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# Dietary inflammatory index and risk of bladder cancer in a large Italian case-control study

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## Abstract

**Objective—**To evaluate the association between diet in relation to its inflammatory property and bladder cancer (BC) risk .

**Methods—**In this study we explored the association between the dietary inflammatory index (DII) and BC risk in an Italian case-control study conducted between 2003 and 2014. Cases were 690 patients with incident, histologically confirmed cases of BC from 4 areas in Italy. Controls were 665 cancer free subjects admitted to the same network of hospitals as cases for a wide spectrum of acute, non-neoplastic conditions. The DII was computed based on dietary intake assessed using a reproducible and valid 80-item food frequency questionnaire. Odds ratios (OR)

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**Disclosure:** Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the dietary inflammatory index (DII) from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. Dr. Nitin Shivappa is an employee of CHI.

were estimated through logistic regression models adjusting for age, sex, total energy intake, and other recognised confounding factors.

**Results—**Quartile 4 (DII=0.41, 4.58; cases=207) had higher number of participants compared to quartile1 (DII=−5.94, −2.41; cases=124) Subjects in the highest quartile of DII scores (i.e., with a more pro-inflammatory diet) had a higher risk of BC compared to subjects in the lowest quartile (i.e., with an anti-inflammatory diet) ($OR_{Quartile4vs1}$= 1.97, 95% confidence interval, 1.28, 3.03; *p*-trend=0.003). Stratified analyses produced stronger associations between DII and BC risk among females ($OR_{Quartile4vs1}$= 5.73; 95%CI=1.46, 22.44), older ≥65 years ($OR_{Quartile4vs1}$= 2.45; 95%CI=1.38, 4.34), subjects with higher education ≥7 years ($OR_{Quartile4vs1}$= 2.22; 95%CI=1.27, 3.88) and never smokers ($OR_{Quartile4vs1}$= 4.04;95%CI=1.51, 10.80).

**Conclusion—**A pro-inflammatory diet as indicated by higher DII scores is associated with increased BC risk.

### Keywords

Bladder Cancer; Dietary Inflammatory Index; Epidemiology; Risk Factor

## Introduction

Bladder cancer (BC) is the 9th most common cancer worldwide, [1] the 6th most common cancer worldwide in men and the 19th most common cancer in women, with approximately 38 000 deaths per year in the European Union.[1, 2] Major recognized risk factors for BC are tobacco smoking, and past occupational exposure to aromatic amines.[2]

Considerable evidence has been gathered over the past few years linking increased cancer risk with chronic inflammation, and several clinical and experimental studies have linked tumour progression with the upregulation of pro-inflammatory molecules, especially during late stages of the disease.[3] In addition to chronic inflammation, intrinsic properties of premalignant cells and other determinants promote tumour initiation and promotion.[4] Evidence from developed countries shows substantial evidence on the role of chronic inflammation in urological cancers, including BC.[5]

Dietary components such as fruits, vegetables and coffee have been studied in relation to incident BC in various studies.[6, 7] Dietary patterns characterizing the Western-type diet; i.e., including high consumption of red meat, high-fat dairy products, and refined grains, have been associated with higher levels of c-reactive protein (CRP), interleukin-6 (IL-6), and fibrinogen.[8] On the other hand, the Mediterranean diet –characterized by a high consumption of whole-grains, fruit and green vegetables, fish, and olive oil, a low consumption of red meat and butter, and a moderate alcohol and dairy products consumption – has been associated with lower levels of inflammation.[9] Despite the circumstantial evidence, the possible relation between inflammation deriving from dietary exposure and BC risk has been investigated widely.

The literature-derived dietary inflammatory index (DII) was developed to assess the inflammatory potential of an individual's diet.[10] Higher DII scores indicate increasing

inflammatory potential of diet. The DII has been validated with various inflammatory markers, including CRP,[11] IL-6,[12] and tumor necrosis factor.[12]

The DII has been associated with a variety of cancers, including urological cancers, such as prostate, [13, 14] colorectal,[15] esophageal,[16] and breast.[17]. DII and urothelial cancer association has been explored in one Australian prospective study before.[18] This large case-control study conducted in Italy,[19, 20] provides us the opportunity to examine the association between DII scores and BC risk. Our working hypothesis is that increasing inflammatory potential of diet is associated with increased risk of BC.

