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SYSTEMATIC REVIEWS AND META-ANALYSES

Vegetarianism and breast, colorectal and prostate cancer risk: an overview and meta-analysis of cohort studies

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Abstract

Background: Vegetarian diets may be associated with certain benefits toward human health, although current evidence is scarce and contrasting. In the present study, a systematic review and meta-analysis of prospective cohort studies was performed with respect to the association between vegetarian diets and breast, colorectal and prostate cancer risk.
Methods: Studies were systematically searched in Pubmed and EMBASE electronic databases. Eligible studies had a prospective design and compared vegetarian, semi- and pesco-vegetarian diets with a non-vegetarian diet. Random-effects models were applied to calculate relative risks (RRs) of cancer between diets. Statistical heterogeneity and publication bias were explored.
Results: A total of nine studies were included in the meta-analysis. Studies were conducted on six cohorts accounting for 686 629 individuals, and 3441, 4062 and 1935 cases of breast, colorectal and prostate cancer, respectively. None of the analyses showed a significant association of vegetarian diet and a lower risk of either breast, colorectal, and prostate cancer compared to a non-vegetarian diet. By contrast, a lower risk of colorectal cancer was associated with a semi-vegetarian diet (RR = 0.86, 95% confidence interval = 0.79–0.94; I^2 = 0%, $P_{heterogeneity}$ = 0.82) and a pesco-vegetarian diet (RR = 0.67, 95% confidence interval = 0.53, 0.83; I^2 = 0%, $P_{heterogeneity}$ = 0.46) compared to a non-vegetarian diet. The subgroup analysis by cancer localisation showed no differences in summary risk estimates between colon and rectal cancer.
Conclusions: A summary of the existing evidence from cohort studies on vegetarian diets showed that complete exclusion of any source of protein from the diet is not associated with further benefits for human health.

Introduction

Cancer is a major malignancy worldwide and a common cause of death in both men and women (1). Among the most frequent and deadly cancers, colorectal cancer, breast cancer in women, and prostate cancer in men, are the most representative (1). Current knowledge suggests that extrinsic environmental factors are the main contributors to carcinogenesis and, among them, diet could play a key role in modifying the risk of cancer (2). Compounds characterising dietary content may potentially exert protective and adverse action toward cancer risk as a result of direct and indirect effects (3). Plant-based dietary patterns high in fruit and vegetables are rich in fibre (4), antioxidant compounds and healthy fatty acids, both monounsaturated fatty acids and polyunsaturated fatty acids (PUFA), which are associated with a decreased risk of cancer (5,6). By contrast, diets characterised by processed fat foods, alcoholic beverages and sweets, rich in trans-fatty acids, alcohol and refined carbohydrates, have been related with an increased risk of cancer, mainly but not limited to digestive tract cancers (7–9).

Following the International Agency for Research on Cancer (IARC) classification of consumption of red meat as 'probably carcinogenic to humans' and of processed meat as 'carcinogenic to humans', vegetarian diets have gained particular attention from the general population, despite current scientific evidence of their effects on human health still being scarce [10]. A vegetarian diet is defined as a dietary profile characterised by abstention from consuming meat (including red meat, fish and poultry) [11]. From a public health point of view, it is unclear whether the restrictive approach related to vegetarian diets (i.e. 'no meat consumption') would result in better health outcomes than plant-based dietary guidelines. Indeed, there is no comprehensive evidence demonstrating that individuals would better benefit from a vegetarian rather than other 'healthy' and sustainable dietary patterns. A dated pooled analysis of cohort studies conducted to explore the association between vegetarian diets and mortality showed no significant differences between vegetarians and non-vegetarians [12]. A more recent study attempted to investigate noncommunicable disease risk and mortality-related outcomes in relation to vegetarian diets, suggesting that an association with decreased incidence and mortality of cardiovascular disease and cancer may exist [13]. However, updated findings have been published recently and there is no summary analysis comparing meat eaters and vegetarians in relation to risk of individual cancers. Thus, the present study aimed to summarise evidence on vegetarian diets and the risk of breast, colorectal and prostate cancer in cohort studies.

Materials and methods

Study search

A systematic search on PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and EMBASE (http://www.embase.com/) databases of English language studies published up to March 2016 was performed. Search terms included the following keywords, used in combination: 'vegetarian', 'vegetarianism', 'vegetarian diet', 'dietary pattern', 'cancer' and their variants. Inclusion criteria were: (i) having a prospective cohort study design; (ii) evaluating the association between adoption of vegetarian compared to a non-vegetarian diet and the risk of breast, colorectal, or prostate cancer; (iii) assessed and reported a measure of association for the outcome considered as hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs). Reference lists of included studies were scrutinised for any article not previously identified. The selection process was independently performed by two investigators.

