Nutrition 63–64 (2019) 205–210

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Dietary inflammatory index and cancer risk in the elderly: A pooled-analysis of Italian case-control studies

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ARTICLE INFO

Article History:
Received 12 October 2018
Received in revised form 17 January 2019
Accepted 11 February 2019

Keywords:
Dietary inflammatory index
Cancer risk
Mediterranean diet
Aging
Elderly

ABSTRACT

Objectives: The aim of this study was to evaluate whether the association between the inflammatory potential of one's diet and cancer risk varies across age groups in a population characterized by widespread use of the Mediterranean diet.

Methods: We analyzed data from a network of case-control studies conducted in Italy between 1991 and 2014. The studies included cancers of the oral cavity (n = 509), pharynx (n = 436), nasopharynx (n = 198), larynx (n = 459), esophagus (n = 304), stomach (n = 230), colon (n = 1225), rectum (n = 728), liver (n = 184), pancreas (n = 326), breast (n = 2569), endometrium (n = 454), ovary (n = 1031), prostate (n = 1294), kidney (n = 767), and bladder (n = 690). Controls were 13 563 patients hospitalized for acute, non-neoplastic conditions. Dietary inflammatory index (DII) scores were computed based on 31 food parameters assessed using a reproducible and validated food frequency questionnaire. Odds ratios were estimated through logistic regression models adjusting for recognized confounding factors.

Results: The DII increased with age, with lower scores among men than women, in individuals located in northern rather than in central or southern Italy, and in controls more than in cancer cases. After adjustment for cancer-specific potential confounders, an increasing DII score was directly associated with cancer risk for all considered cancer sites, except for liver and endometrium. Although the DII level varied across age groups, no heterogeneity in cancer risk emerged for any of the considered cancer sites.

Conclusions: In the Italian population, DII scores were higher in elderly than in middle-aged individuals. Although not directly affecting cancer risk, this finding may have important implications for the older population because elevated DII scores, indicating a proinflammatory diet, also have been associated with frailty.

Introduction

Cancer is one of the leading causes of death worldwide and dietary habits have been consistently associated with risk for several types of cancers [1]. In addition to the relationship between single foods or nutrients and cancer risk, several studies have attempted to evaluate the effect of the overall diet on cancer risk through dietary indexes. Each index assesses a specific aspect of the diet using information on food consumption, such as dietary patterns or

The original studies and data collection were partially supported by the Italian Association for Research on Cancer (AIRC) and Italian League Against Cancer (LILT). JRH owns controlling interest in Connecting Health Innovations LLC (CHI), a company that has lincesed the right to his invention of the dietary inflammatory index (DII) from the University of South Carolina to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. NS is an employee of CHI. The authors have no other conflicts of interest to declare.

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https://doi.org/10.1016/j.nut.2019.02.008
0899-9007/

adherence to healthy diets such as the Mediterranean diet. Among these indexes, the dietary inflammatory index (DII) aims to score the diet according to its potential to modulate inflammation [2]. The DII is a literature-derived tool validated in a variety of longitudinal and cross-sectional studies using various inflammatory markers, including C-reactive protein (CRP) [3], interleukin (IL)-6 [4], and tumor necrosis factor (TNF)-α [5]. Elevated DII levels have been consistently associated with increased risk for several cancers, with the exception of lung cancer [6].

Dietary habits change with age. The third Italian National Food Consumption survey [7] reported a decrease in total energy intake in the elderly (i.e., people ≥65 y of age) compared with those at younger ages. This decrease in energy intake was not paralleled by a substantial modification in contribution of proteins, fats, carbohydrates, and alcohol to total energy. Nonetheless, some changes in the intake of specific foods were observed [8]. This could modify specific aspects of diet, including its inflammatory potential.

Similarly, cancer risk is well known to increase with age [9]. Therefore, it is compelling to understand whether the association between DII scores and the risk for several types of cancers differs across age groups. Using data from a large series of case-control studies conducted in Italy, we investigated the association between DII scores and the risk for cancer at several sites across strata of age, with a focus on the older population. The DII has been successfully validated with low-grade inflammation in Italy [10], a country characterized by widespread use of the Mediterranean diet, and it has been shown to be associated with a reduced risk for various cancers in this population [6,11].

