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Original article

Indices of healthy and unhealthy plant-based diets and the risk of selected digestive cancers

Federica Turati [a], Silvia Mignozzi [a], Giovanna Esposito [a, *], Francesca Bravi [a], Angela D'Angelo [a], Gianfranco Alicandro [b, c], Werner Garavello [d], Livia S.A. Augustin [e], Sara Vitale [e], Attilio Giacosa [f], Ettore Bidoli [g], Jerry Polesel [g], Eva Negri [h], Monica Ferraroni [a, i], Carlo La Vecchia [a]

[a] Department of Clinical Sciences and Community Health, Dipartimento di Eccellenza 2023-2027, University of Milan, Milan, Italy
[b] Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy
[c] Mother and Child Department, Cystic Fibrosis Centre, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[d] School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy
[e] Epidemiology and Biostatistics Unit, Istituto Nazionale Tumori, IRCCS "Fondazione G. Pascale", Naples, Italy
[f] Department of Gastroenterology and Clinical Nutrition, Policlinico di Monza, Monza, Italy
[g] Unit of Cancer Epidemiology, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy
[h] Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
[i] Fondazione IRCCS, Cà Granda Ospedale Maggiore Policlinico, Milan, Italy

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SUMMARY

Background & aims: The relation between various types of plant-based diets and cancer risk is still unclear. We examined the association of the overall plant-based diet index (PDI) and healthy (hPDI) and unhealthy plant-based diet indices (uPDI) with the risk of selected digestive cancers.

Methods: We used data from a network of hospital-based case–control studies including 942 oral/pharyngeal, 304 esophageal, 230 stomach, 1953 colorectal, and 326 pancreatic cancer cases. We calculated PDI, hPDI, and uPDI from a validated food frequency questionnaire. We used multivariable logistic regression models to estimate the odds ratios (OR) of selected digestive cancers across the three indices (in quintiles, Q, or tertiles, T, and in continuous).

Results: The PDI was significantly inversely associated with oral/pharyngeal ($OR_{Q5\ vs\ Q1}$=0.63, 95% confidence interval, CI, 0.47–0.84) and esophageal cancer risk ($OR_{T3\ vs\ T1}$=0.47, 95% CI 0.31–0.72). The inverse associations appeared stronger for the hPDI (oral cavity/pharynx: $OR_{Q5\ vs\ Q1}$=0.52; 95% CI 0.39–0.70; esophagus: $OR_{T3\ vs\ T1}$=0.59, 95% CI 0.39–0.91; stomach: $OR_{T3\ vs\ T1}$=0.42, 95% CI 0.27–0.67; colorectum: $OR_{Q5\ vs\ Q1}$=0.69; 95% CI 0.57–0.84; pancreas: $OR_{T3\ vs\ T1}$=0.60; 95% CI 0.41–0.89). In contrast, the uPDI was directly associated with the risk of oral/pharyngeal ($OR_{Q5\ vs\ Q1}$=1.43, 95% CI 1.06-1.94), colorectal ($OR_{Q5\ vs\ Q1}$=2.28, 95% CI 1.86–2.81), and pancreatic cancer ($OR_{T3\ vs\ T1}$=1.74, 95% CI 1.14–2.65). Esophageal and stomach cancer risks were non-significantly increased by 34% and 46% respectively in the highest uPDI quantile.

Conclusion: A plant-based diet, especially a healthy plant-based diet, may reduce the risk of various digestive cancers, whereas an unhealthy plant-based diet may increase the risk. The quality of plant-based diets is important for digestive cancer risk evaluation and prevention.

1. Introduction

Diet is an important modifiable risk factor for most cancers of the digestive system [1]. Consumption of fruit, vegetables, and fibre is associated with a reduced risk of most digestive cancers [2], whereas high red and processed meat consumption increases the risk of colorectal cancer and, possibly, of other cancers of the

* Corresponding author. Department of Clinical Sciences and Community Health, University of Milan, Via Celoria 22, 20133, Milano, Italy.
E-mail address: giovanna.esposito@unimi.it (G. Esposito).

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digestive system [3–5], suggesting that a plant-based diet may play a favorable role on these neoplasms.

Plant-based diets encompass various dietary patterns that emphasize the consumption of plant-based over animal-based foods [6]. Vegetarian diets are primarily plant-based; they exclude meat, meat-derived foods, and, to varying degrees, other animal products [7]. Variations of the vegetarian diet include lacto-vegetarian, lacto-ovo-vegetarian, pesco-vegetarian, and vegan diets. Vegetarian diets have been associated with multiple health benefits, including reduced risks of cardiovascular diseases, ischemic heart disease, dyslipidemia, diabetes, and selected types of cancer [8–10].

Although vegetarian diets are becoming more common, they still reflect the eating habits of a small proportion of the population [11–13], with the large majority of people consuming both animal and plant foods in varying proportions. Since gradual dietary changes are easier to adopt than drastic dietary overhauls, such as shifting to a dietary pattern that completely excludes animal foods, it is relevant to understand whether diets that emphasize plant-based foods while reducing, but not necessarily excluding, foods of animal origin can also favorably affect the risk of chronic diseases, including cancer. In addition, the definition of vegetarian diets does not distinguish between healthy and unhealthy plant foods. In particular, some studies suggest that refined grains including white bread and high glycemic index grains [14,15], as well as sugar-sweetened plant-based foods and beverages [16], increase the risk of metabolic diseases, and hence of selected cancers [17–19].

In three US cohorts, Satija et al. [20] derived three indices to measure adherence to a dietary pattern characterized by gradual increases in plant foods intake and concomitant reductions in animal food consumption. All three plant-based diet indices attribute negative scores to animal-based products. The overall plant-based diet index (PDI) weighs positively the consumption of all plant foods; the healthy plant-based diet index (hPDI) weighs positively the consumption of healthy plant foods (e.g., fruit, vegetables and wholegrains) and negatively the consumption of unhealthy plant foods (e.g., refined grains and sweets/desserts); conversely, the unhealthy plant-based diet index (uPDI) weighs the consumption of unhealthy plant foods positively and the consumption of healthy plant foods negatively. The overall PDI and hPDI were inversely, but uPDI was directly, related to the incidence of type 2 diabetes.

These indices, as well as other plant-based indices proposed in the literature [21,22], have been examined in relation to cancer risk and cancer mortality in a number of studies [23–25]. In general, a higher adherence to plant-based diets, in particular healthy plant-based diets, has been associated with reduced cancer risk. Notably, a recent pooled analysis of three US cohorts [26] and a large UK cohort [27] found an inverse association between hPDI and the risk of gastrointestinal cancer and individual cancers of the gastrointestinal tract.

The overall epidemiological evidence linking plant-based diets with cancer risk is, however, still limited and focuses mostly on colorectal cancer.

The aim of the present investigation is to evaluate the association of overall, healthy, and unhealthy PDIs with the risk of selected digestive cancers in a network of observational studies from Italy.

2. Material & methods

2.1. Study design

Data were derived from a network of case–control studies on various neoplasms conducted in different Italian areas [28]. We here considered selected digestive cancers, and included in the analysis 942 cases of cancer of the oral cavity/pharynx (with corresponding 2492 controls) [29], 304 of the esophagus (743 controls) [30], 230 of the stomach (547 controls) [31], 1953 of the colorectum (1225 colon cancers, 728 rectal cancers, and 4154 controls) [32] and 326 of the pancreas (652 controls) [33] (Table 1).

All studies included incident cases, identified in the major teaching and general hospitals of the study areas between 1992 and 2009. Controls were patients admitted to the same network of hospitals of cases for a wide spectrum of acute, nonneoplastic conditions unrelated to smoking, alcohol consumption, or long-term diet modification. Controls were frequency matched with cases by recruitment center and age (5-year groups) in the study on oral/pharyngeal cancer; by age, period of interview, and recruitment center in the study on esophageal cancer; by age in the study on stomach cancer; and by age, sex, and recruitment center in the study on pancreatic cancer. For oral/pharyngeal, esophageal and stomach cancer, to compensate for the rarity of the disease in women, an overrepresentation of female vs male control subjects was adopted. The participation rate was >95 % for cases and controls in all studies. The studies were performed in line with the principles of the Declaration of Helsinki. The study protocols were revised and approved by the ethical committees of the hospitals involved, according to the regulations at the time each study was conducted, and all participants gave informed consent.

2.2. Data collection and dietary assessment

Cases and controls were interviewed face-to-face by centrally trained interviewers using the same structured questionnaire. The questionnaire collected data on sociodemographic characteristics, anthropometric measures, physical activity, lifetime smoking and alcohol drinking habits, personal medical history, family history of cancer, aspirin use and, for women, menstrual and reproductive factors, and use of oral contraceptives and hormone replacement therapy (HRT).