## Methods

### Design and Participants

Between 2003 and 2014, we conducted a case-control study on BC in 4 Italian centres: Aviano and Milan (in Northern Italy), and Naples and Catania (in Southern Italy).[19, 20] Controls were patients admitted to the same network of hospitals as cases for a wide spectrum of acute, non-neoplastic conditions unrelated to tobacco smoking and alcohol consumption or long-term diet modification (e.g., bronchitis, myocardial infarction). Overall, 28.9% of controls were admitted for traumas, 22.1% for non-traumatic orthopaedic disorders, 39.3% for acute surgical conditions, and 9.8% for other miscellaneous illnesses. The study protocol was approved by the Institutional Ethics Committees of each of the hospitals, and all subjects signed an informed consent..

Centrally trained and supervised interviewers collected information on socio-demographic characteristics, anthropometric measures, lifestyle habits, including tobacco smoking, and history of selected diseases during their hospital stay using a structured questionnaire. Each subject's usual diet during the 2 years prior to cancer diagnosis (for cases) or hospital admission (for controls) was assessed using an interviewer-administered food frequency questionnaire (FFQ), consisting of 80 items on foods items and 15 (alcoholic and non-alcoholic) beverages. Subjects were asked to indicate the weekly average frequency of consumption of each dietary item; intakes lower than once a week, but at least once a month, were coded as 0.5 per week. Nutrient and total energy intake was determined using an Italian food composition database. [21] The FFQ showed a satisfactory validity [22] and reproducibility.[23]

Details of the steps involved in DII calculation is described elsewhere.[12,25] In order to compute the DII score, dietary information for each study participant were first linked to the regionally representative database that provided a robust estimate of a mean and a standard deviation for each of the 45 parameters (i.e., foods, nutrients, and other food components) considered in the DII definition.[10] These parameters then were used to derive the subject's exposure relative to the standard global mean as a z-score, derived by subtracting the mean of the regionally representative database from the amount reported, and dividing this value by the parameter's standard deviation. To minimize the effect of "right skewing", this value was converted to a centred percentile score, which was computed by doubling the raw percentile score and then subtracting 1. This score was then multiplied by the respective food parameter effect score (derived from a literature review on the basis of 1943

articles).[10, 24] All of these food parameter-specific DII scores were then summed to create the overall DII score for every subject in the study. Higher scores indicate a pro-inflammatory diet while lower scores indicate a more anti-inflammatory diet. The DII computed on this study's FFQ includes data on 31 of the 45 possible food parameters comprising the DII: carbohydrates, proteins, fats, alcohol, fibers, cholesterol, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, omega 3, omega 6, niacin, thiamin, riboflavin, vitamin B6, iron, zinc, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, beta carotene, anthocyanidins, flavan3ols, flavonols, flavanones, flavones, isoflavones, caffeine, and tea.

The DII was analysed as continuous and by quartiles computed among controls. Odds ratios(ORs) and the corresponding 95% confidence intervals (CIs) were estimated using unconditional logistic regression models including terms for age (quinquennial), sex, year of interview, study centre, education (<7; 7-11; ≥12 years), tobacco smoking (never; former; current: <15; 15-24, ≥25 cigarettes/day), and total energy intake (quintiles of the distribution of the controls).We further adjusted for the most frequent weekly occupational exposure to carcinogens in our study (i.e., aromatic amines, ammonia, sulfuric acid or hydrochloric, tar, pitch, asphalt, and soot, mineral oils and lubricants, gasoline, diesel engine fumes, foundry fumes, aluminum powder, concrete, lead, benzene, and other solvents) and selected diseases (i.e., diabetes, hypercholesterolemia, and obesity); however, the estimates did not change materially; thus, these factors were not included in the final, most parsimonious, model. Tests for linear trend were performed using the median value within each quartile as an ordinal variable. Stratified analyses were carried out according to sex, age (<65, ≥65 years), education (<7, ≥7 years) and tobacco smoking (never smokers, and ever smokers), and heterogeneity across strata was tested computing the difference in the -2 log likelihood of the models with and without the interaction terms. Statistical analyses were performed using SAS® 9.3 (SAS Institute Inc., Cary, NC).

## Results

Cases were 690 patients aged 25–80 years (median 67 years) with incident BC (mostly transitional cell carcinoma), admitted to major general hospitals in the study areas. Nearly all BCs (n=642, 93.0%) were confirmed histologically on tumour tissue specimen from biopsy or surgery, while three additional cases were confirmed by cytology. Overall, 460 patients (66.7%) were non-muscle-invasive (NMIBC, TNM pTis/Ta/T1) and 159 (23.0%) were muscle-invasive (MIBC, other T) BCs; 307 (44.5%) were well-differentiated or low grade (G1, G2) and 312 (45.2%) were poorly differentiated or high grade (G3, G4). Stage and grade was undefined for 71 (10.3%) patients. The controls were 665 patients frequency-matched to cases by study centre, sex and 5-year age group (median age 66 years). The distribution of BC cases and controls according to selected factors is given in Table 1. Cases and controls had a similar distribution by study centre, sex, age, and education. Cases were more frequently smokers than controls.