Materials and methods

Between 1991 and 2014, we conducted an integrated series of multicenter, case-control studies on various neoplasms to investigate the association between cancer risk and lifestyle factors, including dietary habits. These studies shared similar study protocol and similar questionnaires for lifestyle assessment. Patients were enrolled in different areas of northern (the greater Milan area; the provinces of Pordenone, Padua, Udine, and Forlì; the urban area of Genoa), central (the provinces of Rome and Latina), and southern (the urban area of Naples and Catania) Italy. All studies included incident cancer cases ≥18 y of age, identified in the major teaching and general hospitals of the study areas. Patients with incomplete dietary information for DII calculation were excluded (Table 1), thus leaving 509 cases of cancer of the oral cavity, 436 of the pharynx, 198 of the nasopharynx, 459 of the larynx, 304 of the esophagus, 230 of the stomach, 1225 of the colon, 728 of the rectum, 184 of the liver, 326 of the pancreas, 2569 of the breast, 454 of the endometrium, 1031 of the ovary, 1294 of the prostate, 767 of the kidney, and 690 of the bladder [12–14].

The original frequency-matched controls were used for comparison. Controls were individuals admitted to the same network of hospitals as cases for a wide spectrum of acute, non-neoplastic conditions unrelated to tobacco and alcohol consumption, to known risk factors for the corresponding cancer site, or to conditions associated to long-term diet modification. Overall, 8% of controls were admitted for traumatic conditions, 23% for non-traumatic orthopedic conditions, 32% for acute surgical conditions, and 37% for miscellaneous other illnesses. In each study, the refusal rate among both cases and controls were similar, ranging between 2% and 5%. Overall, 13 563 patients were enrolled as controls. Of these, 4622 had been included as controls in more than one study, for a total of 20 179 controls. All study participants signed an informed consent, according to the recommendations of the Board of Ethics of each study center approving the study.

Trained interviewers administered a structured questionnaire to cases and controls during their hospital stay. The questionnaire included information on sociodemographic indicators, tobacco smoking, alcohol drinking, dietary habits, and other lifestyle factors. In the study on liver cancer, cases and controls were screened in serum for infection with hepatitis B and hepatitis C [13]. A validated food frequency questionnaire (FFQ) was employed to assess the usual diet during the 2 y before diagnosis or at hospital admission for the controls. Briefly, the FFQ included 78 foods, food groups, or recipes divided into seven sections:

1. Milk, hot beverages, and sweeteners;
2. Bread, cereals, and first courses;
3. Second courses (e.g., meat and other main dishes);
4. Side dishes (i.e., vegetables);
5. Fruits;
6. Sweets, desserts, and soft drinks; and
7. Alcoholic beverages.

For vegetables and fruit subject to seasonal variation, consumption in season and the corresponding duration were elicited. Serving size was defined in "natural" units (e.g., 1 teaspoon of sugar, 1 egg) or as an average in the Italian diet. The FFQ was successfully tested for validity [15] and reproducibility [16]. Nutrient and total energy intake was determined using an Italian food composition database [17]. A revised FFQ was employed for liver cancer (63 food items), which combined nutritionally similar food items rarely consumed in the Italian population. In addition, the FFQ for the bladder cancer study included two additional items on beverages, summing to 80 food items. Nonetheless, the changes in food items in the revised FFQs did not substantially affect the calculation of total energy or specific nutrient intake.

To compute the DII score, dietary information for each study participant was first linked to the regionally representative database that provided a robust estimate of a mean and an SD for each of the 45 parameters (i.e., foods, nutrients, and other food components) considered in the DII definition [2]. These parameters were then used to derive the individual's exposure relative to the standard global mean as a *z*-score by subtracting the mean of the regionally representative database from the amount reported, and dividing this value by the SD of the parameter. The use of *z*-scores eliminates problems with right-skewing of the data by converting *z*-scores to proportions (i.e., with values of 0 to 1). These proportions were then centered by doubling and subtracting 1, thus fixing "null" values to zero. Clinical interpretation remains clear with these additional steps as inappropriate