An interviewer-administered food frequency questionnaire (FFQ) was used to assess study participants' usual diet during the 2 years prior to cancer diagnosis (for cases) or hospital admission (for controls). The FFQ included the average weekly consumption of 78 foods, food groups or recipes; intakes lower than once a week, but at least once a month, were coded as 0.5 per week. For fruit and vegetables subject to seasonal variation, consumption in season and the corresponding duration were elicited. The FFQ included 6 sections: (1) bread, cereals, first courses; (2) second courses (i.e., meat, fish and other main dishes); (3) side dishes (i.e., vegetables, fried/baked potatoes); (4) fruits; (5) sweets, desserts, and soft drinks; (6) milk, hot beverages, and sweeteners. Additional questions aiming at assessing the intake patterns of added fats were also included and used to derive quantitative estimates of intake of various added lipids, including olive oil, specific seed oils (sunflower and peanut), mixed seed oils, and butter.

From FFQ data, the intakes of selected nutrients, food components, and total energy were estimated using an Italian food composition database [34]. The FFQ was tested for reproducibility [35] and validity [36] with satisfactory results.

2.3. Plant-based diet indices

Using FFQ data, we derived the PDI, hPDI, and uPDI as previously reported [20]. Briefly, healthy plant foods included whole grains, fruit, raw and cooked vegetables, nuts, legumes, vegetable oils, and tea and coffee. Unhealthy plants foods included refined grains, potatoes, sugar-sweetened beverages and fruit juices, and sweets and desserts. Animal foods included animal fats, dairy, eggs, fish and seafood, and meat. The original PDI formulation also included a

Table 1
Italian case–control studies on selected digestive cancers contributing to the present analysis.

Cancer site	Total	Cases		Controls	
	No. cases/No. controls	No. (M/W)	Age (yrs), median [IQR]	No. (M/W)	Age (yrs), median [IQR]
Oral cavity/pharynx	942/2492	752/190	58 [52–65]	1497/995	58 [50–66]
Esophagus	304/743	275/29	60 [54.5–66]	593/150	60 [54–67]
Stomach	230/547	143/87	63 [53–69]	286/261	63 [53–69]
Colorectum	1953/4154	1125/828	62 [55–68]	2073/2081	58 [49–65]
Colon	1225/4154	688/537	62 [55–68]	2073/2081	58 [49–65]
Rectum	728/4154	437/291	62 [55–68]	2073/2081	58 [49–65]
Pancreas	326/652	174/152	63 [56–70]	348/304	63 [56–70]

Abbreviations: M, men; W, women; yrs, years; IQR, interquartile range.

"miscellanea animal-based foods" group covering a few other animal-based products (e.g., chowder or cream soup, mayonnaise) and pizza [20]. We did not include such component in our PDIs because information on most of the food items included in this group were not collected in our FFQ. Moreover, since in Italy pizza is traditionally made with yeast-based refined wheat flour dough and few ingredients (tomatoes sauce, mozzarella cheese, and olive oil) where animal products account for half or less of the weight of the finished product, we included half portion among the refined grain group and half among the dairy group. We combined fruit juices and sugarsweetened beverages into a single food group, rather than considering them as separate components as originally proposed [20], due to their infrequent consumption in our study population. The FFQ food items included in the PDIs components are detailed in Supplementary Table S1.

Sixteen food groups were used to derive the PDIs: fruits, vegetables, legumes, vegetable oils, tea and coffee, refined grains, potatoes, sweets and desserts, animal fats, dairy, eggs, fish and seafood, meat, whole grains, nuts and fruit juices/sugar-sweetened beverages.

For 13 (i.e., fruit, raw and cooked vegetables, legumes, vegetable oils, tea and coffee, refined grains, potatoes, sweets and desserts, animal fats, dairy, eggs, fish and seafood, and meat) out of 16 food groups a score from 1 to 5 was assigned according to quintiles of consumption (derived from controls). For PDI, individuals in the 5th, 4th, 3rd, 2nd and 1st quintiles (where the 5th quintile indicates the highest consumption) of each plant-based food group were given scores of 5, 4, 3, 2 and 1, respectively (positive scores); and, individuals in the 5th, 4th, 3rd, 2nd, and 1st quintiles of each animal-based food group were assigned scores of 1, 2, 3, 4 and 5, respectively (reverse scores). For hPDI, positive scores were given to healthy plant-based food groups and reverse scores to unhealthy plant-based and animal-based food groups. For uPDI, positive scores were given to unhealthy plant-based food groups and reverse scores to healthy plant-based and animal-based food groups.

Classification by quintiles of consumption was not feasible for whole grains (consumed by only 10–15% of participants across our cancer studies), fruit juices/sugar-sweetened beverages (consumed by 40–45% of participants) and nuts (collected using an open-ended question and consumed only by 1–2% of study subjects). For whole grains and fruit juices/sugar-sweetened beverages, we classified participants into the following 3 categories: consumers of > median consumption (derived from consumer controls), consumers of < median consumption, non-consumers. For the healthy plant-based food 'whole grains', positive scores of 5, 3 and 1 were assigned in PDI and hPDI, and reverse scores of 1, 3, and 5 in uPDI. For the unhealthy plant-food 'fruit juices and sugar-sweetened beverages', positive scores of 5, 3, and 1 were assigned in PDI and uPDI, and reverse scores of 1, 3, and 5 in hPDI. For nuts, we assigned 2 points to consumers and 1 point to non-consumers in PDI and hPDI, and the reverse in uPDI.

The 16 food group scores were summed to obtain the three indices, with a theoretical range of 16–77. The derivation method used to obtain the PDIs is reported in Table 2**.** Higher values in PDI, hPDI, and uPDI reflect higher intake of overall, healthy, and unhealthy plant-based foods, respectively.

As a sensitivity analysis, since fish/seafood consumption has been associated with reduced risk of several health outcomes [37], including cancer risk [38,39], we derived a variant of the hPDI to score fish consumption positively. In another sensitivity analysis, we derived the hPDI and uPDI after considering pasta together with whole grains within the healthy plant foods as in Italy pasta is made of durum wheat semolina by law (DPR-187-2001. https://www.politicheagricole.it/flex/files/2/f/6/D.34ca305e98ded6c87bfc/DPR_187_2001.pdf.) which is a source of intact cell walls (i.e., dietary fiber) with confirmed health benefits [40,41].

2.4. Statistical analysis

We used unconditional logistic regression models to estimate the odds ratios (OR) of various digestive cancers, and the corresponding 95% confidence intervals (CI), according to quantiles of PDI, hPDI, and uPDI. Quantiles were derived from controls. Based on the sample size of each cancer site, we used quintiles (Q) for oral/pharyngeal and colorectal cancers and tertiles (T) for esophageal, stomach, and pancreatic cancers. All the PDIs were also modeled as continuous variables to estimate the OR for a 3-point increment in the score. To capture potential nonlinear relationships, the PDIs were also included in the model as natural cubic spline with three equally-spaced knots positioned at the quartiles of the distribution among controls. Models included terms for age (5-year categories), sex, study center (in multicentric studies), year of interview, education (<7, 7–11, ≥12 years), body mass index (BMI, <20, 20–24.9, 25–29.9, ≥30 kg/m^2), total energy intake (quintiles derived from controls), smoking habits (never, former, and: current of <15 and ≥ 15 cigarettes/day in studies on colorectal, pancreatic, and stomach cancer; current of <15, 15–24, ≥25 cigarettes/day in studies on esophageal and oral/pharyngeal cancer), and alcohol drinking (never, 1–6, 7–13, 14 - <27, ≥28 drinks/week in studies on colorectal, pancreatic, and stomach cancer; 0–13, 14–27, 28–34, 35–41, ≥42 drinks/week in studies on esophageal and oral/pharyngeal cancer). Models for pancreatic cancer additionally included terms for history of diabetes, and those for colorectal cancer terms for history of diabetes, regular aspirin use, occupational physical activity, age at menopause and use of HRT, and family history of colorectal cancer. A few missing values on adjustment factors were replaced by the median value (continuous variables) or mode category (categorical variables) according to case/control status and sex. Tests for trends across categories of PDIs were performed by treating the variables as ordinal.

