Health risk factors associated with meat, fruit and vegetable consumption in cohort studies: A comprehensive meta-analysis

Giuseppe Grosso¹,²*, Agnieszka Micek³, Justyna Godos¹, Andrzej Pajak³, Salvatore Sciacca¹, Fabio Galvano⁴, Paolo Boffetta⁵

¹ Integrated Cancer Registry of Catania-Messina-Siracusa-Enna, Azienda Ospedaliera Policlinico-Universitaria “Vittorio Emanuele”, Catania, Italy, ² The Need for Nutrition Education/Innovation Programme (NNEdPro), University of Cambridge, Cambridge, United Kingdom, ³ Department of Epidemiology and Population Studies, Jagiellonian University Medical College, Krakow, Poland, ⁴ Department of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy, ⁵ Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, United States of America

* giuseppe.grosso@studium.unict.it

Abstract

The aim of this study was to perform a meta-analysis to test the association between red, processed, and total meat, as well as fruit and vegetable consumption, and selected health risk factors, including body weight status, smoking habit, physical activity level, level of education, and alcohol drinking in cohort studies on non-communicable disease. A systematic search of electronic databases was performed to identify relevant articles published up to March 2017. In a two-stage approach, frequency-weighted linear regression coefficients were first calculated for each variable, and then combined across studies through meta-regression. Ninety-eight studies including 20 on red meat, 6 on processed meat, 12 on total meat, 37 on fruit and vegetable combined, 21 on fruit and 24 on vegetable consumption were analyzed. Intake of red meat was positively associated with BMI, percentage of overweight and obese, low physical activity, and current and ever smoking and inversely associated with percentage of non-smokers and high physically active individuals. Similar associations were found, although based on fewer data. Intake of fruits and vegetables was positively associated with prevalence of non-smokers, high education and high physical activity, and similar results were found when examining fruit and vegetable consumption separately. Stratification by geographical area revealed that some associations were stronger in US rather than European or Asian cohorts. In conclusions, the distribution of health risk factors associated with high meat and fruit/vegetable consumption may differ from those of low-consumers. Some of these differences may mediate, confound, or modify the relation between diet and non-communicable disease risk.
Introduction

Consumption of meat, fruit and vegetable has been the focus of epidemiologic research for its potential association with non-communicable diseases, including cancer risk. Findings from meta-analyses of observational studies indicate that consumption of meat would increase the risk of several cancers [1]. Based on hypotheses supporting the biological plausibility of such association, the Diet and Cancer Report published by the World Cancer Research Fund and American Institute for Cancer Research in 2007 concluded that the positive association between red and processed meat and colorectal cancer was convincing [2]. More recently, the International Agency for Research on Cancer in Lyon, France, published a monograph based on about 800 epidemiological studies that investigated the consumption of meat in relation to cancer risk [3]. The working group observed a significant association between intake of processed meat (meat that has been preserved by smoking, curing, salting, or by adding chemical preservatives) and colorectal cancer risk in 12 out of the 18 prospective cohort studies that provided relevant data [3]. Fourteen cohort studies were meta-analyzed to test the potential association between intake of red meat (meat from animals that have a high proportion of red muscle fibers) and several cancers, despite findings across studies were not consistent [3]. Similar uncertainty has been found on the association between fruits and vegetable consumption and cancer risk [4]. Epidemiological studies have produced contrasting evidence, showing decreased risk of head and neck, esophageal and stomach cancer and a non-linear decreased risk of colorectal cancer and puzzling results on other cancer sites [5]. Also the findings from a pooled analysis of 14 cohort studies are not convincing, reporting that fruit and vegetable intake was not strongly associated with colon cancer risk but may be associated with distant colon cancers [6].

These results have put in question the role of meat in human nutrition [7, 8]. Despite the great amount of scientific progress on the topic, causal link between diet and cancer is complex to demonstrate due to the concomitant consumption of several foods and nutrients, a possible association between unhealthy dietary and lifestyle habits, and methodological limitations in controlling potential confounding and distinguishing between risk factors and mediating effect of variables of interest. Most of the studies included in the reviews mentioned above focused on individual dietary components and adjusted for confounding factors which may be associated with the outcome of interest. Nonetheless, only small efforts have been done to assess whether a cluster of health risk factors associated with the variable of exposure may exist. The role of variables, such as adiposity, smoking habits, alcohol consumption, level of physical activity and education, has been widely assessed in affecting cancer risk [9]. It has been also shown that such variables tend to cluster with dietary habits and need to be targeted in health promotion interventions on multiple behaviors [10]. However, their association with meat (red, processed, and total), fruit and vegetable consumption has been addressed in individual studies [11] and few meta-analyses provided comparative risk estimates for such individual risk factors [12, 13], but no study comprehensively tested the potential association between intake of these food items and health risk factors. Thus, the aim of the present study was to evaluate the association between meat, fruit and vegetable intake and selected health risk factors in prospective cohort studies.

Materials and methods

The reporting of this work is compliant with PRISMA guidelines (S1 Table).

Study selection and data extraction

A systemic search of MEDLINE and EMBASE was performed to identify all articles published up to March 2017 including the keywords ‘meat’, ‘fruit’, and ‘vegetable’ combined with ‘cancer’
cardiovascular’, ‘heart disease’, ‘stroke’, ‘mortality’, ‘hypertension’, ‘diabetes’ in order to collect information on existing cohorts investigated for meat, fruit and vegetable consumption. The inclusion criteria for the underlying studies were as follows: (i) prospective (cohort) design; (ii) results on the association between meat, including red, processed or total meat, or fruit and/or vegetable and any of the aforementioned outcomes; (iii) inclusion of at least one of lifestyle/background (smoking status, physical activity level, alcohol consumption, education level) and biomedical [body mass index (BMI) and weight status] characteristics as confounding variables; (iv) results for at least 3 categories of the exposure variable(s), either expressed as grams per day of intake, or reported in a way that could be converted in grams per day (i.e., servings per day); (v) English language. A search of the references cited in all of the articles selected for review was also conducted. When data of interest on a cohort was available in more than one study, the studies (i) including more individuals, (ii) providing separate information by sex, (iii) providing more variables, and (iv) providing more categories of exposure were selected. Study quality was assessed by applying the STrengthening the Reporting of OBServational studies in Epidemiology (STROBE) checklist for cohort studies [14].