Data extraction and study quality assessment

Data were extracted from selected studies using a standardised extraction form. The information collected comprised: (i) author name; (ii) year of publication; (iii) cohort name, length of follow-up, country; (iv) number, sex, and age of participants and cases; (v) reference category and HR and 95% CI for the other categories of exposure; and (vi) covariates used in adjustments.

The Newcastle-Ottawa Quality Assessment Scale was used to assess the quality of each study [14]. The instrument consists of three domains indicating the study quality as: selection (4 points), comparability (2 points) and outcome (3 points) for a total score of 9 points (with 9 representing the highest quality). Studies scoring 7–9 points, 3–6 points and 0–3 points were identified as high, moderate and low quality, respectively.

Statistical analysis

When more than one study was published on the same cohort or group of patients, only the most comprehensive or the most updated was selected to perform the meta-analyses. Random-effects models were used to calculate risk ratios (RRs) with 95% CIs for various qualitative categories of exposure (i.e., meat eaters versus vegetarians). The risk estimate from the most fully adjusted models in the analysis of the pooled RR was used. Heterogeneity was assessed using the Q test and I^2 statistic. The level of significance for the Q test was defined as $P < 0.10$. The I^2 statistic represented the amount of total variation that could be attributed to heterogeneity. $I^2 > 50$ indicates high heterogeneity. When data were sufficient to perform subgroup analyses, the following variables were tested as a potential source of heterogeneity: menopausal status for breast cancer, cancer topography (i.e. colon and rectum) and sex for colorectal cancer, and stadium (i.e. advanced) for prostate cancer risk. Publication bias was evaluated by a visual investigation of funnel plots for potential asymmetry. All analyses were performed using REVMAN, version 5.2 (The Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Out of the 93 unique citations, 75 were excluded after abstract examination and nine were excluded after full-text reading for the following reasons: five studies explored cancer mortality; two studies explored total cancer incidence risk; and two studies were overlapping (Fig. 1). This selection process led to the consideration of nine studies [15–23] to be included in this meta-analysis.

Study characteristics

The main characteristics of the study included are presented in Table 1. Cohorts investigated included the

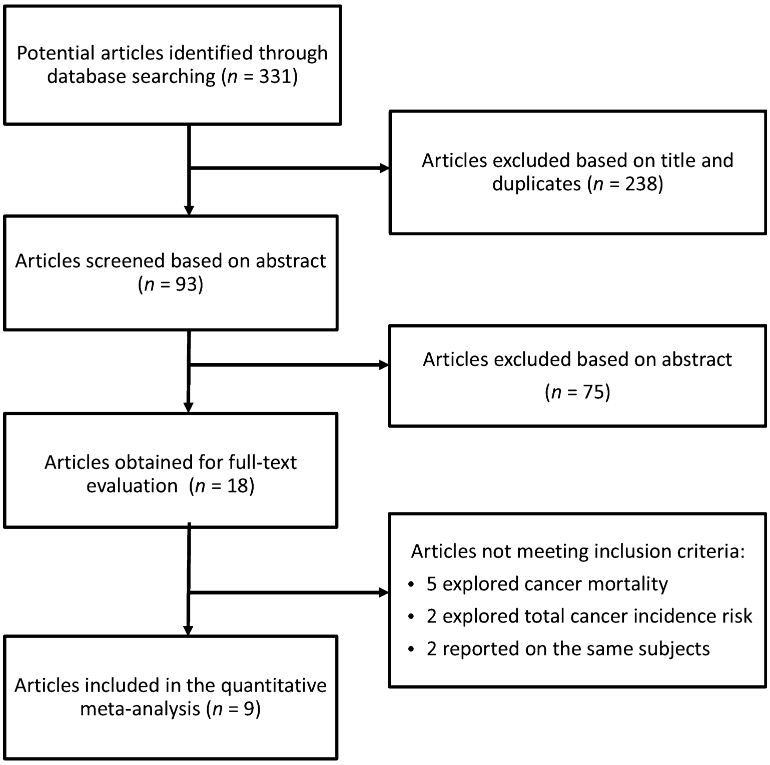

Figure 1 Study selection flow chart.

National Institutes of Health/American Association of Retired Persons (NIH-AARP) Diet and Health Study [16], the Adventist Health Study-2 (AHS-2) [20,22,23], the Oxford Vegetarian Study (OVS) and the European Prospective Investigation into Cancer and Nutrition (EPIC)-Oxford cohort [15,18], the UK Women Cohort Study (UKWHS) [17], and the Netherlands Cohort Study-Meat Investigation Cohort (NLCS-MIC) [19,21], accounting for a total of 686 629 individuals. Two studies on breast cancer [15,18] were conducted on the same cohort but were included in two different analysis: one [18] had a larger sample, which was suitable for the general analysis; the other [15] had specific information on pre- and post-menopausal cancer risk, which was used for the subgroup analysis. The follow-up periods ranged between 5 and 20 years. All studies adjusted for variables potentially related with cancer incidence, including sex, body mass index, smoking status, physical activity, energy intake, and hormonal and parity status in women. Study quality was high for all articles included in the analyses.