Stratified analyses were performed by age, sex, BMI category, smoking status, and alcohol drinking; effect modification was assessed using the likelihood ratio test comparing models with and

Table 2
Derivation of plant-based diet indices.[a]

	PDI	hPDI	uPDI
Plant food groups			
Healthy			
Whole grains	1: non-consumers, 3: <median, 5: ≥median	1: non-consumers, 3: <median, 5: ≥median	5: non-consumers, 3: <median, 1: ≥median
Fruit	1 to 5	1 to 5	5 to 1
Raw and cooked vegetables	1 to 5	1 to 5	5 to 1
Nuts	1: non-consumers, 2: consumers	1: non-consumers, 2: consumers	2: non-consumers, 1: consumers
Legumes	1 to 5	1 to 5	5 to 1
Vegetable oils	1 to 5	1 to 5	5 to 1
Tea and coffee	1 to 5	1 to 5	5 to 1
Unhealthy			
Refined grains	1 to 5	5 to 1	1 to 5
Potatoes	1 to 5	5 to 1	1 to 5
Sweets and desserts	1 to 5	5 to 1	1 to 5
Fruit juices/sugar-sweetened beverages	1: non-consumers, 3: <median, 5: ≥median	5: non-consumers, 3: <median, 1: ≥median	1: non-consumers, 3: <median, 5: ≥median
Animal food groups			
Animal fats	5 to 1	5 to 1	5 to 1
Dairy	5 to 1	5 to 1	5 to 1
Eggs	5 to 1	5 to 1	5 to 1
Fish and seafood	5 to 1	5 to 1	5 to 1
Meat	5 to 1	5 to 1	5 to 1

Abbreviations: PDI, Plant-based diet index; hPDI, Healthy plant-based diet index; uPDI, Unhealthy plant-based diet index.
[a] The Table shows the score assigned for increasing quintiles of consumption, unless otherwise specified.

without the interaction term. P-values <0.05 were considered significant (two-tailed).

All analyses were conducted using SAS version 9.4 and R version 4.1.1.

3. Results

The distribution of socio-demographic and other selected characteristics in cancer cases and controls are given in Tables S2–S6. Cases of oral/pharyngeal, esophageal, and stomach cancer were less educated than the corresponding controls and those of colon and pancreatic cancer more educated. Cases of oral/pharyngeal, esophageal, pancreatic and stomach cancer were more frequently heavy tobacco smokers and heavy alcohol drinkers than controls.

Fig. S1 shows the distribution of PDI, hPDI and uPDI within each cancer study, separately for cases and controls.

The OR of selected digestive cancers according to categories of PDI, hPDI and uPDI are presented in Table 3. As for the overall PDI, significant inverse associations were observed with risk of oral/pharyngeal cancer ($OR_{Q5\ vs\ Q1}$=0.63, 95% CI 0.47–0.84) and esophageal cancer ($OR_{T3\ vs\ T1}$=0.47, 95% CI 0.31–0.72); non-significant inverse associations were found for stomach ($OR_{T3\ vs\ T1}$=0.70, 95% CI 0.46–1.09), colorectal ($OR_{Q5\ vs\ Q1}$=0.87, 95% CI 0.71–1.06), and pancreatic cancer ($OR_{T3\ vs\ T1}$=0.77, 95% CI 0.52–1.15). With regard to hPDI, higher scores in the index were associated with significantly reduced risks of all the considered cancers (oral cavity/pharynx: $OR_{Q5\ vs\ Q1}$=0.52; 95% CI 0.39–0.70; esophagus: $OR_{T3\ vs\ T1}$=0.59, 95% CI 0.39–0.91; stomach: $OR_{T3\ vs\ T1}$=0.42, 95% CI 0.27–0.67; colorectum: $OR_{Q5\ vs\ Q1}$=0.69; 95% CI 0.57–0.84; pancreas: $OR_{T3\ vs\ T1}$=0.60, 95% CI 0.41–0.89). In a sensitivity analysis, we found similar or even stronger inverse associations using a modified hPDI weighing positively fish consumption (Table S8). Higher uPDI scores were associated with increased risks of oral/pharyngeal ($OR_{Q5\ vs\ Q1}$=1.43, 95% CI 1.06–1.94), colorectal ($OR_{Q5\ vs\ Q1}$=2.28, 95% CI 1.86–2.81) and pancreatic cancer ($OR_{T3\ vs\ T1}$=1.74, 95% CI 1.14–2.65). The risks of esophageal and stomach cancers among subjects in the highest quantile of uPDI were non-significantly increased by 34% and 46% respectively. None of the key findings on hPDI and uPDI was materially modified when moving pasta from the refined grains to the whole grains food group (Table S9).

Fig. 1 shows the OR estimates when the PDIs were considered as continuous variables. For PDI, the estimates for a 3-point increment in the score ranged from 0.81 (esophageal cancer) to 0.98 (colon cancer). For hPDI, the ORs were all significantly below 1, with risk reductions ranging from 7% (colorectal cancer) to 16% (stomach cancer). The continuous ORs for the uPDI were significantly above 1 for all cancer sites except esophageal cancer; a 3-point increment in the score was associated with increases in risk ranging from 7% (oral/pharyngeal cancer and esophageal cancer) to 15% (colon cancer).

The exposure-risk functions are shown in Fig. S2. Most of the functions showed decreasing risks of with increasing values of PDI and hPDI, and increasing risks for uPDI. The only exceptions were the relationship between hPDI and esophageal cancer, where the risk started to decline only above a score of 50, and the lack of a relationship between the overall PDI and stomach cancer.

Results from stratified analyses are provided in Table 4. The associations with the three indices were generally consistent in strata of age, sex, BMI, smoking status and alcohol drinking, with a few exceptions. The association of the uPDI with oral/pharyngeal cancer was significant in the young but not the old age group. For esophageal cancer, the inverse association with the overall PDI was stronger in men than women, and a direct association with the uPDI was found in subjects with BMI ≥25 kg/m^2 only. The overall PDI was inversely associated with colorectal cancer risk in men but not in women, in the old age but not in the young one, and in moderate and heavy alcohol drinkers only.

4. Discussion

In a network of studies from Italy including over 3700 cancer cases we found that adherence to plant-based diets, especially a healthy plant-based diet, was associated with a reduced risk of various digestive cancers. Of particular interest, a plant-based diet that emphasizes consumption of unhealthy plant-foods was associated with an increased risk of digestive cancers. These

Table 3
Distribution of cancer cases and controls, adjusted odds ratios[a] (OR) and corresponding 95% confidence intervals (CI) of selected digestive cancers according to approximate quintiles (Q) or tertiles (T) of the overall plant-based diet index[b] (PDI), the healthy plant-based diet index[c] (hPDI), and the unhealthy plant-based diet index[d] (uPDI) in the Italian network of case–control studies. Italy, 1992–2009.

