The inflammatory potential of diet and ovarian cancer risk: results from two prospective cohort studies

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Background: We used a food-based empirical dietary inflammatory pattern (EDIP) score to investigate whether diets with higher inflammatory potential are associated with increased ovarian cancer risk.

Methods: We followed 186 314 women in the Nurses' Health Study and Nurses' Health Study-II, from 1984 to 2013, to examine associations between EDIP scores and ovarian cancer risk, using Cox regression analyses.

Results: During 3 454 514 person-years of follow-up, 989 ovarian cancer cases were identified. In pooled multivariable-adjusted analyses, higher EDIP scores (more pro-inflammatory diets) were not significantly associated with ovarian cancer risk ($HR_{quintile5vs1}$ 0.99; 95% CI: 0.80–1.22; P-trend = 0.97). Similarly, we found no evidence of heterogeneity by histologic subtype (P-heterogeneity = 0.52) or by tumour aggressiveness (P-heterogeneity = 0.63).

Conclusions: In contrast with two previous case-control studies that found a positive association between a literature-derived nutrient-based dietary inflammatory index and ovarian cancer risk, our prospective analyses using a food-based score observed no evidence of an association.

Ovarian cancer has a high fatality rate (Siegel *et al*, 2017), yet few modifiable risk factors have been identified (Faber *et al*, 2013; Tworoger and Huang, 2016). Previous research suggests that dietary factors could influence ovarian cancer risk but no specific dietary factors or dietary patterns have consistently been associated with risk (Crane *et al*, 2014; Xie *et al*, 2014). Studies have found significantly higher pre-diagnosis levels of C-reactive protein (CRP), various interleukins (e.g., IL-6) and tumour necrosis factor alpha (TNF-α), among other markers, in ovarian cancer cases compared to non-cases (Poole *et al*, 2013a; Zeng *et al*, 2016). We hypothesise that diets with higher inflammatory potential may influence ovarian cancer risk.

Two case-control studies that assessed dietary inflammatory potential using a literature-derived nutrient-based dietary inflammatory index (Shivappa *et al*, 2016; Peres *et al*, 2017) reported that higher index scores were associated with higher risk of ovarian cancer. However, these findings may have been influenced by reverse causation due to differential use of nutritional supplements, which influence the score, based on case-control status (Shivappa *et al*, 2014; Peres *et al*, 2017). To elucidate the role of dietary inflammatory potential in ovarian cancer risk, we investigated the association between an empirical food-based dietary inflammatory pattern score (Tabung *et al*, 2016), with ovarian cancer risk in two prospective cohort studies.

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MATERIALS AND METHODS

Study population. The Nurses' Health Study (NHS) and Nurses' Health Study-II (NHS-II) are ongoing prospective cohorts established in 1976 and 1989, respectively. The NHS ($n = 121\,700$) enrolled female registered nurses aged 30–55 years, while the NHS-II ($n = 116\,429$) enrolled younger female registered nurses 25–42 years (Willett *et al*, 1985). For the current study, we excluded participants who reported menopause due to pelvic irradiation, any cancer other than nonmelanoma skin cancer, or bilateral oophorectomy; who did not complete a food frequency questionnaire (FFQ) during follow-up; or who had implausible values for total energy intake (<500 or $>3500\,kcal\,d^{-1}$) at study entry. This resulted in the inclusion of 89 034 women from the NHS and 97 280 women from the NHS-II for a total of 186 314 participants. The Institutional Review Board at Brigham and Women's Hospital approved this study.

Calculation of empirical dietary inflammatory pattern scores. Dietary intake was assessed in 1984, 1986, and every 4 years thereafter in the NHS. In the NHS-II, similar FFQs were initially administered in 1991 and subsequently every 4 years (Willett *et al*, 1985; Feskanich *et al*, 1993). The development of the empirical dietary inflammatory pattern (EDIP) score has been previously described (Tabung *et al*, 2016). The goal was to empirically create a score for overall inflammatory potential of whole diets defined using food groups. The investigators entered 39 pre-defined food groups (Hu *et al*, 1999) in reduced rank regression models followed by stepwise linear regression analyses to identify a dietary pattern most predictive of three plasma inflammation markers, IL6, CRP, and TNFα-receptor 2. The EDIP score is the weighted sum of 18 food groups, with higher (more positive) scores indicating pro-inflammatory diets and lower (more negative) scores indicating anti-inflammatory diets (Tabung *et al*, 2016, 2017).