Data extracted for each category of exposure included (i) number of individuals (cases and non-cases); (ii) median/mean amount of red, processed, and total meat, fruit, vegetable, or fruit and vegetable combined; and (iii) background characteristics, including: mean/median body mass index (BMI); proportion of individuals with BMI >25 and BMI >30; current, former, ever and never smokers; high-school/vocational and college/university education; individuals with high and low physical activity; and mean/median intake of alcohol. The extraction was performed by two researchers (GG and JG) and any disagreements were solved after discussion.

Statistical analysis

When the range of consumption of the investigate exposures was given in the study, the midpoint of the interval was considered for the analysis. For open-ended categories of consumption, we assumed the same width as the adjacent one. One serving was approximated to 100 g when not otherwise specified. When food/serving was expressed as ratio per 1,000 kcal diet, the amount was doubled (approximately referring to a diet of 2,000 kcal). Background characteristics were graphically plotted by category of exposure to evaluate possible associations between dietary exposures and health risk factors.

The linearity of the associations between dietary exposures and health risk factors were tested using \( R^2 \) and retained the association for which at least 50% of datasets had \( R^2 > 0.5 \). Moreover, diagnostic plots were generated to test the independence between the residuals and the fitted values. We found that in most of datasets (ranging from 50% to 100%, depending on the variable explored) the coefficient of determination \( R^2 \) was rather high (i.e., >0.7), without a discernible pattern. However, a low percentage of datasets (i.e., <40%) fitted properly the model for the associations between red meat and low physical activity; processed meat and vegetable intake; and total meat and current smokers. We therefore did not consider further these associations.

Separate bivariate meta-analyses were performed for potential confounders to determine whether it was significantly associated with the exposures of interest. We used a two-stage approach meta-analysis [15]. First, for each exposure variable of interest within each study, ordinary least squares linear regression with frequency weights was used to estimate the coefficients for the intercepts and slopes of the dose-response associations between exposures and outcomes/confounders [16]. In the second step we synthesized the intercept and slope coefficients using bivariate meta-regression. Within each study, intercept and slope were often
correlated and we obtained an overall regression model (rather than a single slope estimate).
To synthesize vectors of coefficients we used generalized least squares, primarily because of the
unequal variances of effects for studies of different sizes [16]. From the first step, we extracted
the estimated model coefficients (intercepts and slopes) and the corresponding variance-
covariance matrices of the sampling errors. We allowed for heterogeneity in the coefficients
and allowed them to be correlated by using an unstructured variance-covariance matrix for
the true outcomes. To further test for evidence of publication bias, subgroup analyses by sex
and geographical area (US, Europe and Asia) were conducted. All analyses were performed
with on R, software version 3.0.3 (Development Core Team, Vienna, Austria).

**Results**

**Study characteristics**

The search strategy resulted in 1,239 citations, 751 of which were potentially relevant and were
retrieved as full-text articles (Fig 1). A total of 653 studies were excluded because they either
did not report data of interest (n = 570) or were duplicates of more complete reports from the
same cohorts (n = 83).

Therefore, a total of 98 univocal references were included in this meta-analysis [17–114],
divided as follow: 20 studies on red meat [17–36], 6 on processed meat [26, 37–41], 12 on total
meat [42–53], 37 on combined fruit and vegetable [37, 54–89], 21 on fruit [73, 90–109], and 24
on vegetable consumption [73, 90–96, 99–114]. All studies included were fully compliant to
the STROBE statement. The list and main characteristics of the cohorts included are listed in
S2 and S3 Tables. There were 18 unique cohorts on red meat, 8 on processed meat, 14 on total
meat, 30 on combined fruit and vegetable, 21 on fruit and 21 on vegetable consumption. Number
of individuals included varied on the basis of the association investigated, accounting for
up to one million and half in most of analyses on the relation between red meat and fruit+-
vegetable intake and BMI levels and smoking status, while reaching up to 2 millions individu-
als in the analyses on educational status.

**Variables associated with meat consumption**

The association between red meat consumption and the potential confounding factors is
shown in Fig 2.

Low intake of red meat was associated with borderline BMI values for overweight [intercept
coefficient 25.3; 95% confidence interval (CI): 24.7, 25.9] and with prevalence of overweight
and obese individuals (Table 1).

A100 gram per day increase in red meat consumption was associated with increased BMI
[1.2 kg/m²; 95% confidence interval (CI): 0.7, 1.8] as well as increased proportion of over-
weight (7.4%, 95% CI: 6.2%, 8.6%) and obese individuals (8.3%, 95% CI: 7.1%, 9.4%) and cur-
rent and ever smokers and decreased proportion of former and non-smokers (Table 1).
Furthermore, there were associations with decreased prevalence of high physical activity. Pre-
valence of individuals with high-school/vocational and college/university education decreased
by 6.4% and 10.2% for each 100 g/d increase of red meat, respectively (Table 1). Regarding
other dietary variables, only fruit intake was significantly lower of about 60 g/d for each 100 g/
d of red meat consumed, while no association was found with alcohol, vegetable, and com-
bined fruit and vegetable consumption (Table 1). When analyses were stratified by sex, results
did not change except for the associations with high physical activity in men and with fruit
intake in women, which were no longer statistically significant (S4 Table); notably, the increase
in BMI was stronger in women than in men (1.6 vs. 0.9 in women and men, respectively, for
each 100 g/d of red meat). Associations with BMI and smoking status were consistent across
regions, while the association with BMI was more evident in US than in European cohorts (1.8 vs. 0.5 increase in BMI each 100 g/d increased consumption of red meat, respectively) while no association was found in Asian cohorts (S5 Table). Moreover, the associations with physical activity were significant only among US cohorts (S5 Table), while the association with alcohol...
consumption was significant only in European cohorts (S5 Table). Finally, the associations with other dietary factors (i.e., fruit intake) were significant in the Asian and US cohorts but not in the European ones (S5 Table).

