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

Nitin Shivappa1,2*, James R. Hébert1,2,3, Antonella Zucchetto4, Maurizio Montella5, Diego Serraino4, Carlo La Vecchia6 and Marta Rossi6
1Cancer Prevention and Control Program, University of South Carolina, Columbia, SC 29208, USA
2Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC 29208, USA
3Department of Family and Preventive Medicine, University of South Carolina School of Medicine, Columbia, SC 29208, USA
4SOC di Epidemiologia e Biostatistica, Centro di Riferimento Oncologico, Aviano (PN), 33081, Italy
5Dipartimento di Epidemiologia, ‘Fondazione G. Pascale’, Istituto Nazionale Tumori, Naples, 80133, Italy
6Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, 20133, Italy

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 (ORquartile 4 = 1.11; 95% CI 1.02, 2.11; Ptrend = 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(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(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(5–8), whereas chronic inflammation is a persistent state of low-grade inflammation(8). Various dietary components are known to modulate inflammation(9–11). Chronic inflammation is one of the major risk factors for development of several types of cancer(5,12), and considerable evidence has accumulated on the role of chronic inflammation in endometrial cancer(13–15). This more recent evidence is consistent with findings of Wynder et al.(13) 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(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 micronutrients. The DII has been validated with various inflammatory markers, including C-reactive protein (CRP) (17,18), IL-6(19,20) and homocysteine(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(21,22), anthropometric measurements of obesity in the PREDIMED trial in Spain(21), asthma in a case–control study in Australia(23), bone mineral density among postmenopausal women in Iran(24), colorectal cancer in two cancer case–control studies: Australia(25), and colorectal cancer in the Nurses’ Health Study(26), although data from the Nurses’ Health Study were not statistically significant(26).

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
Dietary inflammation and endometrial cancer

studies, in Spain\(^{(25)}\) and Italy\(^{(20)}\), and in three cohort studies in women in the USA\(^{(27–29)}\) and pancreatic and prostate cancers in two Italian case-control studies\(^{(30,31)}\).

This study examined the relation between the DII and endometrial cancer risk in an Italian case-control study\(^{(32)}\), 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\(^{(32)}\). 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, menopausal 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 and nutrients. 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\(^{(33,34)}\) and satisfactoriness\(^{(35)}\) 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\(^{(18)}\). 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\(^{(18)}\). 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 = \( b_1 \times x_1 + b_2 \times x_2 + \ldots + b_{45} \times x_{45} \), where \( b_i \) refers to the literature-derived inflammatory effect score for each of the evaluated food parameter and \( x_i \) 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, MUFAs, PUFAs, n-3, n-6, n-9, 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, eugenol 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/perimenopause, ≤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\(^{(18)}\). Stratified analyses were carried out according to age (<55, 55–69, ≥70 years), BMI (<25, ≥25 kg/m²), menopausal status (pre/per 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))
compared with controls (−0·03 (sd 1·48)). 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 vs the lowest energy-adjusted DII quartile and adjusted for all selected covariates. Significant positive associations were found: women in the fourth quartile of DII had an increased OR for endometrial cancer compared with women in the lowest quartile (ORQuartile 4 vs 1 1·46; 95% CI 1·02, 2·11; \( P_{\text{trend}} = 0·04 \)). A nearly significant positive association was observed when considering the DII as continuous OR for one unit increment 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 postmenopausal women (ORQuartile 4 vs 1 1·57; CI 1·05, 2·34) and non-HRT users (ORQuartile 4 vs 1 1·65; 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, 0·03 for parity and 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

