.03; INT_M: 1.63, 95% CI: 0.98–2.70, *p* value = 0.06) (Supplemental Table 2). As with the imputed dataset analysis, the HR associated with having both high E-DII and high IRRS was statistically significant (HR: 1.63, 95% CI: 1.19–2.25). Among the women with complete covariate information, 29% were classified in the high E-DII and high IRRS category, 21% were classified as having a high E-DII and a low IRRS, and 21% were classified as having a low E-DII and a high IRRS.

Table 2. Pre-diagnostic inflammatory-related measures used for the IRRS among women with epithelial ovarian cancer in AACES.

	N = 592 *N* (%) or mean (SD)
BMI in the year before diagnosis (kg/m^2)	32.70 (8.28)
Physical activity in the year before diagnosis Meets PAGA	
No	407 (75.4%)
Yes	133 (24.6%)
Unknown	52 (–)
Aspirin use	
No	444 (83.1%)
Yes	90 (16.9%)
Unknown	58 (–)
Regular NSAID use	
No	417 (78.1%)
Yes	117 (21.9%)
Unknown	58 (–)
Hormone therapy duration	
None	488 (83.0%)
<5 years	61 (10.4%)
5+ years	39 (6.6%)
Unknown	4 (–)
Smoking status	
Never	327 (55.2%)
Former	205 (34.6%)
Current	60 (10.1%)
PCOS	
No	582 (98.6%)
Yes	8 (1.4%)
Unknown	2 (–)
PID	
No	541 (92.2%)
Yes	46 (7.8%)
Unknown	5 (–)
Endometriosis	
No	528 (89.8%)
Yes	60 (10.2%)
Unknown	4 (–)
Regular talc use	
Never	221 (37.4%)
Yes, on non-genital areas	110 (18.6%)
Yes, on genital areas	260 (44.0%)
Unknown	1 (–)
Adulthood secondhand smoke exposure	
No	151 (28.0%)
Yes	389 (72.0%)
Unknown	52 (–)
Alcohol use	
Never	250 (51.4%)
Ever	236 (48.6%)
Unknown	106

BMI Body Mass Index, *PAGA* Physical Activity Guidelines for Americans, 2008; 75+ min of strenuous physical activity weekly, *NSAID* nonsteroidal anti-inflammatory drug, *PCOS* polycystic ovary syndrome, *PID* pelvic inflammatory disease.

Upon inspection of differences between the complete case and the imputed analyses, the distributions of demographic and clinical variables showed a higher percentage of women with high-grade serous tumours, advanced stages at diagnosis, a higher percentage of reported endometriosis, higher education, or

Table 3. Unadjusted and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality by IRRS and E-DII, for women with EOC in AACES (2010–2015).

***N* = 592**						
	Model 1: unadjusted model of IRRS		**Model 2: adjusted IRRS without E-DII[a]**		**Model 3: adjusted IRRS with E-DII[a]**	
	HR (95% CI)	***p* value**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
IRRS						
Quartile 1	1.00 (referent)		1.00 (referent)		1.00 (referent)	
Quartile 2	0.91 (0.67, 1.24)	0.556	1.00 (0.73, 1.38)	0.994	0.93 (0.67, 1.30)	0.684
Quartile 3	1.14 (0.85, 1.55)	0.380	1.12 (0.83, 1.52)	0.466	1.04 (0.76, 1.42)	0.813
Quartile 4	1.35 (1.01, 1.80)	0.043	1.37 (1.02, 1.85)	0.036	1.27 (0.93, 1.73)	0.130
E-DII						
Quartile 1	NA	NA	NA	NA	1.00 (referent)	
Quartile 2	NA	NA	NA	NA	1.07 (0.79, 1.46)	0.648
Quartile 3	NA	NA	NA	NA	1.29 (0.96, 1.74)	0.093
Quartile 4	NA	NA	NA	NA	1.42 (1.05, 1.93)	0.002
IRRS Per Quartile	1.12 (1.02, 1.23)	0.016	1.11 (1.01, 1.22)	0.027	1.09 (0.99, 1.20)	0.096
E-DII Per Quartile	NA	NA	NA	NA	1.12 (1.02, 1.24)	0.016

NA not applicable.
[a]Adjusted for FIGO stage and age at diagnosis, and baseline hazard stratified by histotype, menopause, and residential region, using multiple imputation.

higher income within women who were included in the complete case analysis (Supplemental Table 3).

