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High Prediagnosis Inflammation-Related Risk Score Associated with Decreased Ovarian Cancer Survival

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ABSTRACT

Background: There is suggestive evidence that inflammation is related to ovarian cancer survival. However, more research is needed to identify inflammation-related factors that are associated with ovarian cancer survival and to determine their combined effects.

Methods: This analysis used pooled data on 8,147 women with invasive epithelial ovarian cancer from the Ovarian Cancer Association Consortium. The prediagnosis inflammation-related exposures of interest included alcohol use; aspirin use; other nonsteroidal anti-inflammatory drug use; body mass index; environmental tobacco smoke exposure; history of pelvic inflammatory disease, polycystic ovarian syndrome, and endometriosis; menopausal hormone therapy use; physical inactivity; smoking status; and talc use. Using Cox proportional hazards models, the relationship between each exposure and survival was assessed in 50% of the data. A weighted inflammation-related risk score (IRRS) was developed, and its association with survival was assessed using Cox proportional hazards models in the remaining 50% of the data.

Results: There was a statistically significant trend of increasing risk of death per quartile of the IRRS [HR = 1.09; 95% confidence interval (CI), 1.03–1.14]. Women in the upper quartile of the IRRS had a 31% higher death rate compared with the lowest quartile (95% CI, 1.11–1.54).

Conclusions: A higher prediagnosis IRRS was associated with an increased mortality risk after an ovarian cancer diagnosis. Further investigation is warranted to evaluate whether postdiagnosis exposures are also associated with survival.

Impact: Given that pre- and postdiagnosis exposures are often correlated and many are modifiable, our study results can ultimately motivate the development of behavioral recommendations to enhance survival among patients with ovarian cancer.

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Introduction

Systemic and local inflammatory processes are related to the etiologies of many diseases, including autoimmune disease, cardiovascular disease, and cancer. Chronic inflammation can directly cause DNA damage (1, 2), which is particularly relevant for cancer initiation and progression. Not surprisingly, in invasive epithelial ovarian cancer, hereafter referred to as ovarian cancer, risk is associated with proinflammatory exposures, including smoking history (3), pelvic inflammatory disease (4–6), endometriosis (7, 8), and possibly genital talc powder application (7, 9). However, there remain important gaps in knowledge with respect to inflammation-related exposures and their impact on survival with ovarian cancer.

There is some suggestion that ovarian cancer survival is decreased by proinflammatory exposures. For example, decreased ovarian cancer survival has been associated with prediagnosis high body mass index [BMI; HR = 1.03%; 95% confidence interval (CI), 1.00–1.06 per 5 kg/m^2; ref. 10], physical inactivity (HR = 1.34; 95% CI, 1.18–1.52; ref. 11), and smoking (HR = 1.17; 95% CI, 1.08–1.28 for current smokers and HR = 1.10; 95% CI, 1.02–1.18 for former smokers compared with never smokers; ref. 12). In contrast, better survival has been associated with anti-inflammatory exposures including postdiagnosis use of aspirin (HR = 0.68; 95% CI, 0.52–0.89; ref. 13), other nonsteroidal anti-inflammatory drugs (HR = 0.67; 95% CI, 0.51–0.87; ref. 13), and statins (HR = 0.81; 95% CI, 0.72–0.90; ref. 14). In addition, prediagnosis (15–18) and postdiagnosis (19, 20) menopausal hormone therapy (MHT) use, also thought to have anti-inflammatory properties, has been associated with 10% to 30% and 30% to 40% increased survival, respectively (21–25).

Overall, a summary measure of the relative contribution of pro- and anti-inflammatory factors is needed to better understand the potential impact of inflammation on survival among women with ovarian cancer. Using data from a large, multi-national consortium of epidemiologic studies, we evaluated the association between 12 self-reported prediagnosis exposures related to inflammation and ovarian cancer survival in half of our dataset. We then used those estimates to create an inflammation-related risk score (IRRS) and examine its association with survival in the remaining half of our participants.

Materials and Methods

All studies included in this analysis obtained written informed consent from participants. This analysis used pooled data from the Ovarian Cancer Association Consortium (OCAC), an international ovarian cancer collaboration (http://ocac.ccge.medschl.cam.ac.uk/). Data were sent to the OCAC data-coordinating center (Duke University) for central harmonization (26). Patients with ovarian cancer with low-grade serous, high-grade serous, endometrioid, mucinous, or clear cell cancer and for whom stage data were available were eligible for inclusion.