Cohort profiles

Two cohorts were conducted in the North America and four in Europe. Among the former, the NIH-AARP Diet and Health Study was the largest included in this meta-analysis [16]: the cohort was established in 1995–1996 and involved 492 306 men and women above 50 years of age from six US states. Incident cases of cancer were identified by linkage between the NIH-AARP cohort membership and cancer registry databases of the targeted states. The AHS-2 was a cohort study of 90422 members of the Seventh-Day Adventist churches over all US states and Canada [20,22,23]; their religious beliefs discourage the consumption of meat (especially pork) and recommend abstinence from alcoholic beverages, tobacco and illegal drugs. Cancer cases were identified by computer-matching identifying information from AHS-2 study subjects to lists of cases in state cancer registries. Among the cohorts conducted in Europe, participants of the OVS (n = 11 140) were recruited throughout the UK between 1980 and 1984 through advertisements, the news media and word of mouth, whereas the EPIC-Oxford ones were recruited between 1993 and 1999 by general practitioners (n = 7421) and by mail (n = 57 990) [15,18]. Participants in both studies were followed until 31 December 2010 by record linkage with the UK National Health Service (NHS) Central Register, which provides information on cancer diagnoses and all deaths. Women of the UKWHS were responders to a direct mail survey of the World Cancer Research Fund (WCRF), with 35 372 women aged 35–69 years responders from England, Wales and Scotland [17]. Subjects were flagged with the NHS Central Register for cancer and death notification. The NLCS-MIC started in September 1986 and included 12 852 men and women who were 55–69 years at baseline and

Table 1 Main characteristics of the cohort studies conducted on vegetarian diets and cancer risk included in the meta-analysis

Author (year)	Cancer site	Study cohort, f-up (country)	Number of individuals or controls	Number of cases	Age range, years	Dietary assessment	Factors adjustment	Study quality
Travis (2008) [15]	Breast	EPIC–Oxford cohort, 7.4 years (UK)	37 643	585	20–89	FFQ, 45 items	Height, BMI, age at menarche, age at first birth and parity, alcohol consumption, daily energy intake, menopausal status, and current hormone replacement therapy	High
Wirfalt (2009) [16]	Colon and rectal	NIH-AARP Diet and Health Study 1995–2000, 5 years (USA)	492 306 (293 576 men and 198 730 women)	In men, 631 rectal and 1539 olon. In women 258 rectal and 707 colon	50–71	FFQ, 181 items	Age, BMI, education, ethnicity, smoking, leisure time physical activity and total energy. In women also adjusted for hormone replacement therapy	High
Cade (2010) [17]	Breast	UKWCS, 9 years (UK)	33 725	783	35–69	FFQ, 217 items	Age, energy intake, menopausal status, calorie adjusted fat, BMI, physical activity, hormone replacement therapy use, smoking status, parity, age at menarche, ethanol, total days breast feeding, socioeconomic class and level of education	High
Key (2014)* [18]	Colorectal, breast, and prostate	OVS and EPIC–Oxford cohort, 14.9 years (UK)	61 647 (15 594 men and 46 053 women)	579 colorectal, 1454 breast, 457 prostate	20–89	FFQ, 45 items (Oxford Vegetarian Study); FFQ, 130 items (EPIC-Oxford)	Smoking, alcohol consumption, physical activity level, BMI; + parity and oral contraceptive use for breast cancer	High
Orlich (2015) [20]	Colorectal	AHS-2, 7.3 years (USA and Canada)	77 659	490	≥25	FFQ, 200 items	Age, sex, race, educational level, moderate or vigorous exercise, smoking, alcohol, family history of colorectal cancer, history of peptic ulcer, history of inflammatory bowel disease, treatment for diabetes mellitus within the past year, aspirin use, statin therapy, prior colonoscopy or flexible sigmoidoscopy, supplemental calcium consumption, supplemental vitamin D, dietary energy, hormone therapy among menopausal women, BMI, fibre intake	High

