Association between dietary inflammatory index and prostate cancer among Italian men

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Abstract

Previous studies have shown that various dietary components may be implicated in the aetiology of prostate cancer, although the results remain equivocal. The possible relationship of inflammation derived from dietary exposures with prostate cancer risk has not been investigated. We examined the ability of a newly developed dietary inflammatory index (DII) to predict prostate cancer risk in a case–control study conducted in Italy between 1991 and 2002. A total of 1294 patients aged 75 years with incident, histologically confirmed carcinoma of the prostate served as cases. A total of 1451 subjects aged 75 years who were admitted to the same hospitals as cases for a wide spectrum of acute, non-neoplastic conditions served as controls. The DII was computed based on dietary intake assessed using a previously validated seventy-eight-item FFQ. Logistic regression models were used to estimate multivariable OR adjusted for age, study centre, years of education, social class, BMI, smoking status, family history of prostate cancer and total energy intake. Men with higher DII scores had a higher risk of prostate cancer when analysed using the DII as both continuous (OR 1.06, 95% CI 1.00, 1.13) and categorical, i.e. compared with men in the lowest quartile of the DII, men in the third and fourth quartiles were at elevated risk (ORQuartile 3 v.1 1.32, 95% CI 1.03, 1.69 and ORQuartile 4 v.1 1.33, 95% CI 1.01, 1.76; P trend = 0.04). These data suggest that a pro-inflammatory diet, as indicated by the increasing DII score, is a risk factor of prostate cancer in Italian men.

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

Inflammation is an important factor contributing to cancer(1,2), and considerable evidence for the role of chronic inflammation in prostate cancer is accumulating(3–5). While inflammation typically occurs as part of the body response to tissue insult/injury(2,6), chronic inflammation is a persistent condition in which tissue destruction and repair occur simultaneously(7,8). This involves the continuous recruitment of pro-inflammatory cytokines associated with increased blood flow to the injured tissue, due to histamine released by damaged mast cells(2).

A recent case–control study has shown that the levels of C-reactive protein are higher in men with prostate cancer than in those with benign prostatic hypertrophy(9), and the Melbourne Collaborative Cohort Study has reported higher levels of IL-6, a pro-inflammatory cytokine, among malignant prostate cancer cases compared with those with benign prostate disease(10). These data are consistent with the hypothesis that innate immunity and inflammation play a role in prostate cancer(11).

Diet represents a complicated set of exposures that often interact and whose cumulative effect modifies both inflammatory responses and health outcomes. Although several studies have been conducted, the relationship between diet and prostate cancer is still unclear(12,13). According to the Second Expert Report from the World Cancer Research Fund(14), foods containing lycopene and Se are protective

Abbreviation: DII, dietary inflammatory index.

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against prostate cancer, while diets high in Ca increase its risk. A positive association between elevated intake of meat(12,15,16) and milk and dairy products(17–20) with the risk of prostate cancer has been observed. Conversely, an inverse association has been found for vegetable intake, but the results have been inconsistent(21–24). The possible relationship between inflammation derived from dietary exposure and the risk of prostate cancer has not been investigated.

The paucity of research related to diet and inflammation is probably due to logistic issues resulting from methodological complexity involved in linking diet, inflammation and cancers in the same study. In an effort to fill this methodological gap, researchers at the University of South Carolina’s Cancer Prevention and Control Program developed a dietary inflammatory index (DII), which can be used in diverse populations in order to predict the levels of inflammatory markers and related health outcomes(25,26). The development of the DII involved careful review and scoring of the scientific literature on diet and inflammation, and obtaining of datasets from around the world for comparison with dietary intakes of individuals(25,26). Thus far, the DII has been found to be associated with inflammatory cytokines including C-reactive protein and IL-6(26–28), the glucose-intolerance component of the metabolic syndrome, increased odds of asthma and reduced forced expiratory volume in 1 min (FEV1), shift work and colorectal cancer (CRC) among women from the Iowa Women’s Health Study(27–29).

The purpose of the present study was to examine the association between the DII and the risk of prostate cancer in a case–control study conducted in Italy. A previous case–control study was conducted in Italy. A previous case–control study has been found for vegetable intake, but the results have been inconsistent(21–24). The possible relationship between inflammation derived from dietary exposure and the risk of prostate cancer has not been investigated.