Twelve prediagnosis exposures of interest were included in this analysis: lifetime alcohol use, aspirin use, other nonsteroidal anti-inflammatory drug (NSAID) use, BMI, environmental smoke exposure (ever having been exposed to smoking in the home or at work as defined by each study), history of pelvic inflammatory disease (PID), polycystic ovarian syndrome (PCOS), endometriosis, MHT use, physical inactivity, smoking status, and talc use. Details on the definitions of the exposures have been described elsewhere (5, 27–32) and are presented in Supplementary Table S1. Within each OCAC study, the pattern of missingness among these exposures was investigated. To be included in the analysis, OCAC studies had to have collected data on at least seven of the 12 exposures of interest (Supplementary Fig. S1). Eleven OCAC sites, one from Australia (33) and 10 from the United States (34–44), met this criterion and were included in this analysis. A total of 8,147 people with ovarian cancer were included in this analysis.

Phone or in-person interviews or self-completed questionnaires were used to collect self-reported information from participants about their *prediagnosis* exposures as well as sociodemographic characteristics. All exposure data were collected after diagnosis. Each study site also collected data on histotype, grade, stage at diagnosis, vital status, and survival time. Overall survival was defined as length of time (in days) from diagnosis to either death from any cause or date of last follow-up (for censored women).

Overall analytic approach

The goal of this analysis was to develop a combined measure of inflammation-related risk factors using exposure information before diagnosis and to assess its association with survial among patients with ovarian cancer. First, we selected 12 inflammation-related exposures (see above) and measured the strength of the individual exposure–survival associations in a training set of cases comprising a 50% random sample of the study population (n = 4,073). Using these estimates, we then constructed a weighted inflammation-related risk score (IRRS) and evaluated the association between this score and survival in a test set comprising the other half of the study population (n = 4,074).

Imputation

The missingness across the 11 study sites for these exposures is shown in Supplementary Fig. S1. Multiple imputation (conducted with the *mice* package in *R*) was used to address data missingness across

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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sites. We imputed missing values iteratively and generated 50 imputed datasets (Supplementary Fig. S2). All variables in the dataset were initially considered for imputation, including those that were not used in final models, as this information potentially improved imputation (45). Before imputing, we excluded variables with a missingness of greater than 70% across the entire dataset. The U.S.-based studies were imputed separately from the Australian study. OCAC study site was included as a predictor in the imputation.

Training set analysis

The training set was used to fit a Cox proportional hazards model with all 12 inflammation-related risk factors (Supplementary Table S1) simultaneously. In this model, the hazard ratios (HR) across the 50 imputed training datasets were pooled using Rubin's rule (46) to obtain a single point estimate for each of the 12 risk factors (Supplementary Fig. S2).

The 12 risk factors were fit as follows: lifetime alcohol use status (never, current, former drinker), regular aspirin use (yes/no), regular NSAID use (yes/no), BMI (continuous), environmental smoke exposure (yes/no), history of PID (yes/no), history of PCOS (yes/no), history of endometriosis (yes/no), MHT duration of use (none, <5 years, 5+ years), physical inactivity (yes/no), smoking status (never, current, former), and talc use (never use, use on genital areas, use on nongenital areas). *A priori* covariates included in the model were age at diagnosis (continuous), education level (less than high school, high school, some college, college graduate or above), and stage at diagnosis (local, regional, distant). We stratified by histotype (low-grade serous, high-grade serous, endometrioid, mucinous, or clear cell), menopausal status (pre/post), OCAC study site, and race/ethnicity (Asian, Black, Hispanic White, Non-Hispanic White, Other) within the model, thus allowing the baseline hazard to vary. Adjusting for year of diagnosis or year of interview did not change the results.

Prior to combining these data into a single model, we evaluated heterogeneity across the study sites using standard meta-analysis techniques. The I^2 for the 12 exposures was low, with eight having a value of 0. Given the lack of heterogeneity, we proceeded with fitting a single model as described above (**Table 2**).