Ascertainment of ovarian cancer. Information about new ovarian cancer diagnoses was collected on each biennial questionnaire and confirmed by medical records abstraction or by linking to the appropriate cancer registry or the National Death Index (Stampfer *et al*, 1984).

Statistical analysis. Person-years of follow-up were calculated from the return date of the first completed FFQ until the earliest date of: death, pelvic irradiation, bilateral oophorectomy, any cancer diagnosis (except non-melanoma skin cancer), or end of follow-up (NHS: June 2012; NHS-II: June 2013). EDIP scores were calculated as the cumulative average score from all prior reports up to the start of each 2-year follow-up interval, to best represent habitual long-term dietary intake and reduce within-person variation. We used Cox proportional-hazards regression models with time-varying covariates to estimate hazard ratios (HR) and 95% confidence intervals (CI) for EDIP scores in relation to ovarian cancer risk, with the lowest EDIP quintile as the reference group. Early symptoms of undiagnosed ovarian cancer may alter habitual diet intake; therefore, we used a 2-year lag between dietary assessment and ovarian cancer incidence as the main analytic approach. Multivariable models were adjusted for biennially updated covariates listed in the footnotes to Tables 2 and 3. For analyses of linear trend across EDIP quintiles, we used the continuous residual-adjusted EDIP score.

Duplication method cause-specific Cox regression models (Wang *et al*, 2016) were used in the pooled analysis to examine whether the association of EDIP scores differed by ovarian tumour histologic subtypes (serous/poorly differentiated *vs* non-serous) and by tumour aggressiveness (death due to ovarian cancer within 3 years of diagnosis *vs* not) (Poole *et al*, 2013b). In subgroup analyses, we stratified models in the pooled data by potential effect

modifiers (listed in Supplementary Table 1) selected *a priori*, based on findings in previous studies (Shivappa *et al*, 2016; Peres *et al*, 2017).

In a sensitivity analysis, we derived an alternative dietary pattern that specifically predicted concentrations of plasma CRP, the inflammation marker most consistently associated with higher ovarian cancer risk (Poole *et al*, 2013a; Zeng *et al*, 2016). Further, we replaced cumulatively averaged EDIP score with baseline EDIP score or with recently updated EDIP score, to test the influence of dietary intake in the distant past or in the recent past, respectively. All analyses were performed using SAS software, version 9.4 for UNIX (SAS Institute, NC, USA), at a two-sided *P*-value of 0.05.

RESULTS

We documented 989 cases of incident ovarian cancer (731 in NHS and 258 in NHS-II) over 3 454 514 person-years of follow-up. Over the entire follow-up period in both cohorts (28 years in NHS and 22 years in NHS-II), women consuming the most pro-inflammatory diets (EDIP quintile 5) reported lower physical activity, lower average duration of breastfeeding, higher waist-to-hip ratio, and higher BMI than those consuming the most anti-inflammatory diets (quintiles 1) (Table 1).

In pooled multivariable-adjusted analyses, dietary inflammatory potential was not associated with ovarian cancer risk. The HR for women in the highest compared to the lowest EDIP quintile was 0.99; 95% CI: 0.80, 1.22; *P*-trend, 0.97. The association did not differ by cohort: the HRs comparing extreme index quintiles were: 1.03; 95% CI: 0.80, 1.32; *P*-trend, 0.46 in the NHS and 0.93; 95% CI: 0.63, 1.39; *P*-trend, 0.37 in the NHS-II (Table 2). In subtype analyses, we found no evidence that the inflammatory potential of diet influenced ovarian cancer risk differentially by subtype (*P*-heterogeneity = 0.52) or by tumour aggressiveness (*P*-heterogeneity = 0.63) (Table 3).

Similarly, there were no substantial associations in strata of the potential effect modifiers, and no evidence for interaction (Supplementary Table 1). The findings from our sensitivity analysis of the CRP-specific inflammatory diet score were consistent with the null results for the overall EDIP score (Supplementary Table 2). Similarly, we found no association between EDIP scores and ovarian cancer risk using dietary intake assessed at baseline only or with recently assessed diet (Supplementary Table 3).