	PDI			hPDI			uPDI		
	Cases	Controls	OR[a] (95% CI)	Cases	Controls	OR[a] (95% CI)	Cases	Controls	OR[a] (95% CI)
	No. (%)	No. (%)		No. (%)	No. (%)		No. (%)	No. (%)	
Oral cavity/pharynx									
Q1	251 (26.7)	461 (18.5)	1 (ref)	299 (31.7)	492 (19.7)	1 (ref)	131 (13.9)	489 (19.6)	1 (ref)
Q2	179 (19.0)	437 (17.5)	0.81 (0.62–1.07)	237 (25.2)	543 (21.8)	0.75 (0.59–0.97)	124 (13.2)	383 (15.4)	1.01 (0.73–1.41)
Q3	186 (19.8)	568 (22.8)	0.64 (0.49–0.84)	149 (15.8)	491 (19.7)	0.56 (0.43–0.75)	175 (18.6)	487 (19.5)	1.07 (0.79–1.46)
Q4	166 (17.6)	460 (18.5)	0.82 (0.62–1.10)	122 (13.0)	441 (17.7)	0.55 (0.41–0.74)	240 (25.5)	593 (23.8)	1.13 (0.85–1.52)
Q5	160 (17.0)	566 (22.7)	0.63 (0.47–0.84)	135 (14.3)	525 (21.1)	0.52 (0.39–0.70)	272 (28.9)	540 (21.7)	1.43 (1.06–1.94)
p-trend			0.005			<0.001			0.014
Esophagus									
T1	144 (47.4)	252 (33.9)	1 (ref)	131 (43.1)	266 (35.8)	1 (ref)	75 (24.7)	231 (31.1)	1 (ref)
T2	101 (33.2)	261 (35.1)	0.65 (0.45–0.94)	112 (36.8)	247 (33.2)	0.98 (0.68–1.41)	87 (28.6)	244 (32.8)	0.96 (0.63–1.46)
T3	59 (19.4)	230 (31.0)	0.47 (0.31–0.72)	61 (20.1)	230 (31.0)	0.59 (0.39–0.91)	142 (46.7)	268 (36.1)	1.34 (0.87–2.05)
p-trend			<0.001			0.024			0.155
Stomach									
T1	68 (29.6)	162 (29.6)	1 (ref)	114 (49.6)	190 (34.7)	1 (ref)	65 (28.3)	180 (32.9)	1 (ref)
T2	84 (36.5)	201 (36.7)	0.78 (0.52–1.17)	78 (33.9)	191 (34.9)	0.75 (0.52–1.08)	92 (40.0)	202 (36.9)	1.32 (0.89–1.96)
T3	78 (33.9)	184 (33.6)	0.70 (0.46–1.09)	38 (16.5)	166 (30.3)	0.42 (0.27–0.67)	73 (31.7)	165 (30.2)	1.46 (0.96–2.24)
p-trend			0.086			<0.001			0.082
Colorectum									
Q1	403 (20.6)	801 (19.3)	1 (ref)	453 (23.2)	772 (18.6)	1 (ref)	247 (12.6)	777 (18.7)	1 (ref)
Q2	334 (17.1)	734 (17.7)	0.90 (0.74–1.08)	476 (24.4)	902 (21.7)	0.92 (0.78–1.10)	359 (18.4)	835 (20.1)	1.46 (1.19–1.78)
Q3	398 (20.4)	887 (21.4)	0.89 (0.74–1.07)	381 (19.5)	812 (19.5)	0.79 (0.66–0.95)	455 (23.3)	1001 (24.1)	1.65 (1.35–2.01)
Q4	472 (24.2)	986 (23.7)	0.88 (0.73–1.05)	289 (14.8)	768 (18.5)	0.67 (0.55–0.82)	339 (17.4)	655 (15.8)	1.91 (1.54–2.37)
Q5	346 (17.7)	746 (18.0)	0.87 (0.71–1.06)	354 (18.1)	900 (21.7)	0.69 (0.57–0.84)	553 (28.3)	886 (21.3)	2.28 (1.86–2.81)
p-trend			0.171			<0.001			<0.001
Colon									
Q1	239 (19.5)	801 (19.3)	1 (ref)	283 (23.1)	772 (18.6)	1 (ref)	144 (11.8)	777 (18.7)	1 (ref)
Q2	221 (18.0)	734 (17.7)	0.97 (0.78–1.22)	297 (24.2)	902 (21.7)	0.89 (0.73–1.09)	223 (18.2)	835 (20.1)	1.55 (1.21–1.98)
Q3	239 (19.5)	887 (21.4)	0.84 (0.68–1.05)	237 (19.3)	812 (19.5)	0.77 (0.62–0.95)	282 (23.0)	1001 (24.1)	1.75 (1.38–2.22)
Q4	302 (24.7)	986 (23.7)	0.91 (0.73–1.13)	186 (15.2)	768 (18.5)	0.68 (0.54–0.86)	223 (18.2)	655 (15.8)	2.21 (1.71–2.85)
Q5	224 (18.3)	746 (18.0)	0.91 (0.71–1.15)	222 (18.1)	900 (21.7)	0.68 (0.54–0.85)	353 (28.8)	886 (21.3)	2.59 (2.03–3.32)
p-trend			0.331			<0.001			<0.001
Rectum									
Q1	164 (22.5)	801 (19.3)	1 (ref)	170 (23.4)	772 (18.6)	1 (ref)	103 (14.1)	777 (18.7)	1 (ref)
Q2	113 (15.5)	734 (17.7)	0.80 (0.61–1.05)	179 (24.6)	902 (21.7)	0.96 (0.75–1.23)	136 (18.7)	835 (20.1)	1.37 (1.03–1.82)
Q3	159 (21.8)	887 (21.4)	0.94 (0.72–1.21)	144 (19.8)	812 (19.5)	0.84 (0.64–1.09)	173 (23.8)	1001 (24.1)	1.53 (1.15–2.02)
Q4	170 (23.4)	986 (23.7)	0.83 (0.64–1.08)	103 (14.1)	768 (18.5)	0.68 (0.51–0.91)	116 (15.9)	655 (15.8)	1.56 (1.14–2.13)
Q5	122 (16.8)	746 (18.0)	0.80 (0.60–1.06)	132 (18.1)	900 (21.7)	0.71 (0.54–0.94)	200 (27.5)	886 (21.3)	1.94 (1.44–2.60)
p-trend			0.186			0.002			<0.001
Pancreas									
T1	124 (38.0)	202 (31.0)	1 (ref)	139 (42.6)	208 (31.9)	1 (ref)	99 (30.4)	207 (31.7)	1 (ref)
T2	107 (32.8)	226 (34.7)	0.85 (0.58–1.23)	101 (31.0)	213 (32.7)	0.72 (0.50–1.04)	117 (35.9)	245 (37.6)	1.23 (0.84–1.80)
T3	95 (29.1)	224 (34.4)	0.77 (0.52–1.15)	86 (26.4)	231 (35.4)	0.60 (0.41–0.89)	110 (33.7)	200 (30.7)	1.74 (1.14–2.65)
p-trend			0.205			0.010			0.010

[a] Adjusted for sex, quinquennia of age, study center, year of interview, years of education, tobacco smoking, alcohol drinking, body mass index, and total energy intake. Models for pancreatic cancer were additionally adjusted for history of diabetes; models for colorectal cancer were additionally adjusted for history of diabetes, regular aspirin use, occupational physical activity, age at menopause and use of hormone replacement therapy, and family history of colorectal cancer.
[b] Cut-offs for the definition of quantiles of PDI were: 40, 43, 46 and 50 for cancer of the oral cavity/pharynx; 39, 42, 45 and 49 for colorectal cancer; 42 and 47 for esophageal cancer; 41 and 46 for stomach cancer; 41 and 46 for pancreatic cancer.
[c] Quantiles for the definition of quantiles of hPDI were: 40, 44, 47, 50 for cancer of the oral cavity and pharynx; 40, 44, 47 and 50 for colorectal cancer; 44 and 49 for esophageal cancer; 42 and 48 for stomach cancer; 43 and 48 for pancreatic cancer.
[d] Quantiles for the definition of quantiles of uPDI were: 43, 46, 49, 53 for cancer of the oral cavity and pharynx; 42, 46, 50 and 53 for colorectal cancer; 45 and 50 for esophageal cancer; 46 and 52 for stomach cancer; 45 and 51 for pancreatic cancer.

associations were generally consistent across subgroups of the population defined by age, sex, BMI, smoking status, and alcohol drinking.

Vegetarians avoid meat, including fish and poultry, and vegans exclude all animal products. Although these diets have been associated with multiple health benefits [8–10], they are difficult to maintain and are generally only followed by a small percentage of population, with few exceptions like India. Restrictive vegetarian diets may also be associated with nutrient deficiencies [42] and excess risk of metabolic and other chronic conditions [43]. The PDIs applied in the present study measure the adherence to a plant-dominant diet that allows low to moderate amounts of animal products. Among study participants, the mean number of servings per day of animal foods was approximately 4–4.5 in the lowest quantile and 2.5–3 in the highest quantile of hPDI, and the OR comparing extreme quantiles of the score ranged from 0.45 to 0.70 across different cancer sites. While consumption of red and processed meat was associated with a higher risk of digestive cancers, null or inverse associations were reported for other selected animal foods, including white meat, fish and dairy [44], and our results for hPDI were essentially similar, if not stronger in magnitude, when fish consumption was scored positively (i.e., healthy). Thus, even a largely plant-based diet that includes small to moderate amounts of non-unhealthy animal foods has the potential to substantially reduce the risk of digestive cancers.

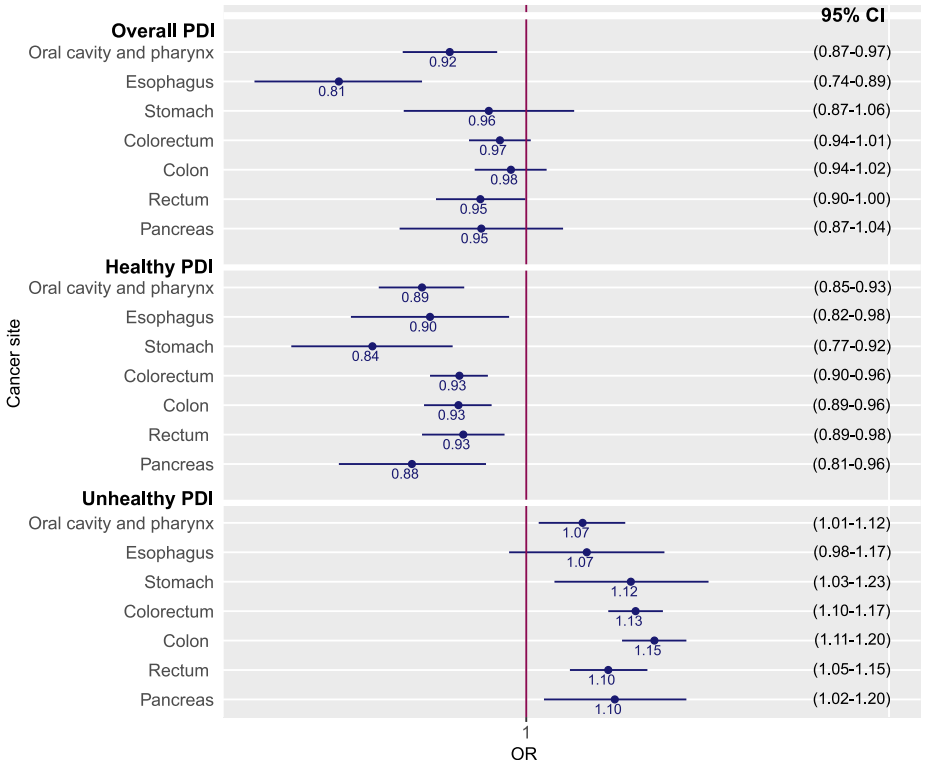

Fig. 1. Adjusted odds ratios[a] (OR) and corresponding 95% confidence intervals (CI) of selected digestive cancers for an increment equal to 3 point of the overall plant-based diet index (PDI), the healthy plant-based diet index (hPDI), and the unhealthy plant-based diet index (uPDI). Italy, 1992–2009.
[a] Adjusted for sex, quinquennia of age, study center, year of interview, years of education, tobacco smoking, alcohol drinking, body mass index, and total energy intake. Models for pancreatic cancer were additionally adjusted for history of diabetes; models for colorectal cancer were additionally adjusted for history of diabetes, regular aspirin use, occupational physical activity, age at menopause and use of hormone replacement therapy, and family history of colorectal cancer.