Test set analysis

The β coefficients obtained in the training set for the 12 exposures of interest were used to create a weighted IRRS within each imputed test dataset. The β coefficients for continuous variables were multiplied by the exposure level and those estimates for binary or categorical variables were summed to create the IRRS for each woman. The score was divided into quartiles.

Cox proportional hazards models were used to evaluate the association between IRRS quartile (categorical and ordinal) and survival. We also fit an additive Cox proportional hazards model with the IRRS in a natural form to assess whether a trend in the association between the IRRS and survival was present. As in the training set analysis, *a priori* covariates included in the model were stage at diagnosis, age at diagnosis, and education level. Likewise, as in the training set, we stratified by histotype, menopausal status, OCAC study site, and race/ethnicity within the model. Adjusted survival curves were generated to evaluate the association between the IRRS and survival over time (Supplementary Fig. S3). In addition, we fit separate histotype-specific models.

Goodness-of-fit tests were conducted to assess model fit in both the training and test sets. Goodness-of-fit tests showed insignificant results ($P > 0.05$) in 32 out of 50 imputed datasets in the training set. The results were insignificant in 34 out of 50 imputed datasets in the test set. Thus, the models in the training and test sets fit the data well.

Sensitivity analyses

In the training set, we conducted a sensitivity analysis for BMI using the World Health Organization (WHO) categories (<18.5, 18.5–24.99, 25–29.99, 30+ kg/m^2) and continuous lifetime alcohol consumption (grams/day) to determine if our categorization of these exposures in the primary analysis were appropriate. We also conducted sensitivity analyses to evaluate whether specific variables were contributing more information to the models. We used a backward stepwise selection approach to select variables in the training set. The backward stepwise selection approach for multiple imputation was described by Stef van Buuren (47). Briefly, in each of the 50 imputed datasets, a backward stepwise selection was conducted to select variables so that the model had the lowest Akaike information criterion (AIC). The variables that were selected by the models in all 50 individual datasets were included in the final model. For the variables that were selected by more than half of the models in the 50 individual datasets, Wald tests were used to determine if they should be included in the final model.We also carried out elastic net analysis; all 12 exposures were selected, and thus these results are not presented as they are nearly identical our main analysis.

As BMI and MHT were the only exposures statistically significantly associated with survival (see Results below), we conducted a sensitivity analysis in the test set that created the IRRS without BMI and MHT and fit the same model described above to determine whether there was still an association between the IRRS and survival. We also conducted a sensitivity analysis with the IRRS created from the variables selected by a backward stepwise approach (BMI and MHT) in the training set.

Statistical significance was defined as $P \leq 0.05$ using two-sided tests. Data were analyzed using R studio 1.1.463.

Results

A total of 8,147 women diagnosed with ovarian cancer from 11 OCAC study sites were included in the study (**Table 1**). A majority of the women had high-grade serous carcinoma (61.4%) and most had advanced stage disease at the time of diagnosis (63.3%; **Table 1**). The mean age at diagnosis was 57.5 years (SD = 11.3 years) and most women were postmenopausal at the time of diagnosis (71.1%). Physical inactivity was reported by 15.0% of the women. Regular use (at least once per week) of aspirin and NSAIDs were reported by 11.2% and 15.4% of women, respectively, and MHT use for less than 5 years and at least 5 years were reported by 12.3% and 15.7% of women, respectively (**Table 1**). The distributions of the factors were similar between the training and test sets (**Table 1**). All of these descriptive statistics were based on unimputed data.

HRs for each individual inflammation-related factor were generated in the training set to create the IRRS (**Table 2**). Only BMI was significantly associated with a higher death rate (HR = 1.01 for one additional kg/m^2; 95% CI, 1.00–1.02; $P = 0.012$). MHT use for 5+ years was significantly associated with a lower death rate (HR = 0.83; 95% CI, 0.74–0.93; $P = 0.001$). However, all 12 factors were included in the IRRS (**Table 2**).

Women in the highest quartile of the IRRS had a 31% increased risk of death (95% CI, 1.11–1.54), compared with those in the lowest quartile during follow-up. There was an increased death rate per quartile increase in the IRRS (HR = 1.09; 95% CI, 1.03–1.14; $P = 0.001$) based on fitting the IRRS as an ordinal variable. The adjusted survival curves show that patients in the highest quartile of the IRRS had worse survival compared with those in the lowest quartile at all time points after diagnosis (Supplementary Fig. S3). When fitting the IRRS in a natural spline form, there was also a clear trend that a

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Table 1. Demographic and clinical information among women with ovarian carcinoma in the OCAC included in the analyses.