Fewer studies reported results on processed meat compared to red meat (S1 Fig). In general, characteristics of the variables of interest for low processed meat intake were similar to those identified for low red meat consumers (S6 Table). Results concerning BMI, smoking and educational status were similar than those related to red meat; however, the associations were stronger than those observed for red meat, as each 100 g/d increase of processed meat was associated with increased BMI of 4.5 (95% CI: 1.6, 7.5), increased 25% of current smokers and decreased 31.4% and 17.1% of never smokers and college/university educated, respectively (S6 Table). Finally, increased intake of 100 mg/d of processed meat was associated with decreased intake of nearly 300 mg/d of fruit (S6 Table). Subgroup analyses revealed that increasing BMI values over increasing categories of processed meat intake were significant only for women, trends on educational status were significant only for men, while trends over smoking status were reported in both sexes (S7 Table). Subgroup analysis by geographical region provided further insights on...
potential differences between populations, as results were significant in both European and US cohorts, but range of variation of all the aforementioned variables was larger in the latter than in the former (S8 Table).

Studies reporting on the associations between total meat consumption and the variables of interest included a number of individuals smaller than that for red meat, but larger than that for processed meat (S2 Fig). Low total meat consumption was associated with reduced BMI, despite the association was weaker than for red and processed meat (23.7, 95% CI: 23.3, 24.2; S9 Table). Trends of BMI values across increasing categories of total meat intake resulted significant, but smaller than those observed for specific type of meat (0.5 BMI increase and 7.6% increased prevalence of obese individuals for each 100 g/d total meat increased intake); no other significant associations were found (S9 Table). Subgroup analyses by sex (S10 Table) and geographical area (S11 Table) showed that previous findings on BMI were significant only among women in both Europe and US, while other associations, such as increasing prevalence of smokers (ever) and decreasing of never smokers, were found. Regarding Asian cohorts, increased intake of total meat was significantly associated with decreasing prevalence of obese individuals, increasing prevalence of individuals with high-school/vocational education, lower intake of alcohol and higher intake of fruit (S11 Table).

### Variables associated with fruit and vegetable consumption

The relations between fruit and vegetable consumption and the variables of interest are shown in Fig 3.

Low fruit and vegetable consumption was associated with BMI values as well as prevalence of overweight and obese similar to those observed for low red meat consumers, with no association with increased intakes of fruit and vegetable (Table 2). Pooled prevalence of ever (current + former) smokers in low fruit and vegetable consumers was slightly higher than in low meat consumers (roughly 60%) while that of non-smokers was lower (Table 2).

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Table 1. Summary associations between selected variables and red meat consumption.

| Variables                           | No. of studies | No. of datasets | No. of cohorts | No. of individuals | Intercept (95% CI) | Slope per 100 g/d (95% CI) |
|-------------------------------------|----------------|----------------|----------------|--------------------|-------------------|--------------------------|
| BMI (mean/median)                   | 13             | 20             | 14             | 1,650,663          | 25.34 (24.71, 25.97) | 1.28 (0.74, 1.83)        |
| BMI >30 (%)                         | 2              | 2              | 2              | 52,441             | 14.32 (13.76, 14.88) | 8.32 (7.18, 9.45)        |
| BMI >25 (%)                         | 3              | 4              | 3              | 133,099            | 43.34 (22.05, 64.62) | 7.46 (6.23, 8.69)        |
| Current smokers (%)                 | 14             | 22             | 15             | 1,704,807          | 14.11 (9.27, 18.95) | 5.96 (4.18, 7.75)        |
| Former smokers (%)                  | 8              | 14             | 8              | 1,230096           | 31.46 (23.97, 38.95) | -2.98 (-5.34, 0.62)      |
| Ever smokers (%)                    | 8              | 14             | 8              | 1,230096           | 46.05 (36.73, 55.37) | 4.33 (1.34, 7.33)        |
| Never smokers (%)                   | 7              | 12             | 7              | 1,149438           | 48.86 (41.27, 56.44) | -6.39 (-9.29, -3.48)     |
| High physical activity (%)          | 8              | 13             | 8              | 1,257227           | 41.82 (26.58, 57.06) | -5.22 (-8.41, -2.04)     |
| Low physical activity (%)           | 3              | 5              | 3              | 519,118            | 15.22 (11.33, 19.12) | 2.21 (0.32, 4.1)         |
| Vocational/high school (%)          | 4              | 7              | 4              | 652,074            | 32.79 (22.67, 42.9)  | -6.44 (-12.08, -0.8)     |
| College/university (%)              | 5              | 8              | 5              | 1,177,778          | 44.09 (27.47, 60.7)  | -10.26 (-14.16, -6.36)   |
| Alcohol (g/d, mean/median)          | 10             | 14             | 11             | 1,409,369          | 8.61 (5.88, 11.34)  | 1.78 (-0.3, 3.87)        |
| Fruit (g/d, mean/median)            | 9              | 14             | 10             | 1,310,820          | 262.59 (198.63, 326.56) | -59.84 (-106.23, -13.46) |
| Vegetable (g/d, mean/median)        | 9              | 14             | 10             | 1,310,820          | 242.59 (173.98, 311.19) | -1.62 (-25.72, 22.47)    |
| Fruit + vegetable (g/d, mean/median)| 2              | 4              | 4              | 195,985            | 471.75 (385.83, 557.66) | 10.18 (-38.25, 58.61)    |