The stronger inverse association observed for hPDI compared to the overall PDI and the unfavorable association found for uPDI highlight the importance of considering the quality of plant-based foods. Across the various cancer studies, subjects in the highest quantile of the uPDI consumed fewer servings of healthy plant foods (about 5–5.5 servings per day depending on the cancer sites) and higher servings of unhealthy plant foods (about 6.5–7 servings per day) compared to those in the highest quintile of the hPDI (about 8–8.5 servings per day of healthy plant foods and about 4–5 of unhealthy plant foods). This level of consumption was associated with a 1.3 to 2-fold increase in the risk of digestive cancers.

A few studies have investigated the association of plant-based diet indices with the risk of digestive cancers [21,26,27,45]. In a pooled analysis of the Nurses' Health Study (NHS), NHS II, and Health Professionals Follow up Study (HPFS) the hPDI was associated with a lower risk of total digestive system cancers as well as gastrointestinal tract cancers. Non-significant inverse associations were found for oral and pharyngeal, esophageal, colorectal and pancreatic cancers. On the other hand, the uPDI was associated with an increased risk of gastrointestinal tract cancers combined, and particularly colorectal cancer [26]. In the UK Biobank cohort, the hPDI was associated with a lower risk of all gastrointestinal cancers combined and individual cancers of the gastrointestinal system, including esophageal, stomach, pancreatic and colorectal cancers [27]. Using the provegetarian plant-based dietary score by Martínez-Gonzáles [21], which is similar to the overall PDI applied in the present investigation, the NutriNet-santè cohort found an inverse association with the risk of digestive cancers combined (e.g., colon-rectum, esophagus, stomach, pancreas and others) [25]. Further, applying the same index by Martínez-Gonzáles [21], as well as the hPDI and uPDI proposed by Satija et al. [20] as in the present study, a Spanish case–control study found inverse associations between both the overall PDI and the hPDI and the risk of esophageal, stomach, and pancreatic cancer [45]; conversely, a higher uPDI was associated with an increased stomach cancer risk. Two other studies focused on colorectal cancer only. In the Multiethnic Cohort Study, the overall PDI and hPDI were inversely related with colorectal cancer in men only, and a lack of association emerged with the uPDI in both sexes [46], and in a Chinese case–control study a higher PDI, and in particular hPDI, was inversely associated with colorectal cancer risk while uPDI showed a positive association [47]. Another Chinese prospective study investigated overall, healthy and unhealthy plant-based diets in relation with esophageal cancer risk. The study found an inverse association with the hPDI and a direct association with uPDI [48]. Thus, overall, the epidemiological evidence is limited but suggestive of a favorable role of healthy plant-based diets on digestive cancers.

A favorable role of a healthy plant-based diet on cancers of the digestive system is not unexpected. Such a diet is rich in food components, such as polyphenols, carotenoids, healthy fatty acids, and fibers, with antioxidant and anti-inflammatory properties, which have potential anti-carcinogenic effects. This diet is also low in high-energy-dense foods, foods with elevated amounts of saturated fatty acids, and those with high glycemic index. Dietary fiber from plant foods regulates the speed, bulk and consistency of stools reducing the contact of possible fecal carcinogens with the colonic mucosa, and traps bile acids and carcinogenic substances [49]. Furthermore, dietary fiber is fermented into short-chain fatty acids, such as butyrate, which improve the intestinal barrier function and regulate gene expression to inhibit cell proliferation and induce apoptosis [50]. Several epidemiological studies consistently

Table 4
Adjusted odds ratios[a] (OR) and corresponding 95% confidence intervals (CI) of selected digestive cancers for an increment equal to 3 point of the overall plant-based diet index (PDI), the healthy plant-based diet index (hPDI), and the unhealthy plant-based diet index (uPDI), stratified by selected participants' characteristics in the Italian network of case–control studies. Italy, 1992–2009.

	Sex		p_{het}	Age		p_{het}	BMI (kg/m^2)		p_{het}	Smoking habit		p_{het}	Alcohol drinking		p_{het}
	Men	Women		<60	≥60		<25	≥25		No	Yes		Non-light[b]	Moderate-high[b]	
Oral cavity/pharynx															
PDI	0.93 (0.88-0.99)	0.88 (0.79–0.98)	0.735	0.92 (0.86–0.99)	0.93 (0.86–1.00)	0.845	0.94 (0.87–1.01)	0.90 (0.84–0.97)	0.228	0.94 (0.88–1.01)	0.88 (0.81–0.95)	0.554	0.92 (0.86–0.99)	0.87 (0.81–0.94)	0.390
hPDI	0.90 (0.85–0.95)	0.87 (0.79–0.95)	0.240	0.87 (0.82–0.93)	0.92 (0.86–0.98)	0.211	0.86 (0.80–0.92)	0.91 (0.85–0.97)	0.200	0.91 (0.86–0.97)	0.86 (0.80–0.93)	0.103	0.89 (0.84–0.95)	0.89 (0.83–0.96)	0.706
uPDI	1.06 (1.00–1.13)	1.07 (0.98–1.16)	0.722	1.11 (1.03–1.19)	1.02 (0.95–1.09)	0.042	1.12 (1.04–1.20)	1.02 (0.95–1.09)	0.136	1.05 (0.98–1.11)	1.10 (1.01–1.19)	0.304	1.08 (1.01–1.15)	1.07 (0.99–1.15)	0.954
Esophagus															
PDI	0.79 (0.72–0.88)	0.87 (0.60–1.26)	0.013	0.74 (0.64–0.85)	0.88 (0.77–1.00)	0.158	0.80 (0.69–0.94)	0.81 (0.71–0.91)	0.731	0.84 (0.73–0.95)	0.76 (0.66–0.88)	0.799	0.84 (0.68–1.03)	0.77 (0.69–0.86)	0.160
hPDI	0.92 (0.84–1.01)	0.74 (0.51–1.07)	0.017	0.81 (0.70–0.93)	0.98 (0.87–1.10)	0.107	0.80 (0.68–0.95)	0.94 (0.85–1.05)	0.104	0.94 (0.83–1.05)	0.87 (0.76–1.01)	0.129	0.87 (0.72–1.06)	0.92 (0.83–1.02)	0.486
uPDI	1.06 (0.97–1.17)	1.15 (0.86–1.53)	0.302	1.04 (0.92–1.18)	1.09 (0.96–1.23)	0.572	0.95 (0.82–1.11)	1.14 (1.02–1.28)	0.047	1.04 (0.93–1.17)	1.10 (0.96–1.26)	0.854	0.97 (0.81–1.17)	1.13 (1.03–1.25)	0.113
Stomach															
PDI	0.92 (0.81–1.04)	1.01 (0.87–1.17)	0.617	0.93 (0.80–1.08)	0.96 (0.85–1.09)	0.971	0.91 (0.79–1.04)	1.02 (0.89–1.18)	0.320	0.95 (0.85–1.06)	0.99 (0.81–1.22)	0.694	0.99 (0.87–1.13)	0.93 (0.80–1.08)	0.589
hPDI	0.82 (0.72–0.92)	0.87 (0.75–1.00)	0.293	0.80 (0.70–0.92)	0.86 (0.76–0.97)	0.427	0.82 (0.71–0.93)	0.88 (0.77–1.00)	0.721	0.86 (0.77–0.95)	0.80 (0.65–0.97)	0.522	0.82 (0.73–0.93)	0.88 (0.76–1.02)	0.646
uPDI	1.10 (0.97–1.23)	1.21 (1.06–1.39)	0.232	1.24 (1.08–1.44)	1.05 (0.94–1.18)	0.060	1.12 (0.99–1.27)	1.11 (0.98–1.26)	0.811	1.08 (0.98–1.19)	1.60 (1.25–2.04)	0.133	1.18 (1.05–1.32)	1.04 (0.90–1.20)	0.125
Colorectum															
PDI	0.94 (0.90–0.98)	1.01 (0.96–1.07)	0.001	1.02 (0.97–1.08)	0.94 (0.90–0.98)	0.039	0.96 (0.91–1.01)	0.98 (0.94–1.03)	0.506	0.98 (0.94–1.02)	0.94 (0.88–1.01)	0.426	1.01 (0.96–1.06)	0.94 (0.90–0.99)	0.013
hPDI	0.92 (0.88–0.96)	0.94 (0.89–0.99)	0.108	0.95 (0.91–0.99)	0.92 (0.88–0.96)	0.437	0.95 (0.91–1.00)	0.90 (0.86–0.94)	0.086	0.93 (0.90–0.97)	0.90 (0.85–0.97)	0.323	0.92 (0.88–0.96)	0.94 (0.89–0.98)	0.497
uPDI	1.15 (1.10–1.20)	1.12 (1.06–1.17)	0.884	1.15 (1.10–1.21)	1.12 (1.07–1.16)	0.333	1.11 (1.06–1.16)	1.15 (1.11–1.20)	0.271	1.13 (1.09–1.17)	1.14 (1.08–1.22)	0.909	1.15 (1.10–1.20)	1.11 (1.07–1.16)	0.204
Pancreas															
PDI	0.98 (0.87–1.11)	0.91 (0.79–1.06)	0.409	0.94 (0.80–1.11)	0.96 (0.86–1.08)	0.581	0.90 (0.77–1.05)	0.97 (0.86–1.10)	0.338	0.96 (0.86–1.07)	0.93 (0.78–1.12)	0.871	0.97 (0.84–1.12)	0.91 (0.80–1.03)	0.449
hPDI	0.88 (0.78–0.98)	0.87 (0.77–1.00)	0.928	0.87 (0.76–0.99)	0.88 (0.79–0.98)	0.455	0.86 (0.75–0.98)	0.88 (0.79–0.99)	0.782	0.90 (0.82–0.99)	0.79 (0.65–0.95)	0.415	0.85 (0.75–0.97)	0.88 (0.78–0.98)	0.770
uPDI	1.09 (0.97–1.22)	1.14 (1.01–1.28)	0.609	1.17 (1.01–1.34)	1.07 (0.96–1.18)	0.276	1.12 (0.99–1.28)	1.08 (0.97–1.20)	0.527	1.11 (1.01–1.21)	1.05 (0.87–1.28)	0.462	1.17 (1.03–1.32)	1.08 (0.97–1.20)	0.236