			All women (%) (*N* = 8,147)	Training set (%) (*n* = 4,073)	Test set (%) (*n* = 4,074)
Study site	**Location**	**Years of recruitment**			
AUS[33]	Australia	2001–2006	1,054 (12.9%)	504 (12.4%)	550 (13.5%)
CON[34]	Connecticut	1999–2003	308 (3.8%)	153 (3.8%)	155 (3.8%)
DOV[35]	Western Washington	2002–2009	849 (10.4%)	412 (10.1%)	437 (10.7%)
HAW[36]	Hawaii	1994–2008	358 (4.4%)	194 (4.8%)	164 (4.0%)
HOP[37]	Western Pennsylvania, Northeast Ohio, Western New York	2003–2009	519 (6.4%)	273 (6.7%)	246 (6.0%)
MAY[38]	Iowa, Illinois, Minesota, North Dakota, South Dakota, Wisconsin	1999–2018	1,017 (12.5%)	512 (12.6%)	505 (12.4%)
NCO[39]	North Carolina	1999–2008	731 (9.0%)	362 (8.9%)	369 (9.1%)
NEC[40]	New Hampshire, Eastern Massachusetts	1992–2008	1,306 (16.0%)	652 (16.0%)	654 (16.1%)
NJO[41]	New Jersey	2005–2009	193 (2.4%)	96 (2.4%)	97 (2.4%)
UCI[42]	Southern California	1994–2004	345 (4.2%)	172 (4.2%)	173 (4.2%)
USC[43,44]	Los Angeles County, California	1994–2010	1,467 (18.0%)	743 (18.2%)	724 (17.8%)
Histology					
Low-grade serous			326 (4.0%)	170 (4.2%)	156 (3.8%)
High-grade serous			5,002 (61.4%)	2,476 (60.8%)	2,526 (62.0%)
Endometrioid			1,508 (18.5%)	787 (19.3%)	721 (17.7%)
Mucinous			561 (6.9%)	263 (6.5%)	298 (7.3%)
Clear cell			750 (9.2%)	377 (9.3%)	373 (9.2%)
Stage					
Local			1,539 (18.9%)	770 (18.9%)	769 (18.9%)
Regional			1,448 (17.8%)	714 (17.5%)	734 (18.0%)
Distant			5,160 (63.3%)	2,589 (63.6%)	2,571 (63.1%)
Age at diagnosis					
Mean (SD)			57.5 (11.3)	57.3 (11.3)	57.7 (11.2)
Median (min, max)			58.0 (20.0, 91.0)	57.0 (20.0, 91.0)	58.0 (20.0, 91.0)
Menopausal status					
Postmenopausal status			5,790 (71.1%)	2,877 (70.6%)	2,913 (71.5%)
Premenopausal status			2,357 (28.9%)	1,196 (29.4%)	1,161 (28.5%)
Education					
Less than high school			877 (10.8%)	481 (11.8%)	396 (9.7%)
High school			2,093 (25.7%)	1,052 (25.8%)	1,041 (25.6%)
Some college			2,339 (28.7%)	1,129 (27.7%)	1,210 (29.7%)
College graduate or above			2,611 (32.0%)	1,300 (31.9%)	1,311 (32.2%)
Missing			227 (2.8%)	111 (2.7%)	116 (2.8%)
Race/ethnicity					
Asian			406 (5.0%)	219 (5.4%)	187 (4.6%)
Black			232 (2.8%)	112 (2.7%)	120 (2.9%)
Hispanic White			289 (3.5%)	149 (3.7%)	140 (3.4%)
Non-Hispanic White			6,954 (85.4%)	3,456 (84.9%)	3,498 (85.9%)
Other			229 (2.8%)	121 (3.0%)	108 (2.7%)
Missing			37 (0.5%)	16 (0.4%)	21 (0.5%)
BMI 1 year prior to diagnosis (kg/m^2)					
Mean (SD)			26.9 (6.30)	26.9 (6.41)	26.9 (6.19)
Median (min, max)			25.5 (13.7, 68.3)	25.6 (13.7, 62.5)	25.5 (15.6, 68.3)
Missing			827 (10.2%)	422 (10.4%)	405 (9.9%)
Physical inactivity					
No			4,443 (54.5%)	2,219 (54.5%)	2,224 (54.6%)
Yes			1,224 (15.0%)	633 (15.5%)	591 (14.5%)
Missing			2,480 (30.4%)	1,221 (30.0%)	1,259 (30.9%)
Aspirin regular use					
No			3,951 (48.5%)	1,976 (48.5%)	1,975 (48.5%)
Yes			916 (11.2%)	466 (11.4%)	450 (11.0%)
Missing			3,280 (40.3%)	1,631 (40.0%)	1,649 (40.5%)
NSAID regular use					
No			3,709 (45.5%)	1,862 (45.7%)	1,847 (45.3%)
Yes			1,255 (15.4%)	618 (15.2%)	637 (15.6%)
Missing			3,183 (39.1%)	1,593 (39.1%)	1,590 (39.0%)
Hormone therapy duration of use					
Never use			4,744 (58.2%)	2,392 (58.7%)	2,352 (57.7%)
<5 years			1,003 (12.3%)	486 (11.9%)	517 (12.7%)
5+ years			1,280 (15.7%)	649 (15.9%)	631 (15.5%)
Missing			1,120 (13.7%)	546 (13.4%)	574 (14.1%)