DISCUSSION

In this large prospective study, we used an empirically derived food-based index to assess dietary inflammatory potential and investigated its association with ovarian cancer risk. Our results revealed no statistically significant associations between the inflammatory potential of diet and ovarian cancer risk; a finding that did not differ by tumour subtype or aggressiveness. Also, we found no difference in the association by BMI category, menopausal status, oral contraceptive use, parity or family history of breast or ovarian cancer.

Two previous case-control studies that examined the association between a literature-derived nutrient-based dietary inflammatory index and ovarian cancer risk reported positive associations (Shivappa *et al*, 2016; Peres *et al*, 2017). However, in the study that derived separate scores with and without inclusion of supplemental intake, the results were attenuated and statistically nonsignificant for the nutrient-based score calculated from dietary intake only (Shivappa *et al*, 2014; Peres *et al*, 2017), which is in line with the null findings in the current study. Limitations of the case-

Table 1. Distribution of participant characteristics (weighted by person-years) across the entire follow-up time, in quintiles of the empirical dietary inflammatory pattern scores in the NHS (1984–2012) and the NHS-II (1991–2013)[a,b,c]

Characteristic	Nurses' Health Study (NHS)			Nurses' Health Study II (NHS-II)		
	Q1	Q3	Q5	Q1	Q3	Q5
Average person-years	390 941	319 212	234 015	271 982	344 572	431 470
Age, year	62.1 ± 9.5[d]	63.8 ± 10.0	61.6 ± 9.8	48.6 ± 7.0	47.1 ± 7.2	45.7 ± 7.2
History of tubal ligation, %	21.0	20.0	21.9	22.8	23.9	25.7
History of hysterectomy, %	19.1	22.4	23.3	7.6	8.6	9.9
Family history of breast or ovarian cancer, %	27.4	30.5	25.9	13.8	12.4	11.3
Current smoker, %	17.2	11.4	13.5	9.8	8.3	10.9
Parous, %	94.4	94.8	94.4	79.6	81.7	79.7
No. of children in parous women[e]	3	3	3	2	2	2
Duration of breastfeeding in parous women, month	6.7 ± 10.4	6.2 ± 10.2	5.6 ± 9.8	16.5 ± 14.4	15.2 ± 14.2	12.5 ± 13.0
Oral contraceptive use, ever, %	52.7	49.4	52.7	86.6	85.8	84.2
Duration of oral contraceptive use in ever users, year	4.1 ± 3.9	4.0 ± 3.8	4.0 ± 3.9	5.4 ± 4.9	5.5 ± 4.9	5.5 ± 4.8
Postmenopausal, %	81.6	84.2	78.6	31.2	23.9	18.4
Estrogen-only HT use[f], %	17.2	19.0	17.2	9.8	10.1	10.0
Duration of estrogen-only HT use[g], year	7.2 ± 6.3	8.0 ± 7.0	7.5 ± 6.6	3.3 ± 3.5	3.9 ± 3.8	4.2 ± 4.1
Estrogen-progestin HT use[f], %	32.0	28.7	23.9	34.5	34.2	30.8
Duration of estrogen-progestin HT use[g], year	5.8 ± 4.1	5.7 ± 4.1	5.2 ± 3.7	3.3 ± 2.9	3.3 ± 2.9	3.1 ± 2.8
Alcohol intake, g d^{-1}	9.7 ± 12.6	4.3 ± 7.2	3.4 ± 6.7	9.6 ± 12.5	4.2 ± 6.0	2.9 ± 4.6
Total energy intake, Kcal d^{-1}	1780 ± 533	1668 ± 527	1814 ± 582	1947 ± 574	1756 ± 550	1857 ± 601
Used ⩾1 of 15 supplements[h], %	76.2	74.9	67.9	72.7	69.9	63.0
Physical activity, MET-hour per week	20.1 ± 23.7	17.4 ± 20.9	15.5 ± 19.2	25.9 ± 28.7	21.2 ± 24.2	18.9 ± 23.2
Waist-to-hip ratio (WHR)	0.81 ± 0.15	0.82 ± 0.11	0.84 ± 0.11	0.80 ± 0.07	0.81 ± 0.07	0.82 ± 0.08
WHR ⩾0.80, %	45.7	53.6	62.0	48.3	52.3	61.7
Body mass index, kg m^{-2}	24.9 ± 4.4	26.3 ± 5.1	28.4 ± 6.2	25.3 ± 5.2	26.2 ± 5.8	28.3 ± 7.2
Overweight/obese, ⩾25 kg m^{-2}, %	41.6	54.4	67.4	41.6	47.8	60.6

