Dietary inflammatory index and endometrial cancer risk in an Italian case–control study

Nitin Shivappa\textsuperscript{1,2,*}, James R. Hébert\textsuperscript{1,2,3}, Antonella Zucchetto\textsuperscript{4}, Maurizio Montella\textsuperscript{5}, Diego Serraino\textsuperscript{4}, Carlo La Vecchia\textsuperscript{6} and Marta Rossi\textsuperscript{6}

\textsuperscript{1}Cancer Prevention and Control Program, University of South Carolina, Columbia, SC 29208, USA
\textsuperscript{2}Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC 29208, USA
\textsuperscript{3}Department of Family and Preventive Medicine, University of South Carolina School of Medicine, Columbia, SC 29208, USA
\textsuperscript{4}SOC di Epidemiologia e Biostatistica, Centro di Riferimento Oncologico, Aviano (PN), 33081, Italy
\textsuperscript{5}Dipartmento di Epidemiologia, 'Fondazione G. Pascale', Istituto Nazionale Tumori, Naples, 80133, Italy
\textsuperscript{6}Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, 20133, Italy

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Abstract

The relation between inflammation deriving from diet and endometrial cancer risk has not yet been investigated. In this study, we explored the association between the dietary inflammatory index (DII) and endometrial cancer risk in an Italian case–control study. Cases comprised 454 patients with incident, histologically confirmed carcinoma of the endometrium, and controls comprised 908 subjects admitted to the same network of hospitals as cases for a wide spectrum of acute, non-neoplastic conditions. DII scores were computed on the basis of dietary intake assessed using a reproducible and valid seventy-eight-item FFQ. OR were calculated through logistic regression models conditioned on age and study centre and adjusted for recognised confounding factors, including total energy intake. Women with the most pro-inflammatory diet had a higher risk for endometrial cancer compared with women with the most anti-inflammatory diet (OR\textsubscript{Quartile 4} \textasciitilde 1.46; 95 % CI 1.02, 2.11; \(P_{\text{trend}} = 0.04\)). A pro-inflammatory diet may increase the risk for endometrial cancer.

Key words: Dietary inflammatory index; Diet: Inflammation; Endometrial cancer; Case–control studies; Italy

Endometrial cancer is the sixth most common form of cancer in women worldwide\textsuperscript{(1)}. It is strongly related to unopposed oestrogens, including both those produced endogenously in adipose tissue and those in the form of hormone replacement therapy (HRT). Other risk factors for endometrial cancer are also hormone related and include earlier menarche, nulliparity, overweight/obesity and older age at menopause, whereas oral contraceptive (OC) use is inversely related to endometrial cancer risk\textsuperscript{(2–4)}. Acute inflammation is the body’s natural response to insult or injury to tissue, which helps to heal wounds and promote tissue regeneration\textsuperscript{(5–8)}, whereas chronic inflammation is a persistent state of low-grade inflammation\textsuperscript{(9)}. Various dietary components are known to modulate inflammation\textsuperscript{(9–11)}. Chronic inflammation is one of the major risk factors for development of several types of cancer\textsuperscript{(5,12)}, and considerable evidence has accumulated on the role of chronic inflammation in endometrial cancer\textsuperscript{(13–15)}. This more recent evidence is consistent with findings of Wynder et al\textsuperscript{(3)} of the relationship between overweight and endometrial cancer from half a century ago. This line of evidence points towards a possible relation between inflammation deriving from dietary exposure and endometrial cancer risk.

A literature-derived, population-based dietary inflammatory index (DII) was developed to assess the inflammatory potential of an individual’s diet\textsuperscript{(16)}. A typical pro-inflammatory diet is characterised by high consumption of foods rich in SFA, carbohydrate and protein and low consumption of foods rich in PUFA, flavonoids and other selected components and micro-nutrients. The DII has been validated with various inflammatory markers, including C-reactive protein (CRP)\textsuperscript{(17,18)}, IL-6\textsuperscript{(19,20)} and homocysteine\textsuperscript{(21)}. The DII has been shown to be associated with possible chronic inflammation-related conditions including intolerance and dyslipidaemia components of the metabolic syndrome in two cross-sectional studies in the USA and Luxembourg\textsuperscript{(21,22)}, anthropometric measurements of obesity in the PREDIIMED trial in Spain\textsuperscript{(21)}, asthma in a case–control study in Australia\textsuperscript{(23)}, bone mineral density among postmenopausal women in Iran\textsuperscript{(24)}, colorectal cancer in two cancer case–control studies: Italy

Abbreviations: CRP, C-reactive protein; DII, dietary inflammatory index; HRT, hormone replacement therapy; OC, oral contraceptive.