(Continued on the following page)

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Table 1. Demographic and clinical information among women with ovarian carcinoma in the OCAC included in the analyses. (Cont'd)

	All women (%) (N = 8,147)	Training set (%) (n = 4,073)	Test set (%) (n = 4,074)
Environmental cigarette smoke			
No	1,034 (12.7%)	530 (13.0%)	504 (12.4%)
Yes	3,804 (46.7%)	1,925 (47.3%)	1,879 (46.1%)
Missing	3,309 (40.6%)	1,618 (39.7%)	1,691 (41.5%)
Smoking status			
Never	4,278 (52.5%)	2,094 (51.4%)	2,184 (53.6%)
Current	978 (12.0%)	520 (12.8%)	458 (11.2%)
Former	2,505 (30.7%)	1,270 (31.2%)	1,235 (30.3%)
Missing	386 (4.7%)	189 (4.6%)	197 (4.8%)
Lifetime alcohol use			
Never	1,671 (20.5%)	864 (21.2%)	807 (19.8%)
Current	1,651 (20.3%)	815 (20.0%)	836 (20.5%)
Former	592 (7.3%)	294 (7.2%)	298 (7.3%)
Missing	4,233 (52.0%)	2,100 (51.6%)	2,133 (52.4%)
History of PCOS			
No	6,519 (80.0%)	3,257 (80.0%)	3,262 (80.1%)
Yes	71 (0.9%)	39 (1.0%)	32 (0.8%)
Missing	1,557 (19.1%)	777 (19.1%)	780 (19.1%)
History of PID			
No	5,933 (72.8%)	2,963 (72.7%)	2,970 (72.9%)
Yes	224 (2.7%)	111 (2.7%)	113 (2.8%)
Missing	1,990 (24.4%)	999 (24.5%)	991 (24.3%)
History of endometriosis			
No	7,065 (86.7%)	3,515 (86.3%)	3,550 (87.1%)
Yes	869 (10.7%)	447 (11.0%)	422 (10.4%)
Missing	213 (2.6%)	111 (2.7%)	102 (2.5%)
Talc use			
Never use	2,242 (27.5%)	1,168 (28.7%)	1,074 (26.4%)
Use on genital area	1,387 (17.0%)	691 (17.0%)	696 (17.1%)
Use on body/nongenital area	793 (9.7%)	398 (9.8%)	395 (9.7%)
Missing	3,725 (45.7%)	1,816 (44.6%)	1,909 (46.9%)
Vital status			
Alive	3,300 (40.5%)	1,638 (40.2%)	1,662 (40.8%)
Death	4,847 (59.5%)	2,435 (59.8%)	2,412 (59.2%)
Follow-up years			
Mean (SD)	6.4 (4.87)	6.4 (4.86)	6.4 (4.88)
Median (min, max)	5.1 (0.1–26.2)	5.1 (0.1–26.2)	5.1 (0.1–25.6)

Abbreviations: max, maximum; min, minimum.

higher IRRS was associated with poorer survival (Supplementary Fig. S4).