The mean DII value was −0.63 (standard deviation, SD=1.94, range −5.42 to +4.48) among cases and −0.93 (SD=2.00, range −5.94 to +4.58) among controls, indicating a more pro-inflammatory diet for cases. Characteristics of control subjects across quartiles of DII are

provided in Table 2. There were significant differences in tobacco smoking across quartiles of DII. Subjects in the highest quartile of DII were more likely to be current smokers.

Table 3 shows OR of BC and 95% CI according to continuous and quartiles of DII score. When used as a continuous exposure, one-unit increase in DII score was associated with increased odds for BC ($OR_{Continuous}$= 1.11, 95% CI=1.03, 1.20), and when used as quartiles subjects in the highest DII score quartiles had 97% increased odds for BC compared to subjects in the lowest quartile ($OR_{Quartile4vs1}$= 1.97, 95% CI=1.28, 3.03; *p*-trend=0.003).

Table 4 shows ORs of BC in strata of selected covariates. A stronger association was observed among females ($OR_{Quartile4vs1}$= 5.73, 95% CI 1.46, 22.44), than males ($OR_{Quartile4vs1}$= 1.83, 95% CI 1.14, 2.91) (*p* value for interaction 0.002), although the former estimate was based on many fewer cases and controls (24 cases and 28 controls in the highest quartile). Stronger associations – although in the absence of significant heterogeneity (*p* values >0.10) – were observed among subjects aged ≥65years ($OR_{Quartile4vs1}$= 2.45, 95% CI 1.38, 4.34), education ≥7 years ($OR_{Quartile4vs1}$= 2.22, 95% CI 1.27, 3.88), and never smokers ($OR_{Quartile4vs1}$= 4.04, 95% CI 1.51, 10.80). We also performed analysis separated by NMIBC and MIBC patients, and found DII to be associated with both NMIBC ($OR_{Quartile4vs1}$= 1.92, 95% CI: 1.19, 3.08) and MIBC ($OR_{Quartile4vs1}$= 2.42, 95% CI: 1.18, 4.93). When we performed separated analysis by grade, we found DII to be associated with both grade 1 BC ($OR_{Quartile4vs1}$= 1.79, 95% CI: 1.04, 3.09) and grade 2 BC ($OR_{Quartile4vs1}$= 2.13, 95% CI: 1.24, 3.67).

## Discussion

This large multicentric Italian case-control study is the first attempt to investigate the association between inflammatory potential of diet and BC. We observed a two-fold excess risk of BC among individuals with a pro-inflammatory diet as expressed by high DII scores

High consumption of fruit and vegetables may reduce BC risk whereas high coffee consumption is inconsistently related to the increased risk of BC .[6, 7] Fruits and vegetables are rich in various vitamins such as thiamin, niacin, vitamin E and carotenoids, which have anti-inflammatory effects and therefore contribute to lower DII scores.[10] In a large European cohort study, consumption of carotenoids, such as beta-carotene, was found to reduce the risk of BC.[25] In a prospective study conducted in Australia, increasing DII was observed to have a non-significant association with urothelial cancer.[18]

We observed a stronger association between DII scores and BC among non-smokers in this study. It is known that tobacco is a strongly pro-inflammatory agent.[26] It could be that among smokers, or people exposed occupationally to pro-inflammatory carcinogens (or both) the pro-inflammatory state induced by smoking, or occupational carcinogens, overwhelms the countervailing anti-inflammatory effects of diet,[27] further research should be conducted to explore this mechanism. It is important to note, however, that heterogeneity across strata of tobacco smoking was non-significant.

A significant positive association between DII and BC risk was observed in both men and women; however, the association was stronger in women. Although women had a lower rate

of smoking than men, tobacco use was accounted for in the analyses. Women also tend to have lower occupational exposures to workplace carcinogens,[28] and this may help to explain the much lower BC incidence in women than men. At this juncture, there is no simple and satisfactory explanation for the stronger effect of the DII seen in women.