Abbreviations: BMI, body mass index; p_{het}, p from the heterogeneity test.

[a] Adjusted for sex, quinquennia of age, study center, year of interview, years of education, tobacco smoking, alcohol drinking, body mass index, and total energy intake, unless the variable was the stratification factor. Models for pancreatic cancer were additionally adjusted for history of diabetes; models for colorectal cancer were additionally adjusted for history of diabetes, regular aspirin use, occupational physical activity, age at menopause and use of hormone replacement therapy, and family history of colorectal cancer.

[b] No-light alcohol drinking was defined as 0 to <14 drinks per week in the stomach, colorectal and pancreatic cancer studies, and as 0 to <28 drinks per week in the oral/pharyngeal and esophageal cancer studies; moderate-high alcohol drinking was defined as ≥14 drinks per week in the stomach, colorectal and pancreatic cancer studies, and as ≥28 drinks per week in the oral/pharyngeal and esophageal cancer studies.

supported a protective role of fiber intake on colorectal cancer [51]; a number of studies also suggested a role on other digestive system cancers [52–54]. Polyphenols, mainly flavonoids [55–57] and, to a lesser extent and consistency, carotenoids [58–60] have been associated with reduced risks of various digestive cancers. As for types of fats, while n-3 polyunsaturated fatty acids may have anti-inflammatory effects and have been favorably associated with some chronic diseases including cardiovascular diseases [61], epidemiological evidence linking these fatty acids with digestive cancers is largely inconsistent [62–64]. Similarly, an association between saturated fats and cancer risk has been suggested, but the evidence on single cancer sites is limited and inconclusive [65,66]. Indirectly, a healthy plant-based diet may protect against certain types of cancer through improvements in body weight, adiposity and metabolic profiles. Various epidemiological studies indeed showed inverse associations between healthy PDIs and the risk of obesity [67] and cardiometabolic diseases [68], including the metabolic syndrome [69]. On the other hand, a study found that an overall plant-based diet which emphasizes all types of plant foods had no effect on anthropometric measures [70].

Among the unhealthy plant foods characterizing the uPDI, refined grains and added sugars contribute to a higher glycemic load, which is associated with insulin resistance with possible hyperinsulinemia and increased insulin-like growth factor 1 (IGF-1), both involved in the etiology and progression of cancer [71]. Furthermore, processed meat contains nitrates and nitrites, and high-temperature cooked meat contains heterocyclic amines, all of which are potential carcinogens. Pasta is a common carbohydrate rich food of the Italian diet. Although it is classified as a refined grain among the unhealthy plant foods in the original formulation of the scores [20], most Italian pasta has a low glycemic index [72] and its consumption, unlike white bread, was not associated with an increased risk of colorectal cancer in a previous analysis within our study network [18]. Also, pasta has been shown to be a healthy food in observational and intervention studies [73,74]. In a sensitivity analysis, we obtained similar findings upon classifying pasta together with whole grains within the healthy plant foods, indicating that pasta can be considered a healthy carbohydrate source in the context of a healthy plant-based diet.

Some study limitations need to be considered. With reference to selection bias, cases were identified in the major teaching and general hospitals of the area under surveillance; the control group was from a comparable catchment area as the case group and excluded patients admitted for chronic conditions or for diseases related to diet modifications or known risk factors for digestive system cancers; and the participation rate was high and similar for cases and controls (>95%). Information bias was likely limited by the similar hospital interview setting of cases and controls. Recall bias and measurement error in dietary assessment are possible. However, the FFQ was tested for validity and reproducibility with satisfactory results [35,36]. Because of the retrospective study design, reverse causation due to disease-related changes in dietary habits among cancer cases is possible. However, concentrating on the habitual diet two years before cancer diagnosis should have limited this bias. Further, thought deriving the three PDIs as originally proposed by Satija et al. [20], we were not able to consider separately fruit juices and sugar-sweetened beverages, to include the “miscellanea animal-based foods” group, and to use quintiles for scoring for some food groups. Also, nut consumption was estimated from open questions in the FFQ, with a limited number of respondents. As for confounding, we were able to adjust for several factors, such as education, alcohol drinking, smoking, and total energy intake. Finally, dietary data were collected between 1992 and 2009, and thus our results may not be applicable to current plant-based dietary patterns which can include plant-based meat alternatives. In any case, these products are still very rarely consumed nowadays in the Italian population.

5. Conclusion

In conclusion, our study found an inverse association between a plant-based diet and the risk of several digestive cancers. The association was stronger for a plant-based diet emphasizing healthy plant foods. Conversely, a plant-based diet that emphasizes unhealthy plant foods was associated with an increased risk of digestive cancers. Our findings thus underscore the importance of considering the healthiness and quality of plant foods in the context of a plant-based diet, supporting current dietary recommendations that promote healthy, nutritious and sustainable plant-based dietary patterns.

Author contributions

Federica Turati: Conceptualization, Methodology, Formal analysis, Writing (Original Draft); Silvia Mignozzi: Formal analysis, Writing (Review & Editing); Giovanna Esposito: Conceptualization, Methodology, Formal analysis, Writing (Review & Editing); Francesca Bravi: Formal analysis, Writing (Review & Editing); Angela D'Angelo: Writing (Review & Editing); Gianfranco Alicandro: Writing (Review & Editing); Werner Garavello: Investigation, Writing (Review & Editing); Livia S.A. Augustin: Investigation, Writing (Review & Editing); Sara Vitale: Writing (Review & Editing); Attilio Giacosa: Investigation, Writing (Review & Editing); Ettore Bidoli: Investigation, Writing (Review & Editing); Jerry Polesel: Investigation, Writing (Review & Editing); Eva Negri: Investigation, Writing (Review & Editing); Monica Ferraroni: Conceptualization, Writing (Review & Editing); Carlo La Vecchia: Conceptualization, Investigation, Writing (Review & Editing). All authors approved the final version of the manuscript.

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Conflict of interest

LSAA is a founding member and CLV a member of the International Carbohydrate Quality Consortium (ICQC). LSAA has received honoraria from the Nutrition Foundation of Italy (NFI). All other authors: no conflict of interest are reported.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2024.11.039.