Results were consistent in direction across histotype, with the exception of mucinous cancers, which showed no association (**Table 3**). These results were consistent when follow-up was restricted to the first 5 years after diagnosis, when most deaths are due to ovarian cancer itself. Also, there was still an association between the IRRS and survival after removing BMI and MHT use from the score; patients in the second, third, and highest quartiles of the IRRS had 3%, 11%, and 18% higher death rates, respectively, compared with the lowest quartile (HR = 1.06; 95% CI, 1.00–1.12; P = 0.043 per quartile).

Sensitivity analyses using a categorical BMI variable rather than a continuous variable did not change the results. In the training set, being obese was statistically significantly associated with a 12% increased death rate (95% CI, 1.00–1.25; P = 0.042). We created an IRRS using BMI categories in the test set and found an increased death rate per quartile of the IRRS (HR = 1.08; 95% CI, 1.03–1.14; P = 0.001), which was nearly identical to the result with continuous BMI (HR = 1.09). Similarly, replacing recency of lifetime alcohol consumption by grams/day did not change the results. In the training set, the consumption of an additional 100 grams of alcohol per day was associated with a 9% increased death rate (95% CI, 0.88–1.35; P = 0.41). There was also an increased death rate per quartile increase in the IRRS created using grams/day alcohol consumption (HR = 1.07; 95% CI, 1.02–1.13; P = 0.004), which was similar to the result with categories of alcohol consumption.

In the sensitivity analysis using a backward stepwise selection approach, only BMI (HR = 1.01; 95% CI, 1.00–1.02; P = 0.02 for one additional kg/m^2, and MHT use for 5+ years (HR = 0.84; 95% CI, 0.75–0.92; P = 0.001, compared with never use) were selected to be in the final model in the training set. In the test set, the IRRS created from only BMI and MHT use for 5+ years was statistically significantly assocociated with death rate (per quartile HR = 1.05; 95% CI, 1.01–1.09). Patients in the second, third, and highest quartiles of the IRRS had 9%, 8%, and 17% higher death rates, respectively, compared with the lowest quartile.

Discussion

The present analyses evaluated the combined effects of multiple inflammation-related exposures using a risk score for ovarian cancer

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Table 2. Association (HR, 95% CI, and *P* value) of each inflammation-related variable to survival in the training set ($n = 4,073$).

Variables		HR[a]	95% CI	*P* value	I^2 (%)[b]
Lifetime alcohol use					
	Never	1.0			
	Current	1.0	0.90–1.11	0.944	0.0
	Former	1.11	0.96–1.27	0.149	0.0
Aspirin, regular use					
	No	1.0			
	Yes	0.93	0.82–1.04	0.191	0.0
NSAID, regular use					
	No	1.0			
	Yes	0.96	0.87–1.07	0.497	0.0
BMI 1 year prior to diagnosis	+1 kg/m^2	1.01	1.00–1.02	0.012	9.1
Environmental smoking					
	No	1.0			
	Yes	1.07	0.96–1.19	0.230	0.0
History of PID					
	No	1.0			
	Yes	0.95	0.75–1.21	0.687	20.0
History of PCOS					
	No	1.0			
	Yes	1.22	0.86–1.73	0.274	21.0
History of endometriosis					
	No	1.0			
	Yes	0.94	0.80–1.09	0.407	0.0
MHT duration use					
	Never use	1.0			
	Use <5 years	0.96	0.84–1.10	0.555	28.4
	Use 5+ years	0.83	0.74–0.93	0.001	26.7
Physical inactivity					
	No	1.0			
	Yes	1.08	0.97–1.20	0.151	0.0
Smoking					
	Never	1.0			
	Current	1.09	0.95–1.24	0.213	0.0
	Former	1.01	0.92–1.11	0.898	0.0
Talc use					
	Never use	1.0			
	Use on genital area	0.94	0.84–1.04	0.222	0.0
	Use on nongenital area	0.95	0.84–1.08	0.463	0.0

[a]HRs (and 95% CIs) were estimated from Cox proportional hazards models, adjusted for stage at diagnosis, age at diagnosis, and education, stratified on menopausal status, race/ethnicity, histotype, and OCAC study site. The results were the pooled estimates from 50 imputed datasets.
[b]I^2 from meta-analyses of 11 OCAC study sites for each variable.

survival in thousands of women across Australia and the United States in the OCAC. Our results suggest that inflammation-related exposures play a role in survival with ovarian cancer. Women in the highest quartile of the IRRS compared with those in the lowest had a 31% higher death rate. There was a clear trend of increasing risk of death per quartile increase of the IRRS ($P = 0.001$).