In the subset of women for whom we had debulking status, suboptimal debulking was associated with a strong increased hazard of mortality (HR: 1.78, 95% CI: 1.30–2.43) (Supplemental Table 4). Including debulking status in the model appeared to increase the estimates of the second and third quartiles of the IRRS (Q2 HR: 1.11, 95% CI: 0.73–1.70; Q3 HR: 1.20, 95% CI: 0.78–1.85), while the second quartile of the E-DII was attenuated (HR: 0.87, 95% CI: 0.57–1.34). However, the estimates for the highest quartiles (IRRS Q4 HR: 1.40, 95% CI: 0.93–2.13; E-DII Q4 HR: 1.43, 95% CI: 0.94–2.17) as well as those for the per-quartile measures (IRRS HR: 1.10, 95% CI: 0.97–1.26; E-DII HR: 1.17, 95% CI: 1.03–1.34) for both scores showed the increase in hazards that was seen in the main results (Supplemental Table 4).

DISCUSSION

Our study suggests that a higher IRRS quartile score is associated with poorer survival among Black women with EOC while controlling for other covariates. Although our study population consisted of only 592 Black women, our estimates are similar in magnitude to the corresponding HRs reported by the larger study by Brieger et al. of over 8000 mostly White women with EOC [14] (Table 5). Due to the smaller sample size, the estimates were less precise in the current study. Additionally, an increasing inflammatory dietary potential as measured by the E-DII was found to be independently associated with OS among Black women with EOC when included simultaneously in the same model with the IRRS. The inclusion of the E-DII in the model attenuated the magnitude of the association between IRRS and OS among Black women with EOC.

Characteristics such as physical inactivity, hormone therapy duration, talc use on genital areas, and PID appear to be driving the higher overall distribution of factors comprising the inflammatory index score, thus resulting in a higher median IRRS among Black women in the AACES Study compared to that of the women with EOC in the report by Brieger et al. However, we were unable to account for alcohol recency in our calculation of the IRRS. Even with a smaller proportion of women in AACES having reported ever alcohol use compared with the women in the Brieger study (48.6% vs 57.3%, respectively), the median IRRS in AACES likely would have been even higher than what we report in this study. We performed a sensitivity analysis including the alcohol use within the year before diagnosis that was measured in the AACES, but this inclusion did not alter the coefficient estimates of the IRRS, and the HR associated with alcohol consumption was null (HR = 0.98).

The E-DII, a measure of the inflammatory potential of diet, has been validated with circulating inflammatory markers in over 40 studies [21]. In our analysis, the E-DII including dietary supplements was observed to be independently associated with worse survival among Black women with EOC when included in the model with the IRRS. The E-DII attenuated the association of the IRRS with OS and was found to be weakly correlated ($r^2 = 0.195$) with the IRRS on a continuous scale. Additional adjustment for LOC and other covariates did not demonstrate an impact on the associations of the IRRS or E-DII scores on OS. In classifying IRRS and E-DII dichotomously as high or low, our evaluation of an interaction suggested the presence of interaction, whereby the risk of shorter OS was almost entirely concentrated in women classified as high on both measures of inflammation (HR 1.54, 95% CI 1.16–2.06). Regardless of whether or not the results were consistent with statistically significant interaction, the results are consistent with the interpretation that inflammation through separate pathways of behaviour and dietary patterns only begin to impact ovarian cancer survival when the cumulative inflammation levels reach a certain threshold. The finding of an additive interaction may suggest a biological effect with the risk of poorer survival concentrated among those with high levels of both indices.

We identified several modifiable factors that particularly influence the IRRS in individuals in our study population. Upon inspection of the women with the highest quartile of IRRS compared to the total sample, some of the starkest differences appeared within BMI, percentage of current smokers, physical inactivity, and secondhand smoke exposure. Of women with complete information on the factors of the IRRS who were classified as the highest quartile ($N = 106$), the average BMI was elevated to 40.58 kg/m^2 (SD = 9.50), compared with the overall

Table 4. Relative excess risk due to interaction (RERI) and multiplicative interaction (INT_M) between IRRS and E-DII, for women with EOC in AACES (2010–2015).

	IRRS					
	Low		High		RERI[b]	INT_M[b]
	N[a]	HR[b]	*N*[a]	HR[b]		
E-DII					0.41 (−0.05, 0.87) $p = 0.07$	1.36 (0.89, 2.07) $p = 0.15$
Low	170	1.00 (referent)	127	1.03 (0.76, 1.40)		
High	127	1.10 (0.81, 1.49)	168	1.54 (1.16, 2.06)		

[a]Since this was done with multiple imputation, the *N* counts are averages over the 50 imputations.
[b]Adjusted for FIGO stage and age at diagnosis, and baseline hazard stratified by histotype, menopausal status, and residential region, using multiple imputation.

Table 5. Comparisons of IRRS Quartile-specific HRs between AACES and Brieger et al. [14].