[a]EDIP = empirical dietary inflammatory pattern score; HT = postmenopausal hormone therapy; NHS = Nurses' Health Study; NHS-II = Nurses' Health Study-II; Q = quintile.
[b]Weighted by follow-up time (person-years) accrued by each participant.
[c]EDIP scores were adjusted for energy intake using the residual method. In the EDIP quintiles, lower EDIP scores indicate anti-inflammatory diets and higher scores, pro-inflammatory diets.
[d]Mean ± s.d. (all such values).
[e]Average rounded to the nearest whole number.
[f]Among postmenopausal women.
[g]Among postmenopausal women using HT.
[h]The 15 supplements included were: multivitamins, vitamin A, beta-carotene, vitamin C, vitamin D, vitamin E, vitamin B-complex, folic acid, niacin (when used separately from B-complex), calcium, iron, selenium, zinc, magnesium and fish oil.

control studies include the potential for recall bias and/or reverse causation due to non-specific symptoms that may include abdominal bloating, constipation and abdominal or pelvic pain (Goff et al, 2004). Undiagnosed cancer cases suffering from non-specific symptoms may be more likely than non-cases, to use over-the-counter medications including supplements, for symptom relief (Rock, 2007; Velicer and Ulrich, 2008). To overcome this limitation, we inserted a 2-year lag between dietary assessment and ovarian cancer diagnosis.

Owing to the prior associations of CRP with ovarian cancer risk, we hypothesised that the CRP-predictive score would be more strongly associated with risk than the EDIP, because of its correlation with CRP. However, we did not observe an association for either score. Notably, although CRP levels varied across quintiles of the EDIP score, those changes were modest and it is possible that greater changes in CRP levels are needed to increase ovarian cancer risk. Other factors, such as incessant ovulation, endometriosis, exposure to asbestos, talc powder, and pelvic inflammatory disease (Rasmussen et al, 2017), may lead to higher inflammation directly in the ovaries which could more strongly influence risk.

Major strengths of our study include using the food-based EDIP score that is correlated with levels of inflammation biomarkers associated with ovarian cancer risk. Dietary and covariate data were assessed at multiple times throughout follow-up, which allowed us to use long-term cumulative average exposures, thus reducing within-person variation. Limitations include potential measurement error in the self-reported dietary and lifestyle data, though the multiple questionnaires during follow-up approximate habitual long-term diet and reduce measurement error.

In summary, findings from this large prospective study do not support a role of dietary inflammatory potential in ovarian cancer development, thus suggesting that other factors besides diet may play important roles in influencing inflammation pathways that impact ovarian carcinogenesis.

Table 2. Pooled and cohort-specific hazard ratios for the association between the empirical dietary inflammatory pattern (EDIP) score and incident epithelial ovarian cancer in the NHS and NHS-II[a,b,c]

Cohort	EDIP quintiles (Q)					
	Q1 −18.8 to < −0.73	Q2 −0.73 to < −0.21	Q3 −0.21 to <0.21	Q4 0.21 to <0.73	Q5 0.73 to 14.6	P-trend[d]
Median EDIP score	−1.17	−0.44	0.01	0.45	1.17	
Pooled						
No. of cases/person-years	218/682 484	197/686 193	219/690 780	188/694 786	167/700 271	
Age, calendar time and cohort-adjusted HR (95% CI)	1.00	0.93 (0.77, 1.13)	1.10 (0.91, 1.33)	1.00 (0.82, 1.22)	1.04 (0.84, 1.27)	0.64
Multivariable-adjusted HR (95% CI)	1.00	0.92 (0.76, 1.12)	1.07 (0.89, 1.30)	0.98 (0.80, 1.19)	0.99 (0.80, 1.22)	0.97
Nurses' Health Study (NHS)						
No. of cases/person-years	173/390 941	153/351 940	167/319 212	135/285 323	103/234 015	
Age, calendar time and cohort-adjusted HR (95% CI)	1.00	0.94 (0.75, 1.17)	1.13 (0.91, 1.39)	1.02 (0.82, 1.28)	1.02 (0.80, 1.30)	0.47
Multivariable-adjusted HR (95% CI)	1.00	0.93 (0.75, 1.16)	1.12 (0.90, 1.38)	1.02 (0.81, 1.29)	1.03 (0.80, 1.32)	0.46
Nurses' Health Study II (NHS-II)						
No. of cases/person-years	45/271 982	44/310 869	52/344 572	53/378 971	64/431 470	
Age, calendar time and cohort-adjusted HR (95% CI)	1.00	0.91 (0.60, 1.38)	1.01 (0.67, 1.50)	0.94 (0.63, 1.40)	1.04 (0.71, 1.53)	0.80
Multivariable-adjusted HR (95% CI)	1.00	0.90 (0.59, 1.36)	0.98 (0.66, 1.47)	0.89 (0.59, 1.34)	0.93 (0.63, 1.39)	0.37