Table 1 Continued

Author (year)	Cancer site	Study cohort, f-up (country)	Number of individuals or controls	Number of cases	Age range, years	Dietary assessment	Factors adjustment	Study quality
Tantamango-Bartley (2016)	Prostate	AHS-2, 7.8 years (USA and Canada)	33 715	1079 (237 advanced)	≥30	FFQ, 200 items	Race, family history of prostate cancer, education, screening for prostate cancer, energy intake and BMI	High
Gilsing (2015) [19]	Colorectal	NLCS-MIC, 20.3 years (Netherlands)	10 210	437 colorectum (307 colon, 92 rectum)	55–69	FFQ, 150 items	Age, sex, total energy intake, cigarette smoking, alcohol consumption, BMI, non-occupational physical activity and level of education	High
Gilsing (2016) [21]	Prostate and breast†	NLCS-MIC, 20.3 years (Netherlands)	11 082	312 breast, 399 prostate (136 advanced)	55–69	FFQ, 150 items	Age, total energy intake, cigarette smoking, frequency of smoking, duration of smoking, alcohol consumption, BMI, non-occupational physical activity, and level of education; + family history of breast cancer, age menarche, age menopause, age first child, hormone replacement therapy, use of oral contraceptives and number of children for breast cancer; + family history of prostate cancer for prostate cancer	High
Penniecook-Sawyers (2016) [22]	Breast	AHS-2, 7.8 years (USA and Canada)	50 404	892	≥30	FFQ, 200 items	Race, height, physical activity, family history of cancer, mammography in the last 2 years after age 42 years, age at menopause, age at menarche, birth control pills, hormone replacement therapy, age at first child, number of children, breastfeeding, educational level, smoking, alcohol, BMI	High

AHS-2, Adventist Health Study 2; BMI, body mass index; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, food frequency questionnaire; NIH-AARP, National Institutes of Health/American Association of Retired Persons; NLCS-MIC, Netherlands Cohort Study – Meat Investigation Cohort; OVS, Oxford Vegetarian Study; UKWCS, UK Women's Cohort Study.

*Also included total cancers and several other cancer sites.

†Also included lung cancer.

monitored for cancer occurrence by repeated record linkage to the Netherlands Cancer Registry, the Dutch Pathology Registry and the cause of death registry [19,21].

Dietary patterns

All cohort studies used food frequency questionnaires to characterise the diet of participants. In all studies but one, diet characteristics were based on the response frequencies of key dietary components: pure vegetarian diet characterised by eating meat less than once per month; semi-vegetarian diet characterised by low consumption of meat (more than once per month but less than once per week); pesco-vegetarian diet characterised by consumption of fish more than once per month; and non-vegetarian diet characterised by eating meat more than once per week [17–23]. One study explored dietary patterns through cluster analysis and compared the consumption of 'several foods' with a dietary pattern characterised by 'fruit and vegetables' that we considered as 'semi-vegetarian'. In this meta-analysis, we compared a non-vegetarian diet with: (i) pure vegetarian; (ii) semi-vegetarian; and (ii) pesco-vegetarian diets.

Vegetarian diets and breast cancer risk

Four datasets from four studies [17,18,21,22] were analysed to test the association of vegetarian compared to a non-vegetarian diet and breast cancer risk (Fig. 2). The cohorts included the OVS and the EPIC-Oxford cohort [18], the UKWCS [17], the NLCS-MIC [21] and the AHS-2 [22], accounting for more than 35 000 individuals (the exact number was not calculated because one study did not provide the number of women) and 3441 breast cancer cases examined. The analysis showed a nonsignificant decreased risk of breast cancer for vegetarian compared to a non-vegetarian diet (RR = 0.96, 95% CI = 0.88–1.05). There was no evidence of heterogeneity (I^2 = 0%, $P_{heterogeneity}$ = 0.93) or publication bias as asymmetry of funnel plot (see Supporting information, Fig. S1). Subgroup analysis by menopausal status showed similar findings, with no significant results in premenopausal (RR = 0.99, 95% CI: 0.82, 1.20; I^2 = 0%, $P_{heterogeneity}$ = 0.63) and postmenopausal women (RR = 0.93, 95% CI: 0.81, 1.06; I^2 = 0%, $P_{heterogeneity}$ = 0.55).

The same cohorts [17,18,21,22] also evaluated the association of pesco-vegetarian compared to a non-vegetarian diet and breast cancer risk (Fig. 2). The analysis showed mainly null results, with no heterogeneity or asymmetry of funnel plot (see Supporting information, Fig. S1) also in the subgroup analysis by menopausal status (data not shown). The analysis on semi-vegetarian compared to a non-vegetarian diet was conducted on only two studies [21,22] with no significant findings (Fig. 2; see also Supporting information, Fig. S1).

Vegetarian diets and colorectal cancer risk

The association of vegetarian compared to a non-vegetarian diet and colorectal cancer risk was explored in three