One of the possible mechanisms through which the observed positive association between DII and BC could occur is through oxidative and nitrative DNA damage in stem cells caused by chronic inflammation.[29] Diet-related chronic inflammation plays a role in the upregulation of various cytokines such as tumour growth factor-b and IL-6 that, in turn, promote cell transformation, survival, proliferation of tumour cells, and metastasis.[30]

This hospital-based case-control study shares some of the limitations of such designs. Potential recall bias is possible; however, the comparability of recall between cases and controls was improved by interviewing all subjects in a hospital setting. As for selection bias, the study was hospital-based, but cases and controls were interviewed in the same hospital setting, came from comparable catchment areas, and their participation was comparable and almost complete. In addition, awareness about any particular dietary hypothesis in BC aetiology was limited in the Italian population. Among the strengths of this study are its large size and the use of a reproducible [23] and valid [22] FFQ. Also, the DII score, which takes into account both pro- and anti-inflammatory food parameters that characterize human diet, more accurately reflects the relationship of the inflammatory potential of diet to affect cancer risk than would single nutrients or diet components considered individually.

In conclusion, this study indicates a detrimental role of a pro-inflammatory diet, as measured by higher DII scores, on BC risk through a process of inflammation. These results have to be established in further studies to confirm this association.

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## Table 1

Distribution of 690 cases of bladder cancer and 665 controls according to centre, sex, age and other selected variables. Italy, 2003-2014.

| | Cases | | Controls | |
|---|---|---|---|---|
| | **No.** | **%** | **No.** | **%** |
| Centre | | | | |
| Pordenone | 242 | 35.1 | 250 | 37.6 |
| Milan | 241 | 34.9 | 238 | 35.8 |
| Naples | 129 | 18.7 | 100 | 15.0 |
| Catania | 78 | 11.3 | 77 | 11.6 |
| Sex | | | | |
| Men | 595 | 86.2 | 561 | 84.4 |
| Women | 95 | 13.8 | 104 | 15.6 |
| Age (years) | | | | |
| < 60 | 148 | 21.5 | 178 | 26.8 |
| 60-64 | 107 | 15.5 | 119 | 17.9 |
| 65-69 | 164 | 23.8 | 147 | 22.1 |
| 70-74 | 155 | 22.5 | 124 | 18.7 |
| ≥ 75 | 116 | 16.8 | 97 | 14.6 |
| Education (years)[a] | | | | |
| < 7 | 292 | 42.4 | 273 | 41.1 |
| 7 - 11 | 224 | 32.5 | 215 | 32.3 |
| ≥ 12 | 173 | 25.1 | 177 | 26.6 |
| Tobacco smoking[a] | | | | |
| Never smokers | 96 | 14.1 | 237 | 35.6 |
| Ex-smokers | 310 | 45.5 | 284 | 42.7 |
| Current smokers | | | | |
| < 15 cigarettes/day | 79 | 11.6 | 53 | 8.0 |
| 15-24 cigarettes/day | 127 | 18.7 | 68 | 10.2 |
| ≥ 25 cigarettes/day | 69 | 10.1 | 23 | 3.5 |

[a]The sum does not add up to the total because of some missing values.

## Table 2

Participants' characteristics across quartiles of dietary inflammatory index (DII) among 665 controls. Italy, 2003-2014.

| Characteristics | DII quartiles | | | | |
|---|---|---|---|---|---|
| | −5.94, −2.41 | −2.40,−0.92 | −0.91,0.41 | 0.42,4.58 | *p* value[a] |
| | No. (%) | No. (%) | No. (%) | No. (%) | |
| Sex | | | | | 0.15 |
| Male | 139 (83.7) | 135 (80.8) | 148 (89.7) | 139 (83.2) | |
| Female | 27 (16.3) | 32 (19.2) | 17 (10.3) | 28 (16.8) | |
| Age (years) | | | | | 0.66 |
| <60 | 37 (22.3) | 41 (24.6) | 52 (31.5) | 48 (28.7) | |
| 60-64 | 33 (19.9) | 30 (18.0) | 27 (16.4) | 29 (17.4) | |
| 65-69 | 44 (26.5) | 36 (21.6) | 38 (23.0) | 29 (17.4) | |
| 70-74 | 28 (16.9) | 34 (20.4) | 29 (17.6) | 33 (19.8) | |
| ≥75 | 24 (14.5) | 26 (15.6) | 19 (11.5) | 28 (16.8) | |
| Education (years) | | | | | 0.29 |
| <7 | 74 (44.6) | 70 (41.9) | 61 (37.0) | 68 (40.7) | |
| 7-11 | 53 (31.9) | 49 (29.3) | 65 (39.4) | 48 (28.7) | |
| >11 | 39 (23.5) | 48 (28.7) | 39 (23.6) | 51 (30.5) | |
| Tobacco smoking[b] | | | | | 0.007 |
| Never smokers | 63 (37.9) | 68 (40.7) | 54 (32.7) | 52 (31.1) | |
| Ex-smokers | 76 (45.8) | 71 (42.5) | 72 (43.6) | 65 (38.9) | |
| Current smokers | | | | | |
| <15 cigarettes/day | 17 (10.2) | 10 (5.9) | 13 (7.9) | 13 (7.8) | |
| 15-24 cigarettes/day | 9 (5.4) | 14 (8.4) | 21 (12.7) | 24 (14.4) | |
| ≥25 cigarettes/day | 1 (0.6) | 4 (2.4) | 5 (3.0) | 13 (7.8) | |