Abbreviations: CI = confidence interval; EDIP = empirical dietary inflammatory pattern score; HR = hazard ratio; NHS = Nurses' Health Study; NHS-II = Nurses' Health Study-II.
[a]EDIP scores were adjusted for energy intake using the residual method. In the EDIP quintiles, lower EDIP scores indicate anti-inflammatory diets and higher scores, pro-inflammatory diets.
[b]EDIP quintiles were based on the distribution in the pooled study population.
[c]Cox proportional hazards models were used for all analyses. Analyses were stratified by age, and calendar time, and were adjusted for parity, duration of breastfeeding, family history of breast cancer or ovarian cancer, duration of oral contraceptive use, menopausal status, postmenopausal hormone duration and type, tubal ligation, hysterectomy, body mass index, and number of supplements used; models were further stratified by cohort in the pooled analysis. Fifteen supplements were included in the variable 'number of supplements used': multivitamins, vitamin A, beta-carotene, vitamin C, vitamin D, vitamin E, vitamin B-complex, folic acid, niacin (when used separately from B-complex), calcium, iron, selenium, zinc, magnesium and fish oil.
[d]Continuous residual-adjusted EDIP scores were used to test for linear trend across EDIP quartiles, adjusted for all covariates previously listed.

Table 3. Pooled hazard ratios for the association between the empirical dietary inflammatory pattern (EDIP) and incident epithelial ovarian cancer by histologic subtype and tumour aggressiveness in the NHS and NHS-II[a,b,c]

Ovarian cancer subtype	EDIP quintiles					P-trend[d]	P-heterogeneity[e]
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5		
Serous and poorly differentiated (n cases = 637)	1.00	0.99 (0.78, 1.26)	1.16 (0.92, 1.47)	1.00 (0.78, 1.29)	0.98 (0.74, 1.28)	0.78	0.52
Non-serous (n cases = 244)	1.00	0.76 (0.51, 1.13)	0.83 (0.56, 1.23)	0.89 (0.60, 1.32)	0.97 (0.64, 1.42)	0.85	
Rapidly fatal[f] (n cases = 330)	1.00	0.86 (0.62, 1.19)	0.89 (0.64, 1.24)	1.04 (0.75 1.45)	0.91 (0.63, 1.32)	0.72	0.63
Less aggressive[f] (n cases = 476)	1.00	0.96 (0.73, 1.28)	1.18 (0.90, 1.55)	1.02 (0.76, 1.37)	1.10 (0.82, 1.49)	0.62	

Abbreviations: NHS = Nurses' Health Study; NHS-II = Nurses' Health Study-II.
[a]EDIP scores were adjusted for energy intake using the residual method. In the EDIP quintiles, lower EDIP scores indicate anti-inflammatory diets and higher scores, pro-inflammatory diets.
[b]EDIP quintiles were based on the distribution in the pooled study population.
[c]Cox proportional hazards models were used for all analyses. Analyses were stratified by age, cohort, and calendar time, and were adjusted for parity, duration of breastfeeding, family history of breast cancer or ovarian cancer, duration of oral contraceptive use, menopausal status, postmenopausal hormone duration and type, tubal ligation, hysterectomy, and body mass index.
[d]Continuous residual-adjusted EDIP scores were used to test for linear trend across EDIP quartiles, adjusted for all covariates previously listed.
[e]A likelihood test was used for the test of heterogeneity in risk by ovarian cancer subtype/aggressiveness.
[f]Death due to ovarian cancer within 3 years of diagnosis vs not.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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