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years of education; BMI; smoking status; family history of prostate cancer. To understand the dietary profile of each quartile of the DII, we examined the distribution of various food groups across the quartiles of the DII. An ANOVA was used to test for the differences among the dietary groups. We estimated the OR and the corresponding 95% CI using logistic regression models, adjusted for age, study centre, years of education, social class, BMI, smoking status, family history of prostate cancer, and total energy intake\(^{[38]}\). The covariates were chosen \textit{a priori} as they have been previously shown to be the risk factors of prostate cancer. Tests for linear trend were performed using the median value of each quartile as an ordinal variable. Statistical tests were performed using SAS\(^{R, 9.3}\) (SAS Institute, Inc.). All \(P\) values were two-sided.

### Results

The distribution of prostate cancer cases and controls according to age, years of education, and other selected variables is presented in Table 1. The cases were somewhat older than the controls (>50 \(v. \leq 50\) years; OR 2.3, 95% CI 1.3, 4.3), were more highly educated (>12 years of education \(v. <7\) years of education: OR 1.9, 95% CI 1.5, 2.3), had a higher social class (lower \(v.\) higher: OR 2.4, 95% CI 1.7, 3.0), and more often reported a first-degree relative with prostate cancer (family history of prostate cancer \(v.\) no family history OR 3.9, 95% CI 2.5, 5.8). No differences in the BMI level were observed between cases and controls. All factors were included in the analysis.

Small differences were observed in sociodemographic characteristics, anthropometric measures and lifestyle habits across the quartiles of the DII (data not shown). However, current smokers were more frequently in the higher quartiles of the DII than in the lower quartile, i.e. 32% of those in the highest quartile \(v.\) 26% of the controls in the lowest quartile. There were fewer men who were overweight or with a family history of prostate cancer in the higher quartiles of the DII.

Concerning the distribution of various food groups, there was a significant reduction in the consumption of vegetables, fruits, poultry and fish, and a significant increase in the consumption of pork, sugars, cheese and bread across the quartiles of the DII (Table 2). The OR and corresponding 95% CI of prostate cancer according to the quartiles of the DII are shown in Table 3. In the age-adjusted models, no meaningful association was found between the DII and the risk of prostate cancer. However, in multivariable analysis, significant positive associations were found, with an OR of 1.06 (95% CI 1.00, 1.13) for a one-unit increment in the DII (corresponding to approximately 7% of its global range).\(^{[43]}\) In the analysis using the DII expressed as quartiles, a significant trend of increasing risk (\(P_{\text{trend}} = 0.04\)) was found; however, there was some indication of flattening in the last two quartiles (OR\(_{\text{Quartile 3}}\) 1.32, 95% CI 1.03, 1.69 and OR\(_{\text{Quartile 4}}\) 1.33, 95% CI 1.01, 1.76) when compared with men in the lowest quartile of the DII.

### Discussion

The present study, being one of the largest case–control investigations on diet and prostate cancer to date in a southern European population, shows a positive association between the DII and the risk of prostate cancer with statistically significant risk estimates for the DII expressed as a continuous variable and for men in the third and fourth quartiles of the DII (\(v.\) the first quartile). However, there was a levelling of risk across the two highest quartiles. We also observed a reduction in the consumption of healthy food items such as vegetables, fruits and fish, and an increase in the consumption of unhealthy food items such as pork, cheese and sugars, with increasing DII scores. This result supports the hypothesis that men who consume a pro-inflammatory diet are at a higher risk of developing prostate cancer.\(^{[11]}\)

Various dietary factors exert an array of effects on prostate cancer; some of these are pro-inflammatory (e.g. meat intake\(^{[41]}\)) and some are anti-inflammatory (e.g. isoflavone\(^{[37]}\) and soya\(^{[38]}\) intake). The positive association of the DII with the risk of prostate cancer found in the present case–control study is of specific interest. One of the possible mechanisms responsible for this association is the effect of the pro-inflammatory diet on systemic inflammation and...
apo
tosis, stimulating cell proliferation (41) and influencing the insulin-like growth factor axis with consequent alterations in sex hormone metabolism. Along this line, a diet high in glycerol, which has been demonstrated to play a role in the development of prostate cancer by inhibiting hyperinsulinaemia, also, a diet rich in pro-inflammatory constituents, such as saturated fat, causes proliferation, inflammation and oxidative stress that can lead to benign prostatic hyperplasia, prostatitis, and possibly cancer of the prostate (43).