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However, increased intake of 100 g/d of fruit and vegetable was associated with significant decreased prevalence of current (-3.1%; 95% CI: -3.9, -2.4) and ever smokers (-2.4; 95% CI: -3.0, -1.8), and increased prevalence of never smokers (2.5%; 95% CI: 1.9, 3.1). Another variable significantly associated with higher consumption of fruit and vegetable was prevalence of high (positively) and low (negatively) physically active individuals, which was roughly varying of +/- 2%, respectively, for each 100 g/d increased intake of fruit and vegetable. College/university education prevalence was also significantly associated with fruit and vegetable consumption (roughly increased of 2% each 100 g/d) while no association was found with alcohol or meat intake (Table 2). When analyses for fruit and vegetable intake were stratified by sex (S12 Table) and geographical region (S13 Table), all the associations remained significant for all subgroups examined. In addition, in Asian cohorts increasing intake of fruit and vegetable was also associated with increasing intake of alcohol (increase of 0.8 g/d of alcohol for 100 g/d increased intake of fruit and vegetable).

Similar pattern of associations were found when analyzing separately fruit (S3 Fig) and vegetable (S4 Fig) intake. Specifically, significant trends over current/never smokers, low/high...
physically active, and college/university education for increasing intake of both fruit (S14 Table) and vegetable consumption (S15 Table) were found. In contrast, 100 g/d increased intake of either fruit or vegetable was associated with decreased intake of alcohol (-3.2 g/d and -1.2 g/d, respectively), and individually with decreased intake of red meat (-3.1 g/d) and processed meat (-2.1 g/d), respectively. Furthermore, increased vegetable intake of about 100 g/d was associated with about 1% increased prevalence of overweight and obese individuals (S15 Table). The subgroup analyses revealed some slight differences in the associations, such as increased intake of fruit and vegetable consumption associated with education only among men and women, respectively, while both fruit and vegetable consumption was associated with physical activity only among women (S16 and S17 Tables). Small differences were found in the subgroup analysis by geographical region, as no associations were retrieved for fruit consumption in Asian cohorts and no association with education status in any of the subgroup areas (S18 Table); the association between vegetable consumption and the variable of interest were similar to those retrieved in the main analysis (S19 Table).

Discussion
In this study we quantified the association between red and processed meat, as well as fruit and vegetable consumption, and some background characteristics in cohorts studied that provided results on the association between diet and cancer risk. There was a clear pattern with several health risk factors occurring in individuals consuming more meat (with a linear relation), including high BMI, obesity and current smoking rates, as well as low education and low consumption of fruits and vegetables. The examination of the same factors in relation to fruit and vegetable intake showed similar associations in the opposite direction (with the exception of BMI, substantially unrelated with the exposure), reinforcing the hypothesis that healthy and unhealthy dietary choices may cluster with health risk factors [115]. Moreover, while physical activity, smoking, and educational status may mediate the effects of meat, fruit and vegetable consumption toward health outcomes, body weight seems to be restricted to mediate the effects of the former. This was the first attempt to assess consistency of the underlying pattern.

### Table 2. Summary associations between selected variables and fruit+vegetable consumption.

| Variables                        | No. of studies | No. of datasets | No. of cohorts | No. of individuals | Intercept (95% CI) | Slope per 100 g/d (95% CI) |
|----------------------------------|----------------|-----------------|----------------|--------------------|--------------------|---------------------------|
| BMI (mean/median)                | 23             | 29              | 25             | 1,618,453          | 25.53 (24.91, 26.15) | -0.01 (-0.05, 0.03)      |
| BMI >30 (%)                      | 6              | 6               | 6              | 289,158            | 18.47 (13.24, 23.7)  | 0.05 (-0.32, 0.43)       |
| BMI >25 (%)                      | 7              | 9               | 7              | 381,247            | 38.63 (25.21, 52.05) | -0.15 (-0.55, 0.26)      |
| Current smokers (%)              | 23             | 30              | 26             | 1,809,001          | 37.06 (31.19, 42.93) | -3.19 (-3.92, -2.47)     |
| Former smokers (%)               | 14             | 18              | 15             | 1,376,136          | 27.87 (21.89, 33.86) | 0.87 (0.03, 1.71)        |
| Ever smokers (%)                 | 15             | 20              | 16             | 1,454,027          | 61.53 (52.77, 70.28) | -2.41 (-3.01, -1.81)     |
| Never smokers (%)                | 15             | 20              | 16             | 1,454,027          | 37.76 (28.82, 46.7)  | 2.51 (1.9, 3.11)         |
| High physical activity (%)       | 11             | 16              | 11             | 1,126,670          | 26.45 (17.71, 35.2)  | 1.95 (0.92, 2.97)        |
| Low physical activity (%)        | 10             | 12              | 10             | 683,590            | 31.78 (20.92, 42.64) | -1.91 (-2.8, -1.01)      |
| Vocational/high school (%)       | 10             | 13              | 11             | 801,769            | 41.05 (30.69, 51.42) | 0.34 (-0.89, 1.57)       |
| College/university (%)           | 18             | 24              | 19             | 2,229,993          | 17.87 (13.38, 22.36) | 2.12 (1.52, 2.72)        |
| Alcohol (g/d, mean/median)       | 10             | 14              | 12             | 1,242,020          | 13.35 (8.11, 18.59)  | -0.44 (-0.92, 0.04)      |
| Red meat (g/d, mean/median)      | 8              | 12              | 10             | 1,433,645          | 105.03 (47.27, 162.8) | -3.35 (-8.33, 1.63)      |
| Processed meat (g/d, mean/median)| 4              | 6               | 5              | 1,136,697          | 47.92 (18.37, 77.47) | -1.94 (-4.27, 0.4)       |

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of factors across cohorts exploring the association between meat, fruit, and vegetable consumption and cancer risk. The present findings could explain the heterogeneity across results from cohort studies included in previous meta-analyses. It would be important to test the effect of such variables as moderators in diet-cancer associations, but this is not feasible based on the published results of these studies.