Table 1
Number of patients, male prevalence, median age, and median dietary inflammatory index (DII) according to cancer site or type

Cancer site or type	Patients		Male (%)		Median age (y)		Median DII		
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Kruskal–Wallis Test (*P*-value)
Oral cavity	509	2491	72.9	60.1	59	58	−0.631	−1.156	<0.001
Pharynx	436	2491	88.7	60.1	58	58	−0.894	−1.156	0.264
Nasopharynx	198	594	79.3	79.3	52	52	−1.667	−1.433	0.525
Larynx	459	1087	90.4	79.3	61	61	−0.886	−1.093	0.075
Esophagus	304	743	90.5	79.8	60	60	−0.501	−0.999	0.002
Stomach	230	547	62.2	52.3	63	63	−0.142	−0.126	0.878
Colon	1225	4154	56.2	49.9	62	58	−0.675	−0.707	0.125
Rectum	728	4154	60.0	49.9	62	58	−0.562	−0.707	0.034
Liver	184	404	80.4	68.8	66	65	−0.584	−0.575	0.965
Pancreas	326	652	53.4	53.4	63	63	−0.767	−0.908	0.200
Breast	2569	2588	0.0	0.0	55	59	−0.641	−0.561	0.994
Endometrium	454	903	–	–	60	61	−1.178	−1.162	0.489
Ovary	1031	2411	–	–	56	57	−0.490	−0.319	0.097
Prostate	1294	1451	100	100	66	63	−0.740	−0.703	0.691
Kidney	767	1534	64.4	64.4	62	62	−0.508	−0.657	0.035
Bladder	690	665	86.2	84.4	67	66	−0.624	−0.925	0.005

weighting is avoided and higher (i.e., more positive) DII scores still represent more proinflammatory diets. The resulting value was then multiplied by the corresponding food parameter effect score (derived from a literature review on the basis of 1943 articles [4]). All of these food parameter-specific DII scores were then summed to create the overall DII score for each study participant. DII score increases with increasing inflammatory potential of diet, with negative DII scores indicating anti-inflammatory diets and positive DII scores indicating proinflammatory diets. The DII computed on FFQs used in these studies considered data on 31 of the 45 possible food indicators (i.e., foods, nutrients, and food components) available for all the studies comprising the DII: carbohydrates; proteins; fats; fiber; cholesterol; saturated fatty acids; monounsaturated fatty acids; polyunsaturated fatty acids; ω-3 and ω-6; niacin; thiamin,; riboflavin; vitamin B_6; iron; zinc; vitamins A, C, D, and E; folic acid; β-carotene; anthocyanidins; flavan3 ols; flavonols; flavanones; flavones; isoflavones; caffeine; alcohol; and tea. Because the analysis was adjusted for energy, it was not used for DII calculation. The remaining 13 missing food parameters were pepper, saffron, turmeric, garlic, ginger, onion, eugenol, *trans*-fat, selenium, magnesium, vitamin B_{12}, thyme or oregano, and rosemary.

Differences in DII scores across age groups according to case-control status, sociodemographic characteristics (e.g., sex, geographic area), and lifestyle habits (e.g., smoking habits) were tested using analysis of variance. Odds ratios for DII (continuous term), and the corresponding 95% confidence intervals, for various cancers were estimated by unconditional multiple logistic regression models [18]. The original control group was used for comparison in each cancer site (Table 1). Regression models included terms for study-specific matching variables (e.g., study center, age, sex, and year of interview, when appropriate), education, energy intake, plus cancer-specific confounders considered in the original analyses [11–14], as detailed in the footnotes to Table 2. To evaluate the potential effect modification of age in the association between DII and cancer risk, the analyses were stratified according to age in three strata: <50, 50 to 64, and ≥65 y. The test for heterogeneity was based on maximum likelihood estimates of DII effect across strata [19].

Results

The variation of DII score according to age was first investigated in the pool of 13 563 controls (Fig. 1), according to sex and geographic area. In all considered strata, the DII score increased with age. Men reported a more anti-inflammatory diet (i.e., more negative DII scores) than women in all age groups ($P < 0.001$). Both men and women from northern Italy reported lower DII scores than those from central or southern Italy in all age groups ($P < 0.001$). Trends by age were further investigated according to tobacco smoking, drinking habits, and body mass index, with no substantial differences across strata ($P > 0.05$).