The influence of diet on prostate cancer is difficult to evaluate, and challenges in dietary exposure assessment are greatest in other food constituents; thus, the DII score, which takes into account both categories of dietary exposure, more accurately reflects the relationship of diet with the risk of cancer than other food constituents; thus, the DII score, which takes into account both categories of dietary exposure, more accurately reflects the relationship of diet with the risk of cancer than population ones (36). Furthermore, the cases and controls were selected from the same catchment areas, the participation rate was high, particular attention was paid to exclude hospital-derived controls should be less prone to information bias than cohort studies (36), several factors argue in support of the validity of the present investigation. Dietary information was elicited using a valid and reproducible FFQ (32–34), which was comprehensive enough to allow adjustment for total energy intake. This was administered to cases and controls by the same interviewers under similar conditions. To minimise any recall bias due to the onset or treatment of the disease, individuals were asked about food intake in the 2 years before the interview. The potential bias in the recall of food intake, however, should be limited in Italy, because the diet and prostate cancer issue has not had widespread interest. Also, controls were selected from the same hospital system as the cases and therefore are more likely to be subject to similar sorts of recall bias. Indeed, hospital-derived controls should be less prone to information bias than population ones (36). Furthermore, the cases and controls were selected from the same catchment areas, the participation rate was high, particular attention was paid to exclude from the control group diseases potentially linked to the diet and long-term dietary modifications, and major confounding factors of prostate cancer were accounted for.

### Table 2. Distribution of food groups across quartiles of the dietary inflammatory index (DII) in the study conducted in Italy between 1991 and 2002

<table>
<thead>
<tr>
<th>Food groups</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All vegetables</td>
<td>16·21 (6·30)</td>
<td>13·17 (5·12)</td>
<td>10·67 (4·56)</td>
<td>7·88 (5·55)</td>
<td>&lt; 0·0001</td>
</tr>
<tr>
<td>Raw vegetables</td>
<td>11·75 (5·92)</td>
<td>9·48 (4·78)</td>
<td>7·67 (4·28)</td>
<td>5·83 (3·53)</td>
<td>&lt; 0·0001</td>
</tr>
<tr>
<td>Cooked vegetables</td>
<td>4·46 (2·35)</td>
<td>3·68 (2·18)</td>
<td>3·01 (1·77)</td>
<td>2·05 (1·44)</td>
<td>&lt; 0·0001</td>
</tr>
<tr>
<td>Fruits</td>
<td>23·20 (10·77)</td>
<td>18·93 (9·11)</td>
<td>14·72 (7·92)</td>
<td>10·46 (7·41)</td>
<td>&lt; 0·0001</td>
</tr>
<tr>
<td>Red meat</td>
<td>4·20 (2·39)</td>
<td>4·50 (2·29)</td>
<td>4·51 (2·33)</td>
<td>4·13 (2·25)</td>
<td>0·57</td>
</tr>
<tr>
<td>Pork</td>
<td>2·45 (1·93)</td>
<td>2·61 (2·02)</td>
<td>2·83 (2·15)</td>
<td>2·76 (2·29)</td>
<td>0·002</td>
</tr>
<tr>
<td>Poultry</td>
<td>1·85 (1·41)</td>
<td>1·90 (1·36)</td>
<td>1·74 (1·26)</td>
<td>1·56 (1·29)</td>
<td>&lt; 0·0001</td>
</tr>
<tr>
<td>Sugars</td>
<td>34·52 (37·03)</td>
<td>42·51 (37·75)</td>
<td>49·33 (49·67)</td>
<td>48·09 (47·54)</td>
<td>&lt; 0·0001</td>
</tr>
<tr>
<td>Artificial sweeteners</td>
<td>1·65 (6·43)</td>
<td>1·71 (7·93)</td>
<td>1·24 (5·12)</td>
<td>1·73 (7·39)</td>
<td>0·83</td>
</tr>
<tr>
<td>Fish</td>
<td>2·04 (1·27)</td>
<td>1·79 (0·99)</td>
<td>1·73 (1·01)</td>
<td>1·45 (1·00)</td>
<td>&lt; 0·0001</td>
</tr>
<tr>
<td>Cheese</td>
<td>3·87 (2·12)</td>
<td>4·68 (2·81)</td>
<td>4·72 (2·93)</td>
<td>4·86 (3·3)</td>
<td>&lt; 0·0001</td>
</tr>
<tr>
<td>Milk</td>
<td>6·09 (6·12)</td>
<td>6·17 (6·17)</td>
<td>5·76 (6·58)</td>
<td>6·10 (6·90)</td>
<td>0·71</td>
</tr>
<tr>
<td>Bread</td>
<td>19·21 (10·50)</td>
<td>22·83 (12·40)</td>
<td>24·38 (14·22)</td>
<td>23·12 (14·79)</td>
<td>&lt; 0·0001</td>
</tr>
</tbody>
</table>