* Corresponding author: Dr N. Shivappa, email shivappa@mailbox.sc.edu
studies, in Spain\textsuperscript{(25)} and Italy\textsuperscript{(26)}, and in three cohort studies in women in the USA\textsuperscript{(27–29)} and pancreatic and prostate cancers in two Italian case–control studies\textsuperscript{(30,31)}.

This study examined the relation between the DII and endometrial cancer risk in an Italian case–control study\textsuperscript{(32)}, in order to test the hypothesis that a pro-inflammatory diet, as indicated by higher DII values, is associated with an increased risk for developing endometrial cancer.

Methods
The study was conducted between 1992 and 2006 in three Italian areas, including the greater Milan area, the provinces of Udine and Pordenone in northern Italy and the urban area of Naples in southern Italy\textsuperscript{(32)}. Cases comprised 454 women (median age, 60 years; range, 18–79 years) with incident, histologically confirmed endometrial cancer (International Classification of Diseases, ninth edition, 182.0), admitted to major teaching and general hospitals of the study areas. Controls comprised 908 women (median age, 61 years; range, 19–80 years) admitted to the same hospital network as cases for a wide spectrum of acute non-neoplastic conditions. Women admitted for gynaecological or hormone-related conditions or for any medical condition related to long-term dietary changes were excluded. Controls were matched with cases by 5-year age groups and study centre, with a case:control ratio of 1:2. Of controls, 36 % were admitted for traumas, 32 % for other orthopaedic disorders, 9 % for acute surgical conditions and 23 % for other illnesses, including eye, nose, ear or skin disorders. Women with a history of hysterectomy were excluded from the control group. Less than 5 % of both cases and controls approached refused to be interviewed. All study participants signed an informed consent, according to the recommendations of the Institutional Review Boards of each study hospital.

Trained interviewers collected information on socio-demographic characteristics, anthropometric characteristics, lifestyle habits – including tobacco smoking and alcohol drinking – personal medical history and family history of gynaecological cancer, menstrual and reproductive factors, and OC and HRT use during their hospital stay using a structured questionnaire. There were few missing data (<1 %, as seen in Table 1); for these, we imputed values based on the most frequent category according to the subgroup to which they belonged. Subjects’ usual diet 2 years before cancer diagnosis or hospital admission (for controls) was assessed using an interviewer-administered FFQ, consisting of seventy-eight items on foods, including the most common Italian recipes, and five items on alcoholic beverages. Subjects were asked to indicate the average weekly frequency of consumption of each dietary item; intakes <1/week, but at least once a month, were coded as 0.5/week. Nutrient and total energy intake was determined using an Italian Food Composition Database. The FFQ showed reproducibility\textsuperscript{(33,34)} and satisfactory validity\textsuperscript{(35)} with Spearman’s correlation coefficients between 0.60 and 0.80 for most food items and nutrients.

Dietary information obtained from the FFQ was used to calculate DII\textsuperscript{(36)}. Briefly, on the basis of a search of the literature from 1950 to the end of 2010, we identified forty-five food parameters among foods, nutrients and other food components that were associated with six plasma inflammatory markers (IL-1β, IL-4, IL-6, IL-10, TNF-α and CRP). We defined a specific DII score for each food parameter on the basis of the literature review and by taking into account the quality and number of published papers (1943 articles were reviewed and scored).

For each study participant, the dietary data were first linked to a global database that was developed on the basis of eleven data sets from around the world and thus provides a robust estimate of the mean and the standard deviation of these forty-five parameters\textsuperscript{(36)}. Each subject’s exposure relative to the ‘standard global mean’ was expressed as a z-score that was derived by subtracting the ‘standard global mean’ from the amount reported and then dividing this value by its standard deviation. To minimise the effect of ‘right skewing’, this value was then converted to a centred percentile score. The subject’s DII score was computed by multiplying these values by the specific DII score for each food parameter and then summing together all these forty-five values according to the following formula, $DII = b_1 \times n_1 + b_2 \times n_2 + \ldots + b_{45} \times n_{45}$, where $b_i$ refers to the literature-derived inflammatory effect score for each of the evaluated food parameter and $n_i$ refers to the food parameter-specific centred percentile, which were derived from the dietary data, per each i from 1 to 45. A higher DII score indicates a more pro-inflammatory diet. The DII computed on this study’s FFQ includes data on thirty-one of the forty-five food parameters comprising the DII including carbohydrate, protein, fat, alcohol, fibre, cholesterol, SFA, MUFA, PUFA, n-3, n-6, niacin, thiamin, riboflavin, vitamin B6, Fe, Zn, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, β-carotene, anthocyanidins, flavanol, flavonol, flavonones, flavones, isoflavones, caffeine and tea. A flow chart of the DII methodology is shown in Fig. 1. Energy, which is one of the components of DII, was adjusted for in the analyses. The thirteen food parameters missing from this study are onions, garlic, trans-fat, saffron, turmeric, thyme/oregano, ginger, vitamin B12, Se, pepper, rosemary, egugenol and Mg. DII scores were analysed both by quartiles of exposure computed among controls and as a continuous variable of an increment corresponding to approximately 10 % of its range (5–49 to 4–67).