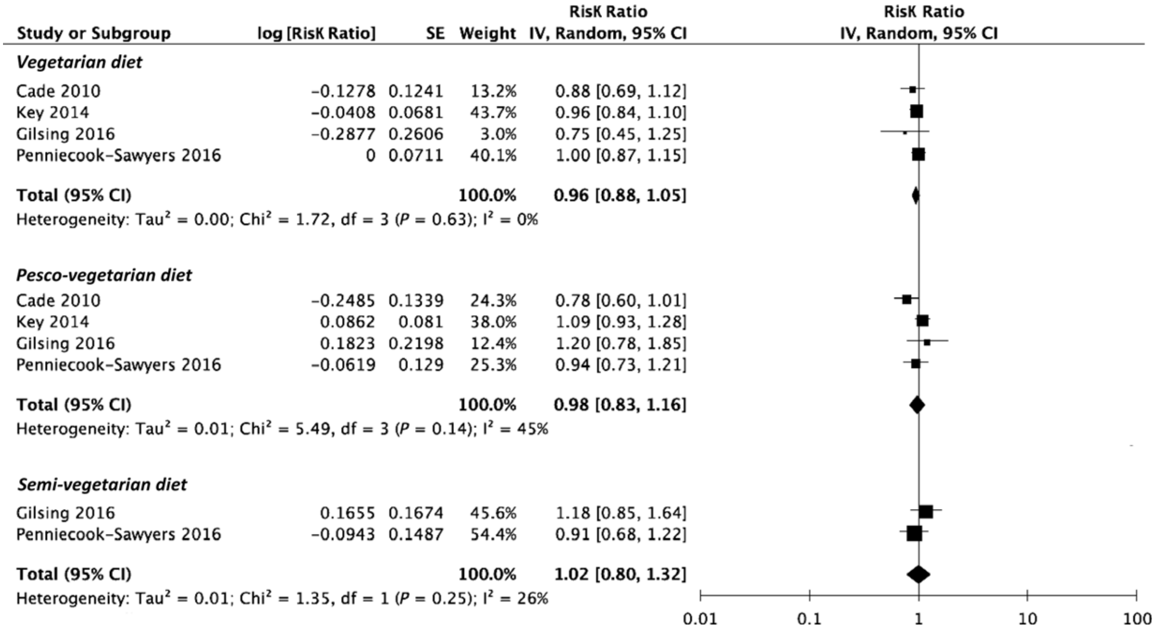

Figure 2 Forest plot of prospective cohort studies evaluating summary risk ratios of breast cancer by adoption of vegetarian, pesco-vegetarian and semi-vegetarian versus non-vegetarian diet (reference). CI, confidence interval.

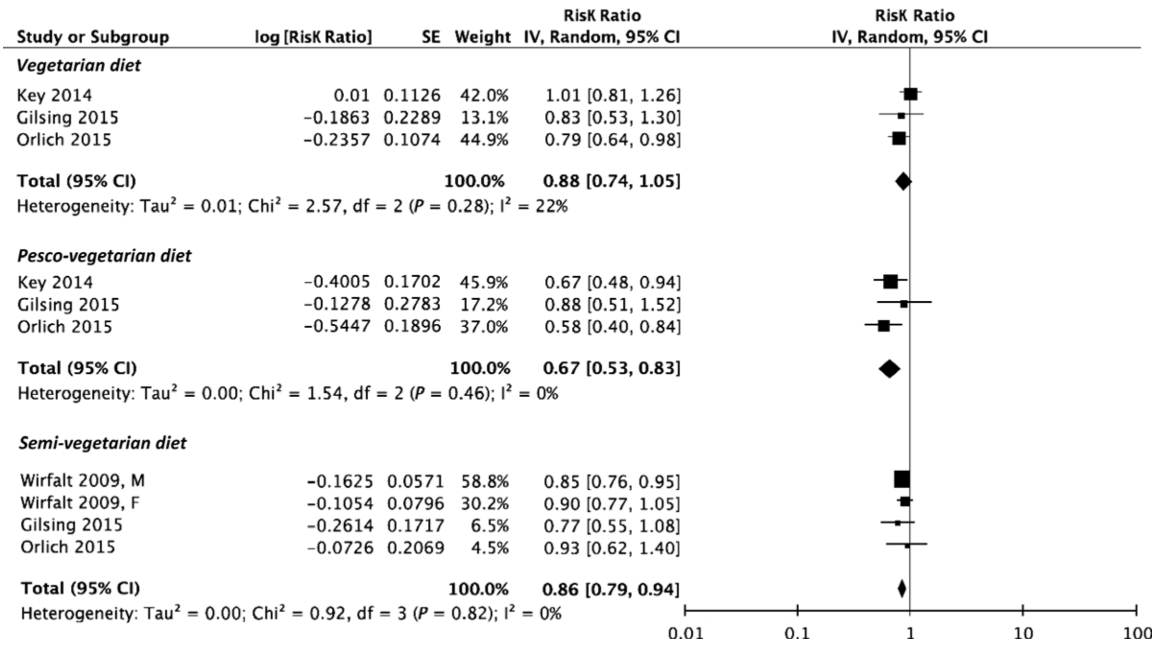

Figure 3 Forest plot of prospective cohort studies evaluating summary risk ratios of colorectal cancer by adoption of vegetarian, pesco-vegetarian and semi-vegetarian versus non-vegetarian diet (reference). CI, confidence interval.