The covariates explored in this study in relation to red and processed meat intake have been long studied as potential risk factors for cancer. Increased risk of several cancers has been associated with higher BMI levels, including esophageal adenocarcinoma, thyroid, colon, and renal cancers, as well as endometrial, gallbladder, pancreas, and post-menopausal breast cancer in women [116]. Moreover, weight gain itself may increase the risk of some cancers, such as renal and postmenopausal breast, ovarian, and endometrial cancers [117]. Mechanisms of action linking body fat to cancer are not fully understood, but the main hypotheses regard alteration of body metabolism and hormonal systems as well as potential oxidative stress (initiated by hyperglycemia) that may play a role in tumorigenesis [118]. Meat intake can be associated to obesity due to its richness in fats or included in dietary patterns rich in processed foods, fries, and refined carbohydrates (especially processed meat). According to the results of the present study, BMI could represent one of the main confounders to explain the increased cancer risk associated with meat consumption. Noteworthy, data on BMI or obesity prevalence used for the present meta-analysis refer to baseline characteristics, and the possible effect of increase in BMI during the following of these longitudinal studies should be taken into account.

Tobacco smoking has been related to the majority of cancers [119]. Despite there is no direct biological relation between smoking and meat consumption, we found a strong and linear relation between these variables. It has been previously demonstrated that cigarette smoking was associated with unhealthy patterns of dietary factors, including higher intake of total energy, total fat, saturated fat, cholesterol and alcohol, and lower intake of polyunsaturated fat, fiber, vitamin C, vitamin E, and beta-carotene [120]. Interestingly, opposite associations were found in relation to fruit and vegetable consumption, with increasing intake associated with lower prevalence of smokers. Smoking habit can be part of a general unhealthy lifestyle that would also affect dietary habits and food choices, including excess of meat intake. Another finding reported in this meta-analysis, namely the association between meat consumption and lower educational status, could support the aforementioned hypothesis. Education level has been associated to cancer risk [121]. Lower educated individuals may be less aware of health issues related to certain behaviors including smoking habits and poor diet quality. In addition, lower education is a proxy of lower socio-economic status, which is also associated with poor health due to lack of resources and economic constraints. Among other possible confounders that have been associated to cancer risk and unhealthy behaviors [122], alcohol resulted only partially related with meat or fruit and vegetable consumption.

Another important confounding factor/effect modifier may be related to cultural and geographical aspects, as suggested by the stronger association between meat consumption and colorectal cancer risk in US than European studies [123]. Interestingly, differences of cancer risk between US and non-US cohorts have been recently shown also in relation to other foods, for instance eggs [124]. We tested this hypothesis by stratifying the analyses by sex and geographical area of the cohorts. As a result, certain differences were found, for instance red meat intake associated with physical activity and intake of fruit only in US cohorts (despite some other observations relied only on a limited number of cohorts); moreover, associations for weight, educational, and smoking status were stronger in US than in non-US cohorts.

The present study had several strengths, including the large number of people investigated, the large number of cohort form multiple countries with lifestyle and genetic heterogeneity,
the high number of subgroup analyses, and consistency of results across different exposures and sensitivity analysis should assure the validity of our findings. Nevertheless, results should be considered in light of some limitations. First, the observational nature of the studies included does not allow defining causal relationships, rather only associations. Second, most of the studies did not specified whether "red meat" included "processed red meat" while only a minority provided this information as well as separate figures. Thus, we cannot exclude a certain degree of overlapping classification of type of exposure and we could only rely on authors’ description in the methodology for their definition of exposure, which in most of cases was exhaustive and should assure a very low rate of misclassification of exposure in our study. Moreover, most of results were similar between "red meat" and "processed meat", suggesting good reliability of our findings. Regarding the quantitative issue, most of data were retrieved from food frequency questionnaires, which is a better tool for ranking participants than estimating true amount of food consumption. Moreover, we estimated the exposure to meat or fruit/vegetable in several studies reporting only serving or other measures (i.e., cups equivalents). However, by using consistent conversions across studies, we should have minimized such issue. Third, a number of potentially relevant cohorts did not report sufficient information to be included in this meta-analysis. However, trends of associations of variables included in our models were quite consistent across studies, suggesting that there is no reason to suspect that results would change by considering also the missing cohorts. Finally, besides the well-known confounding factors examined in this study, residual confounders have not been taken into account in previous analyses or not uniformly comparable. Moreover, categorization of physical activity level was not uniform across studies (i.e., high physical activity may have referred to a certain amount of metabolic equivalents or a certain amount of leisure time physical activity or walking for at least a certain amount of time per week), thus results on this variable should be considered with caution. Regarding potential unknown factors, environmental contaminants may further alter the relation between raw/cooked meat and cancer risk [125]. Finally, the role of susceptibility to modifying genes involved in the metabolism of dietary carcinogens or anti-carcinogens following meat, fruit and vegetable consumption is still under consideration [126–128].