| Table 1. Distribution of 454 endometrial cancer cases and 908 controls according to selected variables (Italy, 1992–2006) (Number of cases and controls and percentages) |
|-----------------|-----------------|-----------------|-----------------|
|                | **Cases**       | **Controls**    | **P**          |
| **Age (years)**| **n**           | **%**           | **n**           | **%**           |                      |
| <55            | 126             | 27·8            | 252             | 27·8            | <0·0001              |
| 55–69          | 247             | 54·4            | 494             | 54·4            |                      |
| ≥70            | 81              | 17·8            | 162             | 17·8            |                      |
| **Education (years)** |        |                  |                  |                  |                      |
| <7             | 263             | 57·9            | 553             | 60·9            | 0·57                 |
| 7–11           | 119             | 26·2            | 225             | 24·8            |                      |
| ≥12            | 72              | 15·9            | 130             | 14·3            |                      |
| **BMI (kg/m²)**        |                  |                  |                  |                  |                      |
| <25            | 131             | 28·9            | 420             | 46·3            | <0·0001              |
| ≥25            | 323             | 71·1            | 484             | 53·7            |                      |
| **Age at menarche (years)** |      |                  |                  |                  |                      |
| <12            | 100             | 22·0            | 142             | 15·6            | 0·0002               |
| 12–13          | 207             | 45·6            | 376             | 41·4            |                      |
| ≥14            | 145             | 32·4            | 383             | 43·0            |                      |
| **Menopausal status** |                  |                  |                  |                  |                      |
| Pre/perimenopause | 85             | 19·2           | 174             | 19·3            |                      |
| Postmenopause   | 358             | 80·8            | 726             | 80·7            |                      |
| **Parity**     |                  |                  |                  |                  |                      |
| 0              | 68              | 15·0            | 126             | 13·9            |                      |
| 1              | 92              | 20·3            | 150             | 16·5            |                      |
| >1             | 294             | 64·7            | 632             | 69·6            |                      |
| **History of diabetes** |            |                  |                  |                  | 0·0002               |
| No             | 401             | 88·3            | 854             | 94·0            |                      |
| Yes            | 53              | 11·7            | 54              | 6·0             |                      |
| **Oral contraceptive use** |      |                  |                  |                  | 0·13                 |
| Never          | 408             | 89·9            | 790             | 87·0            |                      |
| Ever           | 46              | 10·1            | 118             | 13·0            |                      |
| **Hormone replacement therapy** |      |                  |                  |                  | 0·19                 |
| Never          | 405             | 89·2            | 830             | 81·4            |                      |
| Ever           | 49              | 10·8            | 78              | 8·6             |                      |
| **Smoking**    |                  |                  |                  |                  | 0·81                 |
| Non-smoker     | 331             | 72·9            | 646             | 71·2            |                      |
| Ex-smoker      | 48              | 10·6            | 104             | 11·5            |                      |
| Current smoker | 75              | 16·5            | 157             | 17·3            |                      |

* The sum does not add up to the total because of some missing.
endometrial cancer risk \((32,37)\) anti-inflamatory factors are involved. Conversely, dietary patterns rich in animal products, starch and SFA, which contribute to higher DII values \((16)\). This is consistent with a body of evidence from studies indicating that diets low in animal products, and high in fruits and vegetables, are associated with lower endometrial cancer risk \((32,37)\). All of these dietary factors contribute to lower DII values \((16)\). Conversely, dietary patterns rich in animal products, starch and SFA, which contribute to higher DII values \((16)\), were positively related to endometrial cancer risk \((32,37)\). 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 \((43)\). 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 a simulated study, and in the PLCO (Prostate, Lung, Colorectal and Ovarian Colorectal Cancer Screening Trial) cohort. A systematic review showed inverse associations between non-preserved vegetable intake 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 effect.

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.
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 (35), 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 (35, 55). 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.

Acknowledgements

This study was supported by the Italian Foundation for Research on Cancer and by the Italian Ministry of Health, General Directorate of European and International Relations.

N. S. and J. R. H. were supported by grant number R44DK103577 from the United States National Institute of Diabetes and Digestive and Kidney Diseases.

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 revised the manuscript. All authors approved the final version of the manuscript.

There are no conflicts of interest.

References

Dietary inflammation and endometrial cancer