Table 1 reports the sociodemographic characteristics of cases and controls enrolled in the original studies. Generally, both cases and controls reported negative median DII scores, indicating a general anti-inflammatory diet. Nonetheless, controls reported a more anti-inflammatory diet than corresponding cases for cancer of the oral cavity ($P < 0.001$), esophagus ($P = 0.002$), rectum ($P = 0.034$), kidney ($P = 0.035$), and bladder ($P = 0.005$). For these cancers, DII score were lower for controls than for cases across age groups (Fig. 2). However, different distribution of covariates across age groups (e.g., sex, geographic area, smoking, and drinking habits) in the original study populations led to different DII trends. For both cases and controls, DII scores increased with age for cancer of the oral cavity, whereas DII did not substantially change with age for cancers of the rectum, kidney, and bladder.

After adjustment for cancer-specific potential confounders, increasing DII scores were directly associated with cancer risk for all of the considered cancer sites, except for liver and endometrium (Table 2). Although DII scores varied across age groups, no heterogeneity in cancer risk emerged for any of the considered cancer sites.

Discussion

The results of the present analysis revealed that the Italian population has a generally anti-inflammatory diet, although some differences exist in geographic areas and by sex. Furthermore, DII scores increased with age, suggesting that the modifications in

Table 2
OR of cancer and corresponding 95% CIs* for incrementing dietary inflammatory index (DII) according to age

Cancer site or type	Overall	Age (years)			
	OR (95% CI)	<50 OR (95% CI)	50–64 OR (95% CI)	≥65 OR (95% CI)	Test for heterogeneity (*P*-value)
Oral cavity†	1.23 (1.13–1.32)	1.29 (1.08–1.53)	1.21 (1.09–1.36)	1.25 (1.08–1.45)	1.000
Pharynx†	1.24 (1.14–1.34)	1.27 (1.04–1.55)	1.26 (1.12–1.43)	1.22 (1.03–1.44)	0.932
Nasopharynx‡	1.20 (1.05–1.37)	1.05 (0.84–1.30)	1.58 (1.26–1.99)	0.96 (0.69–1.32)	0.566
Larynx†	1.17 (1.07–1.29)	1.34 (0.97–1.85)	1.36 (1.18–1.57)	1.03 (0.88–1.21)	0.740
Esophagus§	1.21 (1.08–1.36)	1.13 (0.70–1.83)	1.31(1.12–1.53)	1.04 (0.85–1.27)	0.849
Stomach‖	1.17 (1.03–1.32)	1.38 (1.03–1.86)	1.17 (0.95–1.45)	1.09 (0.91–1.31)	0.893
Colon§	1.11 (1.06–1.17)	1.13 (1.00–1.27)	1.16 (1.08–1.24)	1.06 (0.97–1.15)	0.951
Rectum§	1.18 (1.11–1.25)	1.18 (1.02–1.37)	1.25 (1.15–1.37)	1.13 (1.02–1.26)	0.949
Liver¶	1.28 (0.97–1.67)	–	1.43 (0.80–2.55)	1.27 (0.90–1.80)	0.844
Pancreas#	1.24 (1.11–1.38)	1.83 (1.10–3.04)	1.27 (1.07–1.50)	1.21 (1.02–1.44)	0.751
Breast**	1.05 (1.01–1.09)	1.14 (1.05–1.22)	1.04 (0.98–1.11)	1.02 (0.93–1.11)	0.908
Endometrium††	1.04 (0.96–1.13)	0.98 (0.78–1.22)	1.01 (0.89–1.14)	1.11 (0.96–1.28)	0.954
Ovary†	1.09 (1.04–1.16)	1.07 (0.97–1.18)	1.14 (1.05–1.24)	1.09 (0.97–1.23)	0.977
Prostate§	1.06 (1.00–1.13)	–	1.10 (1.00–1.20)	1.03 (0.95–1.12)	0.844
Kidney§	1.12 (1.05–1.20)	1.17 (1.07–1.27)	1.05 (0.90–1.22)	1.07 (0.92–1.24)	0.940
Bladder‡‡	1.08 (1.00–1.17)	1.08 (0.95–1.24)	1.15 (0.97–1.38)	1.04 (0.91–1.18)	0.964