In conclusions, the results of this meta-analysis supported by the available data are largely consistent with a potential clustering of health risk factors that may confound the associations between food and cancer, in particular meat, fruit and vegetable. Due to practical and ethical considerations, conducting long-term controlled randomized trial on meat consumption and health outcomes is not possible. The main issue when considering results from observational studies regards the presence of several covariates that may be related to both the exposure and the outcome. The effects of individual foods or nutrients retrieved in observational studies cannot be studied in isolation. Adjusting for confounders may be incomplete and, in some cases, even not sufficient to limit their effect on the final risk estimate. A better understanding of the risk in population subgroups (i.e., smokers vs. non-smokers, normal weight vs. obese individuals, etc.) as well as the variation of the risk estimates by category of consumers of other foods (i.e., fruit and vegetable) or nutrients (fibre, antioxidants) would better elucidate and distinguish between risk factors and mere associations.

Supporting information

S1 Table. PRISMA checklist.
(DOC)

S2 Table. General information of the studies included for evaluation of variables associated with red, processed and total meat consumption.
(DOCX)
S3 Table. General information of the studies included for evaluation of variables associated with fruit and vegetable consumption.
(DOCX)

S4 Table. Summary associations between selected variables and red meat consumption, by sexes. NA, not applicable.
(DOCX)

S5 Table. Summary associations between selected variables and red meat consumption, by geographical region. NA, not applicable.
(DOCX)

S6 Table. Summary associations between selected variables and processed meat consumption.
(DOCX)

S7 Table. Summary associations between selected variables and processed meat consumption, by sexes.
(DOCX)

S8 Table. Summary associations between selected variables and processed meat consumption, by geographical region. NA, not applicable.
(DOCX)

S9 Table. Summary associations between selected variables and total meat consumption.
(DOCX)

S10 Table. Summary associations between selected variables and total meat consumption, by sexes.
(DOCX)

S11 Table. Summary associations between selected variables and total meat consumption, by geographical region. NA, not applicable.
(DOCX)

S12 Table. Summary associations between selected variables and fruit+vegetable consumption, by sexes.
(DOCX)

S13 Table. Summary associations between selected variables and fruit+vegetable consumption, by geographical region. NA, not applicable.
(DOCX)

S14 Table. Summary associations between selected variables and fruit consumption.
(DOCX)

S15 Table. Summary associations between selected variables and fruit consumption, by sexes. NA, not applicable.
(DOCX)

S16 Table. Summary associations between selected variables and vegetable consumption.
(DOCX)
S17 Table. Summary associations between selected variables and vegetable consumption, by sexes. NA, not applicable.

S18 Table. Summary associations between selected variables and fruit consumption, by geographical region. NA, not applicable.

S19 Table. Summary associations between selected variables and vegetable consumption, by geographical region.

S1 Fig. Scatter plot for associations between processed meat consumption and baseline characteristics in prospective cohorts. Symbols represent different cohorts; light lines represent linear regression coefficients of individual studies; bold lines represent summary estimates average increase of each variable for increase of red meat intake.

S2 Fig. Scatter plot for associations between total meat consumption and baseline characteristics in prospective cohorts. Symbols represent different cohorts; light lines represent linear regression coefficients of individual studies; bold lines represent summary estimates average increase of each variable for increase of red meat intake.

S3 Fig. Scatter plot for associations between fruit consumption and baseline characteristics in prospective cohorts. Symbols represent different cohorts; light lines represent linear regression coefficients of individual studies; bold lines represent summary estimates average increase of each variable for increase of fruit and vegetable intake.

S4 Fig. Scatter plot for associations between vegetable consumption and baseline characteristics in prospective cohorts. Symbols represent different cohorts; light lines represent linear regression coefficients of individual studies; bold lines represent summary estimates average increase of each variable for increase of fruit and vegetable intake.

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Author contribution: Giuseppe Grosso conceived the study design, performed the study search, managed the databases, performed part of the analysis, and wrote the manuscript; Paolo Boffetta and Fabio Galvano provided insights on methodology, data interpretation, and manuscript drafting (equal contribution); Agnieszka Micek performed the analysis and edited the figures; Justyna Godos performed the study search and edited figures and tables; Adrzej Pajak and Salvatore Sciacca provided critical revision. All authors have read and approved the final manuscript.

Author Contributions

Conceptualization: Giuseppe Grosso, Salvatore Sciacca.

Data curation: Giuseppe Grosso, Justyna Godos.

Formal analysis: Giuseppe Grosso, Agnieszka Micek.

Investigation: Giuseppe Grosso.
Methodology: Giuseppe Grosso.

Supervision: Giuseppe Grosso.

Writing – original draft: Giuseppe Grosso.

Writing – review & editing: Giuseppe Grosso, Andrzej Pajak, Salvatore Sciacca, Fabio Galvano, Paolo Boffetta.

References

1. Lippi G, Mattiuazzi C, Cervellin G. Meat consumption and cancer risk: a critical review of published meta-analyses. Critical reviews in oncology/hematology. 2016; 97:1–14. Epub 2015/12/04. https://doi.org/10.1016/j.critrevonc.2015.11.008 PMID: 26633248.

2. Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. The Proceedings of the Nutrition Society. 2008; 67(3):253–6. Epub 2008/05/03. https://doi.org/10.1017/S002966510800712X PMID: 18452640.

3. Bouvard V, Loomis D, Guyton KZ, Grosse Y, Ghissassi FE, Benbrahim-Tallaa L, et al. Carcinogenicity of consumption of red and processed meat. The Lancet Oncology. 2015; 16(16):1599–600. Epub 2015/10/31. https://doi.org/10.1016/S1470-2045(15)00444-1 PMID: 26514947.

4. Norat T, Aune D, Chan DS, Vieira R, Greenwood DC, Kampman E, et al. Nonlinear reduction in risk for colorectal cancer by fruit and vegetable intake based on meta-analysis of prospective studies. Gastroenterology. 2011; 141(1):106–18. Epub 2011/05/24. https://doi.org/10.1053/j.gastro.2011.04.013 PMID: 21600207.