OR and the corresponding 95 % CI were estimated using conditional logistic regression models conditioned on study centre and quinquennia of age and adjusted for year of interview, years of education (<7, 7–11, ≥12 years, categorically), BMI (categorically, by quartiles), age at menarche (<12, 12–13, ≥14 years, categorically), menopausal status/age at menopause (pre/perimenopausal, <50, 50–54, ≥55 years, categorically), parity (0, 1, 2, 3, ≥3, categorically), history of diabetes (yes, no), family history of gynaecological cancers, OC use (never, ever) and HRT use (never, ever). Energy adjustment was made using the residual method, including also the term for total energy intake in the model\textsuperscript{(36)}. Stratified analyses were carried out according to age (<55, 55–69, ≥70 years), BMI (<25, ≥25 kg/m²), menopausal status (pre/peri and postmenopause), parity (0/≥1 birth), OC use (yes, no) and HRT use (yes, no). To test for heterogeneity across strata, interaction terms were used. Linear tests for trend were performed using the median value within each quartile as an ordinal variable. Statistical tests were performed using SAS® 9.3 (SAS Institute Inc.).
Results

The distribution of 454 endometrial cancer cases and 908 controls according to age, education and other selected variables is presented in Table 1. By design, cases and controls had the same age distribution. As compared with controls, cases had a higher BMI and a lower age at menarche, reported more frequently a history of diabetes, and were less frequently OC users, multiparous and more frequently HRT users. Cases and controls were comparable in terms of education and menopausal status.

The mean energy-adjusted DII value for this study was 1·16 (SD 1·45). Cases had a higher mean DII value (0·05 (SD 1·40))

Fig. 1. Sequence of steps in creating the dietary inflammatory index (DII) in the Italian endometrial case–control study. CRP: C-reactive protein.

A score for each food parameter was calculated giving:
+1 to each article if the effects were pro-inflammatory (significantly increased IL-1β, IL-6, TNF-α or CRP, or decreased IL-4 or IL-10).
–1 if the effects were anti-inflammatory (significantly decreased IL-1β, IL-6, TNF-α or CRP, or increased IL-4 or IL-10).
0 if the food parameter did not produce any significant change in the inflammatory marker.

The score for each food parameter was weighted according to the study design. The weights were 10 (experimental design), 8 (observational), 7 (case–control), 6 (cross-sectional), 5 (experimental with animals), 3 (cell culture).

A food parameter-specific overall inflammatory effect score was calculated by subtracting the anti-inflammatory fraction from the pro-inflammatory fraction. This score was corrected if the total weighted number of articles was <236. In these cases the raw overall inflammatory score is multiplied by the total weighted number of articles divided by 236.

14 food parameters were not included for this study.

Z-score and centred percentiles for each of the 31 food parameters for each participant of this study were calculated based on the average and standard deviation for each food parameter obtained from the global database that was created from the consumption of the original 45 food parameters from 11 countries from around the world.

The centred percentile for each food parameter was multiplied by the respective ‘overall food parameter-specific inflammatory effect score’ to obtain the ‘food parameter-specific DII score’.

All of the ‘food parameter-specific DII scores’ are summed to create the ‘overall DII score’ for each individual.
comparing with controls (−0.03 (95% CI −0.48)). Characteristics of
control subjects across quartiles of DII are provided in Table 2.
There were small, non-significant differences in socio-demographic
characteristics, anthropometric measures and hormone-related
factors across quartiles of DII.

Table 3 shows the distribution of ten food groups across
energy-adjusted DII quartiles among controls. Servings of fruit,
vegetables and coffee as well as various compounds including
fish decreased significantly across quartiles, whereas servings of pork,
sugar and desserts increased significantly.