Previous work suggests possible mechanisms by which inflammatory factors impact cancer survival. The complex interplay between inflammation and the immune system is key to these processes. For example, tumors infiltrated by intraepithelial effector T cells predict better patient survival (48, 49), while tumors infiltrated by immunosuppressive regulatory T cells confer poor prognosis (50). A systemic immune-inflammation index, which integrates neutrophils, lymphocytes, and platelet counts also predicts overall survival and progression-free survival among women with ovarian carcinoma (51). Another study found that low absolute lymphocyte count (ALC) at the time of diagnosis was prognostic of poor survival of high-grade serous carcinoma, an effect that was independent of intraepithelial $CD8^+$ T-cell density (52). Notably, however, prediagnostic (2+ years prior to diagnosis) ALC values showed no prognostic effect, suggesting that tumor-induced decline of ALC is a more significant prognostic factor. The prediagnosis exposures we studied likely impact the development of the tumor and its microenvironment, including the immune response. Our results suggest that lifestyle exposures associated with inflammation may contribute to these prognostic effects and provide new opportunities for intervention.

Several biologic mechanisms may explain the observed relationship between increased BMI and decreased survival, including chronic inflammation and lower immune function. Ovarian cancer cells localize to the omentum and take up lipids which provide energy (53). This insight also provides the potential therapeutic targets of lipid metabolism and transport. Additionally, the enzyme nicotinamide *N*-methyltransferase (NNMT) regulates methyl metabolism and has been linked to body composition regulation and obesity (54). NNMT is highly expressed in the stroma surrounding ovarian cancer metastases. NNMT has important roles in regulating the epigenetic landscape and

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Table 3. HRs and 95% CIs for the risk of death by quartile of the IRRS for all women with ovarian cancer and by histotype in the test set.

	All (n = 4,074) HR[a] (95% CI)	High-grade serous (n = 2,526) HR[b] (95% CI)	Endometrioid (n = 721) HR[b] (95% CI)	Clear cell (n = 373) HR[b] (95% CI)	Mucinous (n = 298) HR[b] (95% CI)	Low-grade serous (n = 156) HR[b] (95% CI)
Quartile 1	1.0	1.0	1.0	1.0	1.0	1.0
Quartile 2	1.13 (0.97–1.31)	1.10 (0.92–1.31)	1.17 (0.73–1.87)	1.33 (0.68–2.62)	0.70 (0.25–1.95)	1.36 (0.46–4.00)
Quartile 3	1.17 (1.01–1.36)	1.13 (0.94–1.36)	1.37 (0.83–2.25)	1.29 (0.63–2.65)	0.93 (0.39–2.20)	1.72 (0.53–5.58)
Quartile 4	1.31 (1.11–1.54)	1.22 (1.02–1.46)	1.65 (1.02–2.67)	1.39 (0.72–2.68)	1.03 (0.40–2.67)	2.09 (0.73–6.03)
Per Quartile	1.09 (1.03–1.14)	1.07 (1.01–1.13)	1.18 (1.01–1.38)	1.10 (0.89–1.35)	1.03 (0.78–1.37)	1.28 (0.91–1.79)

[a]Stratified on histotype, race/ethnicity, menopausal status, and OCAC study site and adjusted for stage at diagnosis, age at diagnosis, and education level.
[b]Stratified on race/ethnicity, menopausal status, and OCAC study site and adjusted for stage at diagnosis, age at diagnosis, and education level.

NNMT expression contribute to the conversion of normal fibroblasts to cancer-associated fibroblasts (55). These findings support the further exploration of possible inhibitors of NNMT to halt or slow ovarian cancer progression.