BMI, body mass index; CI, confidence interval; OR, odds ratio.
*Estimated from unconditional logistic regression model, adjusting for study center, sex (when appropriate), age, energy intake.
†Further adjusted for tobacco smoking and alcohol drinking.
‡Further adjusted for year of interview, tobacco smoking, and alcohol drinking.
§Further adjusted for tobacco smoking, alcohol drinking, and BMI.
‖Further adjusted for year of interview and BMI.
¶Further adjusted for tobacco smoking, maximal lifetime alcohol intake, BMI, chronic infection with hepatitis B or C virus, and diabetes.
#Further adjusted for year of interview, tobacco smoking, alcohol drinking, diabetes, and BMI.
**Further adjusted for BMI, menopausal status, oral contraceptive use, menopausal status, and family history of hormone-related cancers.
††Further adjusted for alcohol drinking, BMI, menopausal status, oral contraceptive use, and parity.
‡‡Further adjusted for tobacco smoking, alcohol drinking, BMI, and diabetes.

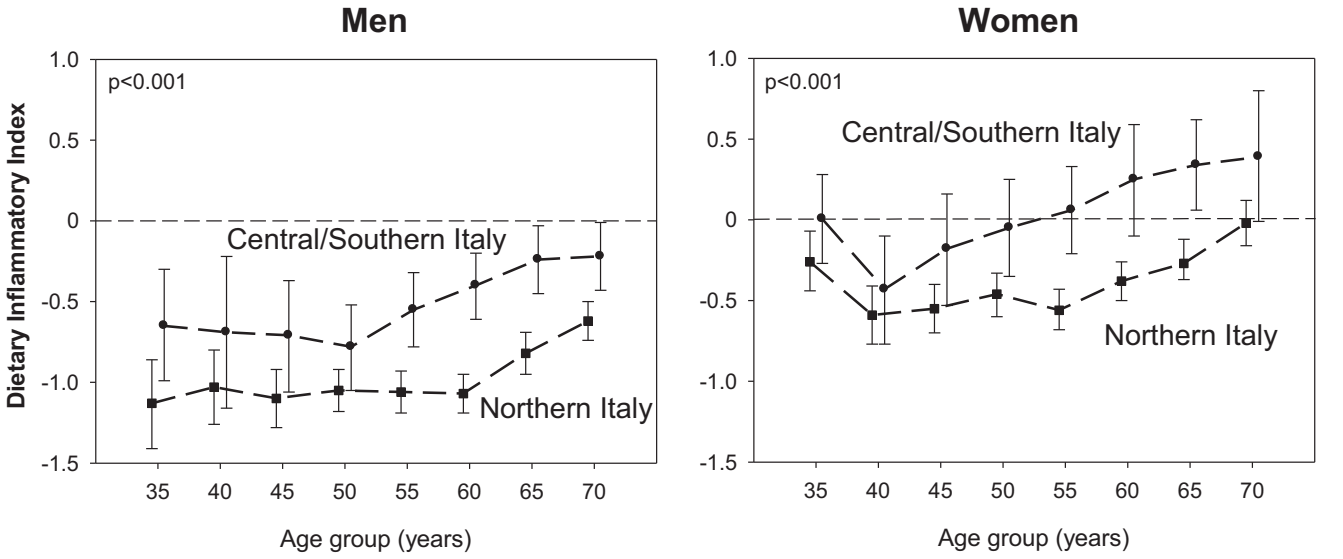

Fig. 1. Mean dietary inflammatory index levels in 13 563 control participants by age, according to sex and geographic area.

dietary habits observed in the elderly [7,8] may reduce the anti-inflammatory effect of diet compared with younger people. Nonetheless, these changes in DII scores were similar in patients who developed a cancer and in those who did not, so that the association between DII and cancer risk remained stable across age groups. However, given the higher cancer incidence in the older group [9], the effect of DII on absolute cancer risk was much higher among them than in middle-aged people.