References

[1] World Cancer Research Fund/American Institute for Cancer Research. Diet, nutrition, physical activity and cancer: a global perspective. Continuous Update Project Expert Report 2018. Available at: dietandcancerreport.org.

[2] Turati F, Rossi M, Pelucchi C, Levi F, La Vecchia C. Fruit and vegetables and cancer risk: a review of southern European studies. Br J Nutr 2015;113(Suppl 2):S102–10.
[3] Ferro A, Rosato V, Rota M, Costa AR, Morais S, Pelucchi C, et al. Meat intake and risk of gastric cancer in the Stomach cancer Pooling (StoP) project. Int J Cancer 2020;147:45–55.
[4] Zhao Z, Yin Z, Pu Z, Zhao Q. Association between consumption of red and processed meat and pancreatic cancer risk: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2017;15:486–93 e10.
[5] Chuang SC, Jenab M, Heck JE, Bosetti C, Talamini R, Matsuo K, et al. Diet and the risk of head and neck cancer: a pooled analysis in the INHANCE consortium. Cancer Causes Control 2012;23:69–88.
[6] Storz MA. What makes a plant-based diet? a review of current concepts and proposal for a standardized plant-based dietary intervention checklist. Eur J Clin Nutr 2022;76:789–800.
[7] Yannakoulia M, Scarmeas N. Diets. N Engl J Med 2024;390:2098–106.
[8] Dybvik JS, Svendsen M, Aune D. Vegetarian and vegan diets and the risk of cardiovascular disease, ischemic heart disease and stroke: a systematic review and meta-analysis of prospective cohort studies. Eur J Nutr 2023;62:51–69.
[9] Dinu M, Abbate R, Gensini GF, Casini A, Sofi F. Vegetarian, vegan diets and multiple health outcomes: a systematic review with meta-analysis of observational studies. Crit Rev Food Sci Nutr 2017;57:3640–9.
[10] Parra-Soto S, Ahumada D, Petermann-Rocha F, Boonpoor J, Gallegos JL, Anderson J, et al. Association of meat, vegetarian, pescatarian and fish-poultry diets with risk of 19 cancer sites and all cancer: findings from the UK Biobank prospective cohort study and meta-analysis. BMC Med 2022;20:79.
[11] Paslakis G, Richardson C, Nohre M, Brahler E, Holzapfel C, Hilbert A, et al. Prevalence and psychopathology of vegetarians and vegans - results from a representative survey in Germany. Sci Rep 2020;10:6840.
[12] Greenwell J, Grant M, Young L, Mackay S, Bradbury KE. The prevalence of vegetarians, vegans and other dietary patterns that exclude some animal-source foods in a representative sample of New Zealand adults. Publ Health Nutr 2023;27:e5.
[13] Valdes M, Conklin A, Veenstra G, Black JL. Plant-based dietary practices in Canada: examining definitions, prevalence and correlates of animal source food exclusions using nationally representative data from the 2015 Canadian Community Health Survey-Nutrition. Publ Health Nutr 2021;24:777–86.
[14] Hu EA, Pan A, Malik V, Sun Q. White rice consumption and risk of type 2 diabetes: meta-analysis and systematic review. BMJ 2012;344:e1454.
[15] Augustin LSA, Kendall CWC, Jenkins DJA, Willett WC, Astrup A, Barclay AW, et al. Glycemic index, glycemic load and glycemic response: an international scientific consensus summit from the international carbohydrate quality consortium (ICQC). Nutr Metabol Cardiovasc Dis 2015;25:795–815.
[16] Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC, Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. Diabetes Care 2010;33:2477–83.
[17] Turati F, Galeone C, Augustin LSA, La Vecchia C. Glycemic index, glycemic load and cancer risk: an updated meta-analysis. Nutrients 2019;11:2342.
[18] Augustin LSA, Malerba S, Lugo A, Franceschi S, Talamini R, Serraino D, et al. Associations of bread and pasta with the risk of cancer of the breast and colorectum. Ann Oncol 2013;24:3094–9.
[19] Chazelas E, Srour B, Desmetz E, Kesse-Guyot E, Julia C, Deschamps V, et al. Sugary drink consumption and risk of cancer: results from NutriNet-Sante prospective cohort. BMJ 2019;366:l2408.
[20] Satija A, Bhupathiraju SN, Rimm EB, Spiegelman D, Chiuve SE, Borgi L, et al. Plant-based dietary patterns and incidence of type 2 diabetes in US men and women: results from three prospective cohort studies. PLoS Med 2016;13:e1002039.
[21] Martinez-Gonzalez MA, Sanchez-Tainta A, Corella D, Salas-Salvado J, Ros E, Aros F, et al. A provegetarian food pattern and reduction in total mortality in the Prevencion con Dieta Mediterranea (PREDIMED) study. Am J Clin Nutr 2014;100(Suppl 1). 320S-8S.
[22] Chen Z, Zuurmond MG, van der Schaft N, Nano J, Wijnhoven HAH, Ikram MA, et al. Plant versus animal based diets and insulin resistance, prediabetes and type 2 diabetes: the Rotterdam Study. Eur J Epidemiol 2018;33:883–93.
[23] Kim J, Kim H, Giovannucci EL. Plant-based diet quality and the risk of total and disease-specific mortality: a population-based prospective study. Clin Nutr 2021;40:5718–25.
[24] Li H, Zeng X, Wang Y, Zhang Z, Zhu Y, Li X, et al. A prospective study of healthful and unhealthful plant-based diet and risk of overall and cause-specific mortality. Eur J Nutr 2022;61:387–98.
[25] Kane-Diallo A, Srour B, Sellem L, Deschasaux M, Latino-Martel P, Hercberg S, et al. Association between a pro plant-based dietary score and cancer risk in the prospective NutriNet-sante cohort. Int J Cancer 2018;143:2168–76.
[26] Kim J, Khil J, Kim H, Keum N, Zhang X, Giovannucci E. Plant-based dietary patterns and the risk of digestive system cancers in 3 large prospective cohort studies. Eur J Epidemiol 2023;38:617–27.
[27] Cai Y, Hong C, Han J, Fan L, Xiao X, Xiao J, et al. Healthy dietary patterns, genetic risk, and gastrointestinal cancer incident risk: a large-scale prospective cohort study. Am J Clin Nutr 2024;119:406–16.
[28] Turati F, Edefonti V, Bosetti C, Ferraroni M, Malvezzi M, Franceschi S, et al. Family history of cancer and the risk of cancer: a network of case-control studies. Ann Oncol 2013;24:2651–6.
[29] Bravi F, Polesel J, Garavello W, Serraino D, Negri E, Franchin G, et al. Adherence to the World cancer research fund/American institute for cancer research recommendations and head and neck cancers risk. Oral Oncol 2017;64:59–64.
[30] Bosetti C, La Vecchia C, Talamini R, Simonato L, Zambon P, Negri E, et al. Food groups and risk of squamous cell esophageal cancer in northern Italy. Int J Cancer 2000;87:289–94.
[31] Pelucchi C, Tramacere I, Bertuccio P, Tavani A, Negri E, La Vecchia C. Dietary intake of selected micronutrients and gastric cancer risk: an Italian case-control study. Ann Oncol 2009;20:160–5.
[32] Franceschi S, Favero A, La Vecchia C, Negri E, Conti E, Montella M, et al. Food groups and risk of colorectal cancer in Italy. Int J Cancer 1997;72:56–61.
[33] Lucenteforte E, Talamini R, Bosetti C, Polesel J, Franceschi S, Serraino D, et al. Macronutrients, fatty acids, cholesterol and pancreatic cancer. Eur J Cancer 2010;46:581–7.
[34] Gnagnarella P, Parpinel M, Salvini S, Franceschi S, Palli D, Boyle P. The update of the of the Italian food composition database. J Food Compos Anal 2004;17:502–5022.
[35] Franceschi S, Negri E, Salvini S, Decarli A, Ferraroni M, Filiberti R, et al. Reproducibility of an Italian food frequency questionnaire for cancer studies: results for specific food items. Eur J Cancer 1993;29A:2298–305.
[36] Decarli A, Franceschi S, Ferraroni M, Gnagnarella P, Parpinel MT, La Vecchia C, et al. Validation of a food-frequency questionnaire to assess dietary intakes in cancer studies in Italy. Results for specific nutrients. Ann Epidemiol 1996;6:110–8.
[37] Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. JAMA 2006;296:1885–99.
[38] Aglago EK, Huybrechts I, Murphy N, Casagrande C, Nicolas G, Pischon T, et al. Consumption of fish and long-chain n-3 polyunsaturated fatty acids is associated with reduced risk of colorectal cancer in a large European cohort. Clin Gastroenterol Hepatol 2020;18:654–666 e6.
[39] Fernandez E, Chatenoud L, La Vecchia C, Negri E, Franceschi S. Fish consumption and cancer risk. Am J Clin Nutr 1999;70:85–90.
[40] Edwards CH, Ryden P, Mandalari G, Butterworth PJ, Ellis PR. Structure-function studies of chickpea and durum wheat uncover mechanisms by which cell wall properties influence starch bioaccessibility. Nat Food 2021;2:118–26.
[41] Augustin LSA, Aas AM, Astrup A, Atkinson FS, Baer-Sinnott S, Barclay AW, et al. Dietary fibre consensus from the international carbohydrate quality consortium (ICQC). Nutrients 2020;12:2553.
[42] McEvoy CT, Temple N, Woodside JV. Vegetarian diets, low-meat diets and health: a review. Publ Health Nutr 2012;15:2287–94.
[43] Wang T, Masedunskas A, Willett WC, Fontana L. Vegetarian and vegan diets: benefits and drawbacks. Eur Heart J 2023;44:3423–39.
[44] World Cancer Research Fund/American Institute for Cancer Research. Continuous update project expert report. Meat, fish and dairy products and the risk of cancer 2018. Available at: dietandcancerreport.org.
[45] Oncina-Canovas A, Gonzalez-Palacios S, Notario-Barandiaran L, Torres-Collado L, Signes-Pastor A, de-Madaria E, et al. Adherence to pro-vegetarian food patterns and risk of oesophagus, stomach, and pancreas cancers: a multi case-control study (the PANESOES study). Nutrients 2022;14:5288.
[46] Kim J, Boushey CJ, Wilkens LR, Haiman CA, Le Marchand L, Park SY. Plant-based dietary patterns defined by a priori indices and colorectal cancer risk by sex and race/ethnicity: the Multiethnic Cohort Study. BMC Med 2022;20:430.
[47] Wu B, Zhou RL, Ou QJ, Chen YM, Fang YJ, Zhang CX. Association of plant-based dietary patterns with the risk of colorectal cancer: a large-scale case-control study. Food Funct 2022;13:10790–801.
[48] Zhang X, He F, Li J, Chen R, Li X, Li L, et al. Plant-based dietary patterns and risk of esophageal cancer: a prospective cohort study spanning 17 years. Chin J Cancer Res 2024;36:36–45.
[49] Cummings JH, Bingham SA, Heaton KW, Eastwood MA. Fecal weight, colon cancer risk, and dietary intake of nonstarch polysaccharides (dietary fiber). Gastroenterology 1992;103:1783–9.
[50] Bultman SJ. Molecular pathways: gene-environment interactions regulating dietary fiber induction of proliferation and apoptosis via butyrate for cancer prevention. Clin Cancer Res 2014;20:799–803.
[51] Aune D, Chan DS, Lau R, Vieira R, Greenwood DC, Kampman E, et al. Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies. BMJ 2011;343:d6617.
[52] Collatuzzo G, Cortez Lainez J, Pelucchi C, Negri E, Bonzi R, Palli D, et al. The association between dietary fiber intake and gastric cancer: a pooled analysis of 11 case-control studies. Eur J Nutr 2024;63:1857–65.
[53] Kawakita D, Lee YA, Gren LH, Buys SS, La Vecchia C, Hashibe M. Fiber intake and the risk of head and neck cancer in the prostate, lung, colorectal and ovarian (PLCO) cohort. Int J Cancer 2019;145:2342–8.
[54] Sun L, Zhang Z, Xu J, Xu G, Liu X. Dietary fiber intake reduces risk for Barrett's esophagus and esophageal cancer. Crit Rev Food Sci Nutr 2017;57:2749–57.
[55] Chang H, Lei L, Zhou Y, Ye F, Zhao G. Dietary flavonoids and the risk of colorectal cancer: an updated meta-analysis of epidemiological studies. Nutrients 2018;10:950.
[56] Rossi M, Garavello W, Talamini R, Negri E, Bosetti C, Dal Maso L, et al. Flavonoids and the risk of oral and pharyngeal cancer: a case-control study from Italy. Cancer Epidemiol Biomarkers Prev 2007;16:1621–5.
[57] Vitelli-Storelli F, Rossi M, Pelucchi C, Rota M, Palli D, Ferraroni M, et al. Polyphenol intake and gastric cancer risk: findings from the stomach cancer pooling project (StoP). Cancers (Basel) 2020;12:3064.
[58] Leoncini E, Edefonti V, Hashibe M, Parpinel M, Cadoni G, Ferraroni M, et al. Carotenoid intake and head and neck cancer: a pooled analysis in the international head and neck cancer epidemiology consortium. Eur J Epidemiol 2016;31:369–83.