Table 4 shows the OR of endometrial cancer for the highest
quartile of the DII (corresponding to approximately 10% of its range)
(OR 1.07; 95% CI 0.98, 1.17; P = 0.1), suggesting caution of
interpretation. When we further adjusted for tobacco smoking
and alcohol, the OR did not substantially change.

In Table 5, results are presented according to strata of
selected covariates. Apparently, stronger associations were
observed between DII and endometrial cancer among post-
menopausal women (ORQuartile 4 vs 1 1.57; CI 1.04, 2.38), parous
women (ORQuartile 4 vs 1 1.57; CI 1.05, 2.34) and non-HRT users
(ORQuartile 4 vs 1 1.63; CI 1.10, 2.39). These results should be
viewed with caution because of the absence of significant
heterogeneity. The P value for heterogeneity was 0.44 for age,
0.34 for BMI, 0.16 for menopausal status, 0.78 for parity and
0.70 for HRT.

Discussion

The present study, one of the largest case-control investigations
on diet and endometrial cancer to date in a southern European
population, shows positive associations between DII and
endometrial cancer. This result supports the hypothesis that
women with a pro-inflammatory diet have a higher risk for
developing endometrial cancer.

Previous results from this study indicate foods such as
vegetables and coffee as well as various compounds including
proanthocyanidins and β-carotene to be inversely related to endometrial cancer risk. All of these dietary factors contribute to lower DII values. Conversely, dietary patterns rich in animal products, starch and SFA, which contribute to higher DII values, were positively related to endometrial cancer risk. An anti-inflammatory diet – as reflected in lower DII scores – also contains foods that are rich in antioxidant vitamins, flavonoids and fibre. These nutrient-dense, low-energy-content components combine to help keep the BMI low. Thus, it may not be possible to disentangle these different aspects.

The positive relationship between DII and endometrial cancer is consistent with a body of evidence from studies...
examining the effect of various dietary components on endometrial cancer. These include observational studies indicating a modest positive association between high glycaemic load, but not glycaemic index, and endometrial cancer. A meta-analysis of case-control studies suggests that meat consumption, particularly red meat, increases endometrial cancer risk, whereas poultry, fish and eggs produce inconsistent associations. A protective role was observed for coffee consumption in endometrial cancer risk in the NIH-AARP study and endometrial cancer, but a direct association with preserved vegetable intake. The latest report from World Cancer Research Foundation on diet and endometrial cancer indicated a probable protective role of coffee and increased risk from glycaemic load. Additionally, in a simulated study, macronutrient and Mediterranean meal plans exhibited anti-inflammatory potential, based on the derived DII scores, whereas a fast food diet had a pro-inflammatory score.

Previous studies have shown inflammation to be associated with endometrial cancer. Results from the Women’s Health Initiative showed that CRP was positively associated with endometrial cancer. In a Canadian case-control study, endometrial cancer cases had consistently higher mean levels of TNF-α, IL-6 and CRP compared with controls in predominantly postmenopausal women. In a case-control study, nested within the European Prospective Investigation into Cancer and Nutrition, higher levels of pro-inflammatory cytokines (CRP, IL-6 and IL-1Ra) were associated with increased risk for endometrial cancer.

One of the possible mechanisms responsible for the observed positive association between the DII and endometrial cancer could be through the effect of pro-inflammatory diet on insulin resistance via increasing systemic inflammation.

### Table 4. Odds ratios of endometrial cancer for energy-adjusted quartiles of dietary inflammatory index (DII) among 454 cases and 908 controls (Italy, 1992–2006) (Odds ratios and 95% confidence intervals)

<table>
<thead>
<tr>
<th>Energy-adjusted DII quartiles</th>
<th>OR</th>
<th>95% CI</th>
<th>P_\text{trend}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases/controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;−1.07</td>
<td>1†</td>
<td>0.94, 1.82</td>
<td></td>
</tr>
<tr>
<td>−1.07, −0.08</td>
<td>1.31</td>
<td>0.94, 1.91</td>
<td></td>
</tr>
<tr>
<td>−0.07, 1.04</td>
<td>1.34</td>
<td>0.94, 1.92</td>
<td></td>
</tr>
<tr>
<td>&gt;1.04</td>
<td>1.46</td>
<td>1.02, 2.11</td>
<td></td>
</tr>
</tbody>
</table>

### Table 5. Odds ratios of endometrial cancer according to energy-adjusted quartiles of dietary inflammatory index (DII) among 454 cases and 908 controls in strata of selected covariates (Italy, 1992–2006) (Odds ratios and 95% confidence intervals)