The results of the present study revealed differences in DII levels according to sex and geographic areas. Surprisingly, women reported eating diets with higher DII scores than men. Also, participants from central or southern Italy had higher scores compared with those from northern Italy. It is worth noting, however, that the DII score was generally low in all strata, probably due to the benefits of the Mediterranean diet [20,21]. Although these differences are not easy to interpret, considering that the DII summarizes the consumption of the whole diet, some differences in dietary habits between the considered groups should be reported. Compared with women, men generally had higher absolute intake of anti-inflammatory food components, such as zinc, most vitamins, and alcohol [7], which may lower their DII scores. Similarly, the diet in central or southern Italy is richer in carbohydrates, a nutrient category directly associated with DII score [2], than the diet in the North.

The DII has been investigated extensively in relation to several diseases affecting people of all ages. Nonetheless, few studies reported DII data over a wide range of ages. Therefore, this study is unique in its ability to evaluate variation in the elderly compared with middle-aged adults. Similar to our findings, data from the U.S. National Health and Nutrition Examination Survey showed that low-income American adults ≥65 y of age had higher DII scores than younger individuals [22]. It is worth noting that this increase in DII score in the ≥65 group was reported in a population with a baseline DII score much higher than the one reported in our study. Similarly, a direct association between age and diet-associated inflammation in men was reported in the Health Professionals Follow-up Study [23], a finding consistent with what we found between the DII score and age in a cohort in Pakistan [24]. Conversely, an inverse association between DII and age was reported in the Japanese [25] and Canadian [26] populations, whereas no association was reported in the Women's Health Initiative [27]. This is not surprising because the DII is strongly related to dietary habits, and it is, therefore, likely that DII baseline level, and its association with age, may vary according to geographic areas. Cultural difference across different countries may have an effect on DII scores much greater than the one observed in this study across Italian geographic areas.

Despite variation of DII according to age, the risk for cancer for increasing DII remained quite stable across strata of age for all cancer sites. Similar cancer relative risks between the population ≥65 y of age and other adults were reported in other populations for head and neck and esophageal cancer [25]. Only a study on ovarian cancer in black women [28] reported higher risk for elevated DII in women >60 y of age than younger women. However, age strongly correlated with menopausal status, which has been consistently reported to modify the association between DII and female genital cancers [29,30]. It would have been interesting to estimate the contribution of age, DII, and their interaction on cancer risk. However, this was not possible in the present analysis because age was a matching criterion for controls in the original case-control studies.

The present analysis is based on case-control studies, and therefore is prone to potential information and selection bias. Information bias, however, was minimized through the direct interview of cases and controls by the same trained interviewers, under similar conditions in a hospital setting. Furthermore, careful attention was paid to excluding from the control group participants admitted for any condition that might have induced a modification of the usual diet. Differential recall between cases and control was possible, but it was limited by interviewing all individuals in a hospital setting and by the lack of awareness of most of dietary hypotheses on cancer etiology at the time that the original studies were conducted. An additional source of information bias might derive from the fact that the FFQ used in these case-control studies did not include 14 food parameters for a complete DII calculation. However, some food parameters such as saffron, ginger, and turmeric are infrequently consumed in Italy; therefore, the lack of these parameters may not have had a major effect. Furthermore, the almost complete participation of both cases and controls in this large series of studies limited concerns with selection bias.

The availability of a pool of >13 500 cancer-free patients who served as controls in the original studies should be accounted for among the study strengths. This large size and geographic variability are reassuring with respect to the representativeness of this sample of the Italian population within each age group. Furthermore, the