[59] Leenders M, Leufkens AM, Siersema PD, van Duijnhoven FJ, Vrieling A, Hulshof PJ, et al. Plasma and dietary carotenoids and vitamins A, C and E and risk of colon and rectal cancer in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 2014;135:2930–9.
[60] Jenab M, Riboli E, Ferrari P, Friesen M, Sabate J, Norat T, et al. Plasma and dietary carotenoid, retinol and tocopherol levels and the risk of gastric adenocarcinomas in the European prospective investigation into cancer and nutrition. Br J Cancer 2006;95:406–15.
[61] Marventano S, Kolacz P, Castellano S, Galvano F, Buscemi S, Mistretta A, et al. A review of recent evidence in human studies of n-3 and n-6 PUFA intake on cardiovascular disease, cancer, and depressive disorders: does the ratio really matter? Int J Food Sci Nutr 2015;66:611–22.
[62] Nguyen S, Li H, Yu D, Cai H, Gao J, Gao Y, et al. Dietary fatty acids and colorectal cancer risk in men: a report from the Shanghai Men's Health Study and a meta-analysis. Int J Cancer 2021;148:77–89.
[63] Hirabayashi M, Wilunda C, Murai U, Yamaji T, Iwasaki M, Inoue M, et al. Association between fish and shellfish consumption, n-3 polyunsaturated fatty acids, and gastric cancer risk: the Japan Public Health Center-based Prospective Study. Eur J Nutr 2024;63:1529–44.
[64] Tavani A, Pelucchi C, Parpinel M, Negri E, Franceschi S, Levi F, et al. n-3 polyunsaturated fatty acid intake and cancer risk in Italy and Switzerland. Int J Cancer 2003;105:113–6.
[65] Sellem L, Srour B, Gueraud F, Pierre F, Kesse-Guyot E, Fiolet T, et al. Saturated, mono- and polyunsaturated fatty acid intake and cancer risk: results from the French prospective cohort NutriNet-Sante. Eur J Nutr 2019;58:1515–27.
[66] Mei J, Qian M, Hou Y, Liang M, Chen Y, Wang C, et al. Association of saturated fatty acids with cancer risk: a systematic review and meta-analysis. Lipids Health Dis 2024;23:32.
[67] Jarvis SE, Nguyen M, Malik VS. Association between adherence to plant-based dietary patterns and obesity risk: a systematic review of prospective cohort studies. Appl Physiol Nutr Metabol 2022;47:1115–33.
[68] Nikparast A, Mirzaei P, Tadayoni ZS, Asghari G. The association between overall, healthy, and unhealthy plant-based diet index and risk of prediabetes and type 2 diabetes mellitus: a systematic review and dose-response meta-analysis of prospective studies. Nutr Rev 2024.
[69] Jafari F, Amini Kahrizsangi M, Najam W, Fattahi MR, Nouri M, Ghalandari H, et al. Association of plant-based dietary patterns with metabolic syndrome: baseline results from the Persian Kavar cohort study (PKCS). Int J Food Sci Nutr 2023;74:291–301.
[70] Siqueira C, Esteves LG, Duarte CK. Plant-based diet index score is not associated with body composition: a systematic review and meta-analysis. Nutr Res 2022;104:128–39.
[71] Gallagher EJ, LeRoith D. The proliferating role of insulin and insulin-like growth factors in cancer. Trends Endocrinol Metabol 2010;21:610–8.
[72] Jenkins DJ, Wolever TM, Jenkins AL, Lee R, Wong GS, Josse R. Glycemic response to wheat products: reduced response to pasta but no effect of fiber. Diabetes Care 1983;6:155–9.
[73] Huang M, Lo K, Li J, Allison M, Wu WC, Liu S. Pasta meal intake in relation to risks of type 2 diabetes and atherosclerotic cardiovascular disease in postmenopausal women : findings from the Women's Health Initiative. BMJ Nutr Prev Health 2021;4:195–205.
[74] Vitale M, Masulli M, Rivellese AA, Bonora E, Babini AC, Sartore G, et al. Pasta consumption and connected dietary habits: associations with glucose control, adiposity measures, and cardiovascular risk factors in people with type 2 diabetes-TOSCA.IT study. Nutrients 2019;12:101.