studies [18–20], including the OVS and the EPIC-Oxford cohort, the NLCS-MIC and the AHS-2, for a total of 61 647 individuals and 1056 cases (Fig. 3). The analysis showed a nonsignificant decreased risk of colorectal cancer (RR = 0.88, 95% CI = 0.74–1.05) with no evidence of heterogeneity (I^2 = 22%, $P_{heterogeneity}$ = 0.28) or asymmetry of funnel plot (see Supporting information, Fig. S1). A subgroup analyses by cancer localisation showed no significant difference for colon (RR = 0.91, 95% CI = 0.77–1.08; I^2 = 0%, $P_{heterogeneity}$ = 0.51) and rectal cancer risk (RR = 0.78, 95% CI = 0.46–1.33; I^2 = 63%, $P_{heterogeneity}$ = 0.07). Heterogeneity was a result of the study on the OVS and the EPIC-Oxford cohort [18], despite there being no apparent reasons to explain this; however, exclusion of the study did not lead to significant results.

The association of a pesco-vegetarian diet with colorectal cancer risk was evaluated in three studies, including the four aforementioned cohorts (Fig. 3). The analysis showed the lowest summary risk estimates for adherence to a pesco-vegetarian compared to a non-vegetarian diet (RR = 0.67, 95% CI = 0.53–0.83) with either no evidence of heterogeneity (I^2 = 0%, $P_{heterogeneity}$ = 0.46) or asymmetry of funnel plot (see Supporting information, Fig. S1). By contrast, the subgroup analysis by cancer localisation led to inconclusive results, with a nonsignificant decreased risk of colon (RR = 0.74, 95% CI = 0.52–1.06; I^2 = 6%, $P_{heterogeneity}$ = 0.30) and rectal cancer (RR = 0.70, 95% CI = 0.43–1.13; I^2 = 0%, $P_{heterogeneity}$ = 0.97).

The analysis on semi-vegetarians included four datasets from three cohorts (the NLCS-MIC, the AHS-2, and the NIH-AARP Diet and Health Study) accounting for a total of 580 175 individuals and 4062 cases of colorectal cancer (Fig. 3). The analysis showed a significant association with reduced cancer risk (RR = 0.86, 95% CI = 0.79–0.94) with no evidence of heterogeneity (I^2 = 0%, $P_{heterogeneity}$ = 0.82) or asymmetry of funnel plot (see Supporting information, Fig. S1). However, the summary risk estimates were mainly driven by the two datasets (men and women) provided by the NIH-AARP Diet and Health Study; when these were excluded, the results of the other two cohorts were not significant. Findings were consistent also when considering colon (RR = 0.89, 95% CI = 0.81–0.98; I^2 = 0%, $P_{heterogeneity}$ = 0.86) and rectal cancer risk (RR = 0.81, 95% CI = 0.68–0.96; I^2 = 0%, $P_{heterogeneity}$ = 0.38) independently.

Vegetarian diets and prostatic cancer risk

The analysis on prostate cancer risk was conducted summarising risk estimates from four cohorts [18,21,23] (the OVS and the EPIC-Oxford cohort, the NLCS-MIC and the AHS-2) (Fig. 4) accounting for more than 50 000 individuals (the exact number was not calculated because one study did not provide the number of men), 1935 prostate and 373 advanced prostate cases. A vegetarian diet was associated with a nonsignificant decreased risk of prostate cancer (RR = 0.83, 95% CI = 0.63–1.10)