	AACES HR (95% CI)[a]	Brieger HR (95% CI)[b]
IRRS		
Quartile 1	1.00 (referent)	1.00 (referent)
Quartile 2	1.00 (0.73, 1.38)	1.13 (0.97, 1.31)
Quartile 3	1.12 (0.83, 1.52)	1.17 (1.01, 1.36)
Quartile 4	1.37 (1.02, 1.85)	1.31 (1.03, 1.14)
Per Quartile	1.11 (1.01, 1.22)	1.09 (1.03, 1.14)

[a]Adjusted for stage, and age at diagnosis, and stratifying baseline hazard by geographic region, menopause, and histotype, using multiple imputation.
[b]Adjusted for stage, age at diagnosis, and education, and stratifying baseline hazard by study site, menopause, histotype, and race/ethnicity, using multiple imputation.

mean of 32.70 kg/m^2 (SD = 8.28). Current smokers were more concentrated among women within the highest quartile, as compared with the overall sample (21.7% vs 10.1%), as was physical inactivity (93.4% vs 75.4%), and adulthood secondhand smoke exposure (87.7% vs 72.0%).

We also evaluated the influence of some of these exposures that were prominent in determining a high IRRS. When we removed BMI from the IRRS, the association of the IRRS with survival that was evident in the fourth quartile and the per-quartile estimates were attenuated (Supplemental Table 5), and the overall distribution of the IRRS was greatly reduced, from a mean of 0.361 (SD = 0.126) to 0.036 (SD = 0.093). Removing only physical activity, secondhand smoking, and smoking status also decreased the mean of the IRRS, albeit not to the same extent with mean scores of: 0.303 (SD = 0.118), 0.312 (SD = 0.123), 0.349 (SD = 0.124), respectively. This underscores the potential importance of BMI to the IRRS within Black women with EOC.

When included in the same model, our data support that both the IRRS and the E-DII are each independently associated with EOC survival, with per-quartile HRs that are of similar magnitude, with the per quartile increase in HR associated with the E-DII being slightly higher in magnitude compared to the per quartile magnitude of the IRRS. The IRRS and the E-DII represent different inflammation-related exposures that contribute to poor survival. While the E-DII has been validated with circulating inflammatory markers, such validation has not been undertaken for the IRRS. The low correlation between the E-DII and IRRS ($r^2 = 0.195$) supports that these indices are indicative of unrelated exposures. That summarising complex inflammatory-related exposures into two streamlined indices had separate impacts on survival support the idea that inflammation is a key pathway between EOC and survival outcomes. In addition to being inflammation related, several of the factors included in IRRS such as postmenopausal hormone therapy, PCOS and endometriosis also affect or are a result of the woman's hormonal environment. Further biomarker validation of the IRRS is necessary to confirm the interpretation of our findings.

In interpreting our results, there are some important limitations to consider. One limitation is that we did not have the power to build an IRRS tailored to our population and therefore incorporated the variable weights derived from the mostly White population in the report by Brieger et al. [14]. Another limitation is that all of our inflammation-related exposure variables represent pre-diagnostic exposures and we were unable to assess whether post-diagnostic changes in modifiable inflammation-related exposures would impact EOC survival. Our analysis was conducted for all EOC histotypes, and the categories used in the model were only comparing high-grade serous to all other histotypes. Unlike the earlier report in over 8000 women in Brieger et al., our small sample of women in AACES did not permit us to examine the associations within EOC histotypes, and it is possible that the relationships may vary by histotype. All of our exposure data were based on self-report; therefore, it is likely that misclassification of the exposures occurred. However, this misclassification is likely nondifferential with respect to overall EOC survival and therefore likely led to an attenuation of our HR estimates.

Even with the omission of recent alcohol use, the AACES population appeared to have more exposure to pro-inflammatory factors leading to a higher median IRRS score, with a similar impact upon survival. Overall, our results support that inflammatory-related exposures, including lifestyle and dietary factors, play a significant role in overall EOC survival among Black women. While it cannot be said that changing these behaviours post-diagnosis would improve survival, hopefully further work investigating the IRRS and dietary patterns will illuminate the pathway to improving survival among this marginalised population with EOC. Although our findings suggest that modifiable inflammatory-related exposures affect EOC survival in Black women, further validation with biomarkers assessments and evaluation of post-diagnostic inflammatory exposures will be valuable for designing tailored behavioural interventions aiming to reduce racial disparities in mortality after an EOC diagnosis.

DATA AVAILABILITY

The datasets generated and/or analysed during the current study are available on reasonable request, in accordance with the NIH data sharing policy.

CODE AVAILABILITY

All analyses were performed using R (version 4.2.0), and the code is available on reasonable request.

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AUTHOR CONTRIBUTIONS

The following authors were a part of the writing group: CEJ, JMS, AJA, EVB, PT, ESP, BQ, HBM, MLC, MA, TAH, and LJC. The analysis was completed by: CEJ. The following authors provided comments and edits to the manuscript: LVP, AGS, ABL, and JRH. The following authors helped in data collection: JMSchildkraut, AJA, EVB, PT, MA, ESP, MLC, JRM, MB, AGS, and HBM. JRH developed the energy-adjusted dietary inflammatory index.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Western Institutional Review Board-Copernicus Group (WCG IRB). The study was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Joellen M. Schildkraut.

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