5. Koushik A, Hunter DJ, Spiegelman D, Beeson WL, van den Brandt PA, Buring JE, et al. Fruits, vegetables, and colon cancer risk in a pooled analysis of 14 cohort studies. Journal of the National Cancer Institute. 2007; 99(19):1471–83. Epub 2007/09/27. https://doi.org/10.1093/jnci/djm15 PMID: 17895473.

6. Gallus S, Bosetti C. Meat consumption is not tobacco smoking. International journal of cancer Journal international du cancer. 2016; 138(10):2309–11. https://doi.org/10.1002/ijc.30009 PMID: 26918639.

7. Giovannucci EL. Are Most Cancers Caused by Specific Risk Factors Acting on Tissues With High Underlying Stem Cell Divisions? Journal of the National Cancer Institute. 2015;108(3). Epub 2015/11/11. https://doi.org/10.1093/jnci/djv343 PMID: 26553782.

8. Huxley RR, Ansary-Moghaddam A, Clifton P, Czernichow S, Parr CL, Woodward M. The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence. International journal of cancer Journal international du cancer. 2009; 125(1):171–80. https://doi.org/10.1002/ijc.23434 PMID: 19350627.

9. Johnson CM, Wei C, Ensror JE, Smolenski DJ, Amos CI, Levin B, et al. Meta-analyses of colorectal cancer risk factors. Cancer causes & control: CCC. 2013; 24(6):1207–22. Epub 2013/04/09. https://doi.org/10.1007/s10552-013-0201-5 PMID: 23563998; PubMed Central PMCID: PMC4161278.

10. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandebroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014; 12(12):1495–9. https://doi.org/10.1016/j.ijsu.2014.07.013 PMID: 25046131.
15. Stukel TA, Demidenko E. Two-stage method of estimation for general linear growth curve models. Biometrics. 1997; 53(2):720–8. Epub 1997/06/01. PMID: 9192460.

16. MJ BBaW. The synthesis of regression slopes in meta-analysis. Statistical Science. 2007; 22(3):414–29. https://doi.org/10.1214/07-STS243

17. Babio N, Sorli M, Bullo M, Basora J, Ibarrola-Jurado N, Fernandez-Ballart J, et al. Association between red meat consumption and metabolic syndrome in a Mediterranean population at high cardiovascular risk: cross-sectional and 1-year follow-up assessment. Nutr Metab Cardiovasc Dis. 2012; 22(3):200–7. https://doi.org/10.1016/j.numecd.2010.06.011 PMID: 20875949.

18. Bellavia A, Stilling F, Wolk A. High red meat intake and all-cause cardiovascular and cancer mortality: is the risk modified by fruit and vegetable intake? The American journal of clinical nutrition. 2016; 104(4):1137–43. https://doi.org/10.3945/ajcn.116.135335 PMID: 27557655.

19. Chao A, Thun MJ, Connell CJ, McCullough ML, Jacobs EJ, Flanders WD, et al. Meat consumption and risk of colorectal cancer. JAMA. 2005; 293(2):172–82. https://doi.org/10.1001/jama.293.2.172 PMID: 15644544.

20. Cho E, Chen WY, Hunter DJ, Stampfer MJ, Colditz GA, Hankinson SE, et al. Red meat intake and all-cause cardiovasc ular and cancer mortality: is the risk modified by fruit and vegetable intake? The American journal of clinical nutrition. 2016; 104(4):1137–43. https://doi.org/10.3945/ajcn.116.135335 PMID: 27557655.

21. Ferrucci LM, Sinha R, Huang WY, Berndt SI, Katki HA, Schoen RE, et al. Meat consumpt ion and the risk of incident distal colon and rectal adenoma . British journal of cancer. 2012; 106(3):608–16. https://doi.org/10.1038/bjc.2011.549 PMID: 22166801; PubMed Central PMCID: PMC3281548.

22. Larsson SC, Virtamo J, Wolk A. Processed and unprocessed red meat consumption and risk of heart failure: prospective study of men. Circ Heart Fail. 2014; 7(4):552–7. https://doi.org/10.1161/CIRCHEARTFAILURE.113.000921 PMID: 24926309.

23. Pan A, Sun Q, Bernstein AM, Schulze MB, Manson JE, Stampfer MJ, et al. Red meat consumption and mortality: results from 2 prospective cohort studies. Archives of Internal medicine. 2012; 172(7):555–63. https://doi.org/10.1001/archinternmed.2011.2287 PMID: 22412075; PubMed Central PMCID: PMC3712342.
33. Pan A, Sun Q, Bernstein AM, Schulze MB, Manson JE, Willett WC, et al. Red meat consumption and risk of type 2 diabetes: 3 cohorts of US adults and an updated meta-analysis. The American journal of clinical nutrition. 2011; 94(4):1088–96. https://doi.org/10.3945/ajcn.111.018978 PMID: 21831992; PubMed Central PMCID: PMC3173026.

34. Takachi R, Tsubono Y, Baba K, Inoue M, Sasazuki S, Iwasaki M, et al. Red meat intake may increase the risk of colon cancer in Japanese, a population with relatively low red meat consumption. Asia Pacific journal of clinical nutrition. 2011; 20(4):603–12. Epub 2011/11/19. PMID: 22094846.

35. Tasevska N, Cross AJ, Dodd KW, Ziegler RG, Caporaso NE, Sinha R. No effect of meat, meat cooking preferences, meat mutagens or heme iron on lung cancer risk in the prostate, lung, colorectal and ovarian cancer screening trial. International journal of cancer International du cancer. 2011; 128(2):402–11. Epub 2010/03/17. https://doi.org/10.1002/ijc.25327 PMID: 20232386; PubMed Central PMCID: PMC2970721.

36. Wagemakers JJ, Pryne CJ, Stephen AM, Wadsworth ME. Consumption of red or processed meat does not predict risk factors for coronary heart disease; results from a cohort of British adults in 1989 and 1999. Eur J Clin Nutr. 2009; 63(3):303–11. https://doi.org/10.1038/sj.ejcn.1602954 PMID: 18000518; PubMed Central PMCID: PMC2766766.