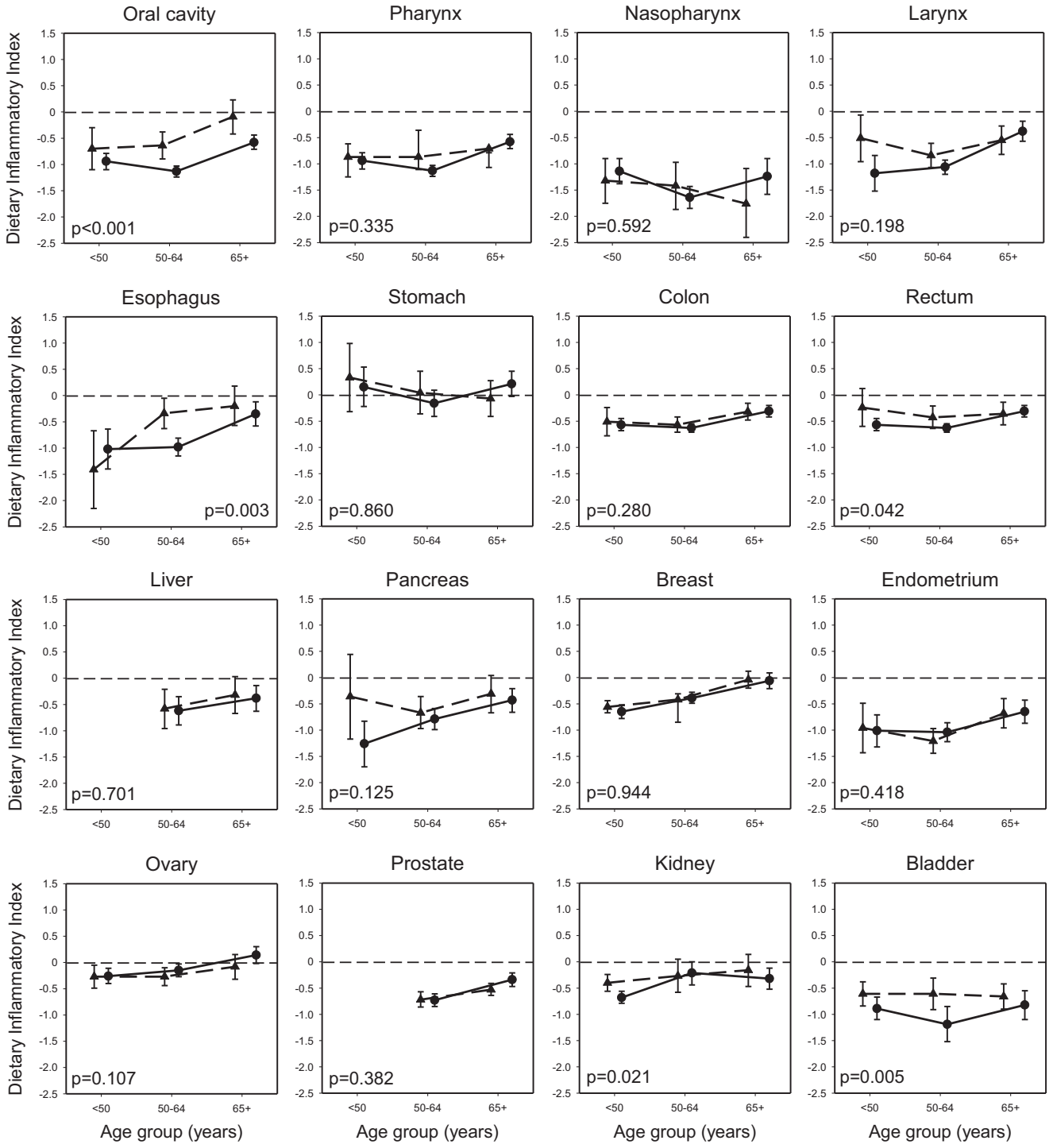

Fig. 2. Mean dietary inflammatory index levels in cases (▲) and controls (•) according to age. The difference by age between cases and controls was tested through the analysis of variance.

use of a validated and reproducible questionnaire to assess dietary habits [15,16] may have contributed to improving the internal and external validity of study findings.

Conclusion

The present analysis provided a description of DII scores in the Italian population, highlighting differences according to sex, age, and geographic areas. In particular, inflammatory potential of diet was higher in adults ≥65 y of age than in younger adults. Although this does not affect relative cancer risk, it may still have important implications for the older age group because elevated DII levels have been associated with several other diseases and with patient frailty [31]. These findings focus attention on the relevance of dietary habits in all age groups, especially the population ≥65 y of age.

Acknowledgment

The authors acknowledge L. Mei for editorial assistance.

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