* P values were obtained from ANOVA.

### Table 3. Odds ratios of prostate cancer according to quartiles of the dietary inflammatory index (DII), among 1294 cases and 1451 controls, in the study conducted in Italy between 1991 and 2002

<table>
<thead>
<tr>
<th>DII quartile cut-points (median)</th>
<th>OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1·98 (&lt; 2·61)</td>
<td>315</td>
<td>95 % CI</td>
</tr>
<tr>
<td>1·98–3·39 (1·39)</td>
<td>363</td>
<td></td>
</tr>
<tr>
<td>0·48 (0·20)</td>
<td>383</td>
<td></td>
</tr>
<tr>
<td>&gt; 0·49 (1·44)</td>
<td>388</td>
<td></td>
</tr>
</tbody>
</table>

* Continuous OR for a one-unit increment in the DII, corresponding to approximately 7 % of its global range.

† Adjusted for age, study centre, BMI, years of education, social class, smoking status, family history of prostate cancer, and total energy intake.
It also should be made clear that not all of the forty-five food parameters mentioned in the study on the development of the DII (25) were used for the calculation of the DII. For the current DII calculation, we used the data from thirty-two food parameters, and most of these had article weights of >236 (indicating optimal confidence in the evidence base). However, we do understand that about half of the food parameters had article weights below the median level of 236. Many of these food parameters were not studied extensively in the current scenario. These include foods such as rosemary, thyme and oregano that are consumed in relatively small amounts. Hence, we feel that there is no immediate need to update the literature review; however, we may consider updating in the future.

The regionally representative database was created to include dietary consumption of the forty-five food parameters from eleven countries. These eleven countries were selected from different regions of the world, in order to obtain a wide spectrum of consumption of these food parameters. The countries included are the USA, Mexico, England, Denmark, India, Australia, New Zealand, Bahrain, Scotland, South Korea and Japan (25). So, the mean values of the food parameters from this database should be representative of the average consumption of these parameters across the world. Notwithstanding the limitations of case–control studies in general, we believe that our findings of a positive association of the DII with the risk of prostate cancer are plausible and could be related to immune and hormonal factors (34,35,41).

In conclusion, this uniquely large study on prostate cancer and the DII conducted in a southern European population indicates a possible role of diet in prostate cancer risk through the process of inflammation. However, confirmatory results from other studies conducted in different populations with different study designs are required to truly establish this association.

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The authors’ contributions are as follows: N. S. computed the dietary inflammatory index, contributed to the design of the analyses, led statistical analyses, interpreted results and wrote initial drafts of the manuscript; C. B. helped with the design and implementation of the study, data management, consulted on statistical analyses, interpretation of results of statistical analyses, and writing and revising of the manuscript; A. Z., M. M., D. S. and C. L. V. contributed to the study design, data collection, data interpretation, and revision of the manuscript; J. R. H. invented the dietary inflammatory index, helped to design statistical analyses, interpreting results of statistical analyses, and writing of the manuscript.

The authors declare that there are no conflicts of interest.

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