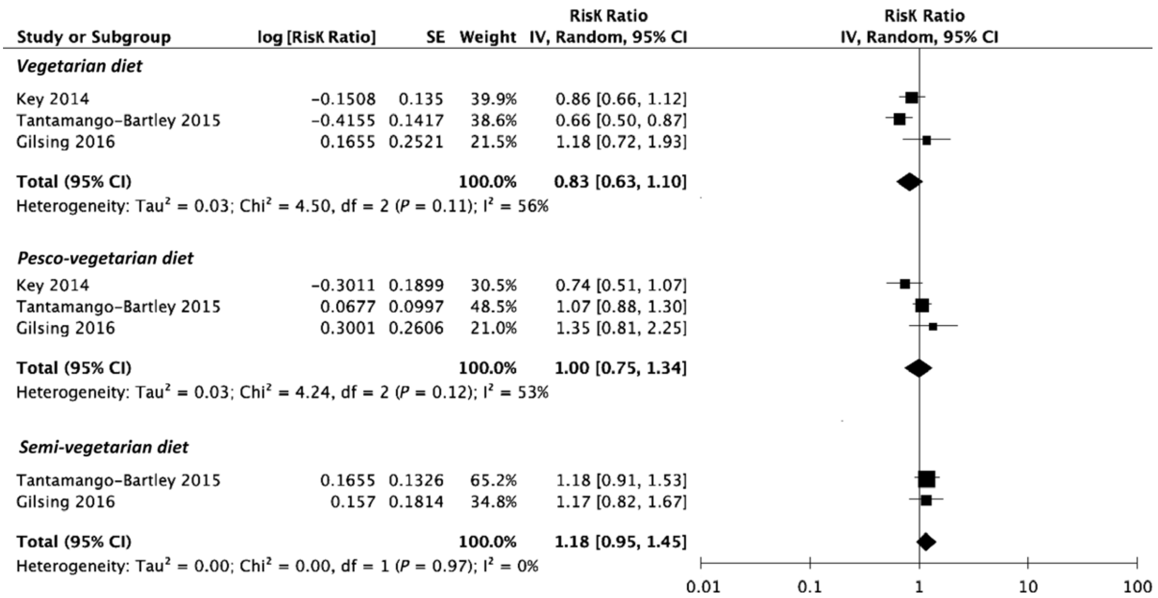

Figure 4 Forest plot of prospective cohort studies evaluating summary risk ratios of prostate cancer by adoption of vegetarian, pesco-vegetarian and semi-vegetarian versus non-vegetarian diet (reference). CI, confidence interval.

with some evidence of heterogeneity ($I^2 = 56\%$, $P_{\text{heterogeneity}} = 0.11$) but not of asymmetry of funnel plot (see Supporting information, Fig. S1). Risk estimates ranged from significantly lower to a higher prostate cancer risk associated with a vegetarian compared to a non-vegetarian diet with no particular difference between the cohorts. Data from the same four cohorts [18,21,23] were used to calculate summary risk of prostate cancer for a pesco-vegetarian compared to a non-vegetarian diet, resulting in null findings (Fig. 4; see Supporting information, Fig. S1). Finally, data on semi-vegetarians were available only for two cohorts [21,23] (the NLCS-MIC and the AHS-2) resulting in no significant findings (Fig. 4; see Supporting information, Fig. S1).

A further analysis was conducted on advanced prostate cancer [21,23]. Vegetarian, semi- and pesco-vegetarian diets were associated with the risk of advanced prostate cancer (data not shown).

Discussion

The summary of existing evidence on the association between a pure vegetarian diet and the risk of cancer demonstrated scarce findings from prospective cohort studies. The results from the present meta-analysis are in line with previous pooled analyses on vegetarian diets and mortality risk (including some of the cohorts also presented in the present analysis) reporting no increased length of survival in vegetarians compared to non-vegetarians. However, we found that some benefits may be related to the adoption of a mainly plant-based dietary pattern because semi- and pesco-vegetarian diets were associated with a lower risk of colorectal cancer compared to a non-vegetarian diet. This finding confirm the corroborated hypothesis that dietary patterns rich in fruit and vegetables, accompanied by the consumption of fish, may exert benefits toward human health and, in particular, may lower the risk of colorectal cancer.

Reports in the scientific literature on vegetarian diets is scarce. Summary of risk estimates derived by existing cohort studies on vegetarian diets were weaker than those obtained from pesco-vegetarian dietary patterns, suggesting that the complete exclusion of any source of protein from the diet is not associated with further benefits for human health. These findings are supported by biological plausibility. Vegetarian diets are rich in fibre, magnesium, phytochemicals, antioxidants, vitamins C and E, Fe^{3+} , folic acid and *n*-6 PUFA, whereas they are low in cholesterol, total fat and saturated fatty acid, sodium, Fe^{2+}, zinc, vitamins A, B_{12} and D, and *n*-3 PUFA [24]. Antioxidant vitamins, phenolic compounds and PUFA may exert anti-inflammatory effects, as well as protective effects toward DNA damage by preventing oxidation and improving biological pathways related to cancer initiation, such as cell signalling, cell cycle regulation, angiogenesis and inflammation [25,26]. Thus, unbalanced vegetarian diets may be deleterious in terms of nutritional adequacy, and the exclusion of major food groups from the diet (i.e. not limited to meat, but also fish and animal-derived foods) may be likely to result in nutrient deficiencies [24]. However, compared to uncontrolled omnivorous diets, vegetarian diets have been reported to have a better quality [27], suggesting that nutritional adequacy may not be strictly related to the dietary profile but rather to the overall balance of food consumed.