[a] *p* value for Chi-square test

[b] The sum does not add up to the total because of some missing values

## Table 3

Odds ratios (OR) of bladder cancer and corresponding 95% confidence intervals (CI) according to dietary inflammatory index (DII) among 690 cases and 665 controls. Italy, 2003-2014.

| | DII quartiles, OR (95% CI) | | | | *p* value for trend | DII continuous |
|---|---|---|---|---|---|---|
| | **−5.94, −2.41** | **−2.40, −0.92** | **−0.91,0.41** | **0.42,4.58** | | |
| Cases/Controls | 124/166 | 180/167 | 179/165 | 207/167 | | 690/665 |
| Model 1[a] | 1 [b] | 1.56 (1.11,2.17) | 1.64 (1.11, 2.35) | 2.11 (1.41, 3.14) | <0.0001 | 1.17 (1.08, 1.26) |
| Model 2[c] | 1 [b] | 1.46 (1.02, 2.08) | 1.46 (0.99, 2.14) | 1.97 (1.28, 3.03) | 0.003 | 1.11 (1.03, 1.20) |

[a]Adjusted for age, sex, year of interview, study centre, and total energy intake.

[b]Reference category.

[c]Model 1 additionally adjusted for education (<7; 7-11; ≥12 years), and tobacco smoking (never; former; current: <15; 15-24; ≥25 cigarettes/day).

## Table 4

Odds ratios (OR) of bladder cancer and corresponding 95% confidence intervals (CI) according to quartiles of dietary inflammatory index (DII), among 690 cases and 665 controls, in strata of selected covariates, Italy, 2003-2014.

| | Cases/ Controls | DII quartiles, OR (95% CI)[a] | | | | *p*trend | *p*interaction |
|---|---|---|---|---|---|---|---|
| | | **−5.94, −2.41** | **−2.40,−0.92** | **−0.91,0.41** | **0.42,4.58** | | |
| Sex | | | | | | | 0.002 |
| Male | 595/561 | 1 [b] | 1.39 (0.95, 2.03) | 1.12 (0.74, 1.70) | 1.83 (1.14, 2.91) | 0.03 | |
| Female | 95/104 | 1 [b] | 2.56 (0.83, 7.89) | 11.27 (3.23, 39.31) | 5.73 (1.46, 22.44) | 0.004 | |
| Age (years) | | | | | | | 0.59 |
| <65 | 255/297 | 1 [b] | 1.25 (0.70, 2.22) | 1.30 (0.71, 2.38) | 1.53 (0.79, 2.96) | 0.21 | |
| ≥65 | 435/368 | 1 [b] | 1.63 (1.04, 2.56) | 1.53 (0.92, 2.52) | 2.45 (1.38, 4.34) | 0.004 | |
| Education (years) | | | | | | | 0.88 |
| <7 | 292/273 | 1 [b] | 1.46 (0.84, 2.53) | 1.42 (0.77, 2.61) | 1.56 (0.77, 3.14) | 0.23 | |
| ≥7 | 397/392 | 1 [b] | 1.52 (0.95, 2.44) | 1.41 (0.85, 2.33) | 2.22 (1.27, 3.88) | 0.009 | |
| Tobacco smoking | | | | | | | 0.36 |
| Never smokers | 96/237 | 1 [b] | 1.42 (0.64, 3.14) | 3.06 (1.26, 7.44) | 4.04 (1.51, 10.80) | 0.003 | |
| Ever smokers | 585/428 | 1 [ba] | 1.58 (1.06, 2.34) | 1.41 (0.92, 2.15) | 1.96 (1.22, 3.15) | 0.01 | |

[a] Adjusted for age, sex, year of interview, study centre, education (<7; 7-11; ≥12 years), tobacco smoking (never; former; current: <15; 15-24; ≥25 cigarettes/day), and total energy intake, when appropriate.

[b] Reference category.