<table>
<thead>
<tr>
<th>Case/controls</th>
<th>OR</th>
<th>95% CI</th>
<th>P_\text{trend}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55</td>
<td>126/252</td>
<td>1†</td>
<td>0.94, 2.22</td>
</tr>
<tr>
<td>55–69</td>
<td>247/494</td>
<td>1†</td>
<td>0.75, 1.97</td>
</tr>
<tr>
<td>≥70</td>
<td>51/162</td>
<td>1†</td>
<td>0.69, 7.25</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>131/420</td>
<td>1†</td>
<td>0.67, 2.24</td>
</tr>
<tr>
<td>≥25</td>
<td>323/486</td>
<td>1†</td>
<td>0.69, 2.21</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre/Perimenopause</td>
<td>87/179</td>
<td>1†</td>
<td>0.31, 1.76</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>367/772</td>
<td>1†</td>
<td>0.59, 2.06</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>68/126</td>
<td>1†</td>
<td>0.59, 2.06</td>
</tr>
<tr>
<td>≥1</td>
<td>386/782</td>
<td>1†</td>
<td>0.67, 2.19</td>
</tr>
<tr>
<td>HRT use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>49/78</td>
<td>1†</td>
<td>0.59, 2.10</td>
</tr>
<tr>
<td>No</td>
<td>405/830</td>
<td>1†</td>
<td>0.59, 2.10</td>
</tr>
</tbody>
</table>
Consumption of foods such as meat and butter have been shown to increase systemic inflammation by increasing levels of high-sensitivity CRP, E-selection and soluble vascular cell adhesion molecule-1 (55), which then are responsible for increasing insulin resistance (56, 57). Increasing insulin resistance then leads to increased circulating levels of insulin that has been demonstrated to play a role in the development of endometrial cancer by inhibiting apoptosis and stimulating cell proliferation (15) and by influencing the insulin-like growth factor axis, resulting in alterations in sex hormone metabolism (57). The association was apparently stronger in postmenopausal women, as for several reproductive and hormonal correlates of endometrial cancer (58). These results indicate a possible aetiological role of diet-associated inflammation, as indicated by the DII, in the development of endometrial cancer in scenarios where hormonal exposures are generally low.

With reference to possible sources of bias, dietary habits of hospital controls may differ from those of the general population (59). In this study, however, we excluded from the control group all diagnoses that might have involved any obvious connection to dietary intake or to health-related changes in diet. With reference to information bias, cases and controls were interviewed in similar settings, and data provided by hospital controls have shown satisfactory reproducibility (60). The nearly complete participation of cases and controls and the inclusion of acute conditions unrelated to diet in the comparison group mitigate against a major role of selection bias. Furthermore, awareness of dietary hypotheses in endometrial cancer aetiology was unlikely in this Italian population. Another limitation is the non-availability of the remaining thirteen food parameters for the DII calculation. DII scores calculated from these thirty-one food parameters have not been validated with inflammatory markers. However, in previous validation studies, DII scores have been calculated from food parameters ranging from seventeen to forty-four (17, 19). Moreover, there could be a possible overestimation due to the inclusion of food items in the DII calculation that are also a source of nutrients. It also should be noted, however, that each of these food items has an inflammatory effect score, which is derived from an extensive review of the literature looking at the association between these foods and inflammation. Among the strengths of our study were the large data set, the similar catchment areas across cases and controls and the satisfactory validity of information collected on dietary habits (33, 35). Also, the DII score, which takes into account both pro- and anti-inflammatory food parameters that characterise virtually all human diets, more accurately reflects the relationship of the inflammatory potential of diet to affect cancer risk than would nutrients considered individually.

In conclusion, this unique, large study on endometrial cancer and DII indicates a possible role of diet in endometrial cancer risk through the process of inflammation. Confirmatory results from other studies are required to establish this association.

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J. R. H. owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the dietary inflammatory index from the University of South Carolina in order to develop computer and smart phone applications for patient counselling and dietary intervention in clinical settings. N. S. is an employee of CHI. The subject matter of this paper has not had any direct bearing on that work, nor has that activity exerted any direct influence on this project.

The authors’ contributions were as follows: A.Z., M.M., C.L.V. and D.S. designed and conducted the case-control study, M.R. created the dataset for analyses, N.S. calculated DII and conducted all analyses and wrote the first draft of the manuscript, J.R.H., C.L.V., M.M., C.L.V., A.Z. and M.R. provided suggestions and reviewed the manuscript. All authors approved the final version of the manuscript.

There are no conflicts of interest.

References