Our findings of the beneficial effect of MHT use and the detrimental effect of smoking were also consistent with previous findings and proposed biologic mechanisms. Our previous findings with OCAC data showed a positive prognostic impact of MHT use of at least 5 years duration prior to diagnosis; this association may be partly explained with evidence that estrogen has anti-inflammatory properties (56–58). In addition to evidence that hormone status alters the course of many common inflammatory disease processes, there is molecular evidence that activation of the estrogen receptor accelerates the resolution phase of the inflammation in macrophages (59). On the other hand, cigarette smoke and environmental cigarette smoke exposure are proinflammatory. Tobacco smoke exposure directly causes cellular changes that increase production of proinflammatory cytokines (60, 61) and enhance recruitment of immune cells (62) in the lung and at the systemic level. The association of former (but not current) alcohol use with decreased survival was somewhat surprising and could simply be due to chance or reflect the lack of important detail in this variable. The quantity of current consumption is likely important, as alcohol has anti-inflammatory effects at low levels (63) and proinflammatory effects at high levels (once there is liver damage).

BMI and MHT use for 5+ years appeared to contribute the most to survival. These two factors were the only ones significantly associated with survival in the training set (**Table 2**). In the sensitivity analysis using a backward stepwise approach, only these two factors were selected in the final model. However, the magnitude of the association between survival and the IRRS created using only BMI and MHT use for 5+ years was smaller than that between survival and the IRRS including all 12 factors, which indicates that other factors also mattered. This is consistent with our sensitivity analysis result that there was still an association between the IRRS and survival after removing BMI and MHT from the score. We therefore kept all factors in the score.

The strengths of this study include the novel analytic approach, the large sample from harmonized data across 11 studies, the ability to take a training and test set approach, and the clear link between the epidemiology and a well-established biologic mechanism around inflammation and survival. There are also a few limitations to our study. First, exposure missingness necessitated imputation of exposures. Because certain variables were completely missing at some OCAC sites (Supplementary Fig. S1), we cannot rule out the possibility that imputation relied on the relationship between variables that ideally should have only been applied within site. We did imputation by region separately (Australia vs. the United States), allowing for regional differences in the distributions of the predictors. We also recognize that the inferences drawn from the analysis would be even more convincing with confirmation that the exposure–survival relationships was correlated with the strength of the exposure–inflammation relationship. Because we do not have the relevant biomarkers of inflammation for these data, this could not be confirmed. Also, although we have accounted for education level, it is possible that we have residual confounding related to socioeconomic status which could be related to access to better health care.

This analysis was based on prediagnosis exposures, but because prediagnosis exposures and behaviors are often correlated with postdiagnosis exposures and behaviors (64, 65), the effect of a measured prediagnosis exposure may be due at least in part to the postdiagnosis exposure; for instance, certain diet and lifestyle factors may remain consistent. In a related analysis, Hansen and colleagues in a related analysis have shown that both pre- and postdiagnosis exposures are relevant (66). In their study of ovarian cancer survivors, they generated a healthy lifestyle index including smoking status, BMI, physical activity, diet, and alcohol consumption based on both pre- and postdiagnosis exposures. Women in the highest tertile of the healthy lifestyle index were 21% less likely to die based on prediagnosis exposures and 39% less likely to die based on postdiagnosis exposures compared with those in the lowest tertile (95% CIs, 0.59–1.04 and 0.40–0.93, respectively; ref. 66).

Our findings highlight potential ovarian cancer biology and offer insight into the combined effect of inflammation-related factors on ovarian cancer survival. Using data from multiple regions in the United States and Australia extends the representativeness of these findings. Survival cohorts should aim to collect information about medications and behavior postdiagnosis to examine whether the relationships that we have found remain consistent with use after diagnosis. Because many contributors to inflammation are modifiable, their associations with survival can ultimately be used to motivate and develop behavioral recommendations to enhance survival among people with ovarian cancer. These factors also have the potential to be included in risk stratification tools to identify women with a high risk of mortality who may need further tertiary prevention. Future work should continue to explore the role of inflammation-related factors in ovarian cancer survival, using advanced methods to allow for summary of inflammation information. Further, both pre- and postdiagnosis exposures should be examined, including the incorporation of laboratory measures and tumor characteristics. Also, conducting integrated analyses incorporating detailed tumor characteristics such as immune infiltration status, sequencing data, and copy-number variation with epidemiologic exposures before and after diagnosis will be informative with respect to prognosis among patients with ovarian cancer.

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