The rationale behind the hypothesis that a plant-based dietary pattern could protect against cancer relies on the benefits of a high fibre and antioxidant intake characterising the dietary content of fruit, vegetables and whole grains [28–30]. Dietary fibre may exert anti-carcinogenic effects through a direct action in the gastrointestinal tract, by reducing transit time and the contact of carcinogens with the colonic mucosa, and increasing the binding of carcinogens and the production of short-chain fatty acids [31]. Fish may provide an adequate amount of *n*-3 PUFA, which exert anti-oxidant effects at a systemic level [32,33]. Nutraceuticals and functional food ingredients may also improve vascular health and improve metabolic disorders, which may be associated with an increased cancer risk [34]. Mechanistic studies are promising and support evidence from epidemiological studies. A decreased risk of colorectal cancer has been associated with the consumption of fruit and vegetables [35]. Findings from a pooled analysis of 14 cohorts show that fruit and vegetable intake was associated with rectal cancer risk [36]. In addition, the consumption of fish has been associated with a decreased risk of colorectal cancer, despite stratified analyses showing most of the association being with rectal cancer [37]. Studies on dietary patterns are able to capture various aspects of the dietary experience that is adopted by a population and may provide insights into the synergistic effect of several components of a diet [38]. The findings on colorectal cancer and adenomas (a cancer precursor) appear to be consistent in that high compared to low adherence to a plant-based dietary pattern could be associated with a decreased risk of disease, whereas high compared to low adherence to a 'Western' dietary pattern may result in the opposite outcomes [39,40]. Finally, adherence to the Mediterranean dietary pattern, which is characterised by the high consumption of plant-derived foods, olive oil and fish as the main source of fats, as well as low intakes of meat, has been associated with a decreased risk of cancer, including colorectal cancer [41,42]. When considering animal protein intake, dietary sources suggest that other components in protein-rich foods (i.e. sodium, nitrates and nitrites in processed red meat), in addition to protein content *per se*, may have a critical health effect [43].

The main issue when examining the role of dietary patterns is represented by the potential confounding factors related to the overall lifestyle associated with dietary choices. Lifestyle behaviours are complex and multidimensional, generallying tend to cluster into healthy or unhealthy, including with respect to smoking and alcohol drinking habits, physical activity levels, and dietary choices [44,45]. The outcome mostly affected by diet is body weight, which in turn is a major contributor to cancer risk [46]. In this context, exploring the relationship between diet and cancer is challenging because most of the aforementioned factors generally cluster and, more or less directly contribute to modifying cancer risk. For example, the consumption of animal protein has been associated with an increased risk of mortality only in participants with at least one of the unhealthy behaviours, including smoking, heavy alcohol intake, being overweight or obesity, and physical inactivity [43]. By contrast, when considering observational studies, a common feature found across populations is that vegetarians are likely to exhibit an overall healthier lifestyle compared to the general population [47]. Despite being far from definitive, the results of the present study provide some insights regarding this issue because the significant association between dietary patterns high in vegetables, fruit and fish and a lower risk of gastrointestinal cancers suggests that a qualitative role of the diet may affect locally the risk of malignancy; for example, by limiting oxidative stress, inflammation and the effects of carcinogens [48].

There are some other limitations that should be addressed. The main issue when considering results from the present study is that the number of studies was generally limited for all the meta-analyses performed. Despite the results are not definitive, the studies included large samples and the findings are quite consistent across datasets with no evidence of heterogeneity and publication bias, which could somehow offset this issue. Second, differences in the background characteristics of the populations included in the cohort studies may weaken the results. For example, part of the existing evidence on a vegetarian diet is derived by the AHS-2, which involved a group of individuals with religious beliefs influencing their lifestyle choices, according to which it is uncertain whether the observed outcomes could be replicated or even applied to the general population. Third, despite all studies used validated instruments to collect dietary data, with most of them not providing repeated measurements during the follow-up periods, thus not registering any possible change in diet over time. Finally, vegetarian diets may differ each other for type and content of fruit/vegetables and dietary sources of proteins; we were unable to add further variation of vegetarian diets (e.g. lacto-ovo-vegetarian) as a result of the limited data available, and future studies on variants of vegetarian diets are needed to improve current evidence and to better define the dietary profiles more likely to be associated to positive health outcomes.

In conclusion, plant-based and fish-based dietary patterns represent a healthy dietary choice compared to meat-based dietary patterns when considering cancer as an outcome. Significant associations were found with respect to risk of colorectal cancers, suggesting a possible direct role in the aetiological pathway of gastrointestinal cancers. However, the limited evidence retrieved regarding pure vegetarian diets highlights the possibility that very low meat intake can be associated with a lower risk of cancer, despite there being no strong evidence that a total depletion of sources of protein from the diet improves the outcome under consideration. Further studies are needed to provide more evidence and to better investigate the potential causative roles. However, from a public health perspective, claims regarding vegetarian diets should be evaluated carefully before informing the general population.

Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.

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JG and FB performed the searches and study analysis, and wrote the manuscript (equal contributions). SS and FG designed the study and provided critical revision. GG designed the study, performed the analysis and wrote the manuscript. All authors critically reviewed the manuscript and approved the final version submitted for publication

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained. The reporting of this work is compliant with PRISMA guidelines.

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Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article:
Figure S1. Funnel plots of prospective cohort studies evaluating summary risk ratios of breast, colorectal and prostate cancer by adoption of vegetarian, pesco-vegetarian and semi-vegetarian versus non-vegetarian diet (reference).