37. Dubrow R, Darefsky AS, Park Y, Mayne ST, Moore SC, Kilfoy B, et al. Dietary components related to N-nitroso compound formation: a prospective study of adult glioma. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2010; 19(7):1709–22. https://doi.org/10.1158/1055-9965. EPI-10-0225 PMID: 20570910; PubMed Central PMCID: PMC2901412.

38. Fretts AM, Howard BV, McKnight B, Duncan GE, Beresford SA, Mete M, et al. Associations of processed meat and unprocessed red meat intake with incident diabetes: the Strong Heart Family Study. The American journal of clinical nutrition. 2012; 95(3):752–8. https://doi.org/10.3945/ajcn.111.029942 PMID: 22277554; PubMed Central PMCID: PMC3278249.

39. Lajous M, Bijon A, Fagherazzi G, Rossignol E, Boutron-Ruault MC, Clavel-Chapelon F. Processed meat consumption, dietary nitroso compounds and stomach cancer risk in a cohort of Swedish women. International journal of cancer International du cancer. 2006; 119(4):915–9. https://doi.org/10.1002/ijc.21925 PMID: 16550597.

40. Larsson SC, Bergkvist L, Wolk A. Processed meat consumption, dietary nitrosamines and stomach cancer risk in a cohort of Swedish women. International journal of cancer International du cancer. 2006; 119(4):915–9. https://doi.org/10.1002/ijc.21925 PMID: 16550597.

41. Michaud DS, Holick CN, Batchelor TT, Giovannucci E, Hunter DJ. Prospective study of meat intake and dietary nitrites, nitrates, and nitrosamines and risk of adult glioma. The American journal of clinical nutrition. 2009; 90(3):570–7. https://doi.org/10.3945/ajcn.2008.27199 PMID: 19587083; PubMed Central PMCID: PMC2728643.

42. Flood A, Velie EM, Sinha R, Chatterjee N, Lacey JV Jr., Schairer C, et al. Meat, fat, and their subtypes as risk factors for colorectal cancer in a prospective cohort of women. American journal of epidemiology. 2003; 158(1):59–68. PMID: 12835287.

43. Gilsing AM, Weijenberg MP, Goldbohm RA, Dagnelie PC, van den Brandt PA, Schouten LJ. The Netherlands Cohort Study-Meat Investigation Cohort; a population-based cohort over-represented with vegetarians, pescetarians and low meat consumers. Nutr J. 2013; 12:156. https://doi.org/10.1186/1475-2891-12-156 PMID: 24289207; PubMed Central PMCID: PMC420685.

44. Kurotani K, Nani A, Goto A, Mizoue T, Noda M, Oba S, et al. Red meat consumption is associated with the risk of type 2 diabetes in men but not in women: a Japan Public Health Center-based Prospective Study. Br J Nutr. 2013; 110(10):1910–8. https://doi.org/10.1017/S0007114513001128 PMID: 23651531.

45. Larsson SC, Johansson JE, Andersson SO, Wolk A. Meat intake and bladder cancer risk in a Swedish prospective cohort. Cancer causes & control: CCC. 2009; 20(1):35–40. https://doi.org/10.1007/s10552-008-9214-x PMID: 18704711.

46. Mannisto S, Kontto J, Kataja-Tuomola M, Albanes D, Virtamo J. High processed meat consumption is a risk factor of type 2 diabetes in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Br J Nutr. 2010; 103(12):1817–22. https://doi.org/10.1017/S0007114510000073 PMID: 20187985; PubMed Central PMCID: PMC3496924.

47. Mari-Sanchis A, Gea A, Basterra-Gortari FJ, Martinez-Gonzalez MA, Beunza JJ, Bes-Rastrollo M. Meat Consumption and Risk of Developing Type 2 Diabetes in the SUN Project: A Highly Educated Middle-Class Population. PLoS one. 2016; 11(7):e0157990. https://doi.org/10.1371/journal.pone.0157990 PMID: 27437689; PubMed Central PMCID: PMC4954662.

48. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Dietary meat, dairy products, fat, and cholesterol and pancreatic cancer risk in a prospective study. American journal of epidemiology. 2003; 157(12):1115–25. PMID: 12796048.
49. Nagao M, Iso H, Yamagishi K, Date C, Tamakoshi A. Meat consumption in relation to mortality from cardiovascular disease among Japanese men and women. Eur J Clin Nutr. 2012; 66(6):687–93. https://doi.org/10.1038/ejcn.2012.6 PMID: 22333876.

50. Rohrmann S, Platz EA, Kavanagh CJ, Thuさta L, Hoffman SC, Helzlsouer KJ. Meat and dairy consumption and subsequent risk of prostate cancer in a US cohort study. Cancer causes & control: CCC. 2007; 18(1):41–50. PMID: 17315319.

51. Sato Y, Nakaya N, Kuriyama S, Nishino Y, Tsubono Y, Tsuji J. Meat consumption and risk of colorectal cancer in Japan: the Miyagi Cohort Study. Eur J Cancer Prev. 2006; 15(3):211–8. https://doi.org/10.1097/01.c ej.0000197455.87356.05 PMID: 16679863.

52. Taunk P, Hecht E, Stolzenberg-Solomon R. Are meat and heme iron intake associated with pancreatic cancer? Results from the NIH-AARP diet and health cohort. International Journal of cancer Journal international du cancer. 2016; 138(9):2172–89. https://doi.org/10.1002/ijc.29964 PMID: 26666579; PubMed Central PMCID: PMCPMC4764390.

53. Taylor EF, Burley VJ, Greenwood DC, Cade JE. Meat consumption and risk of breast cancer in the UK Women’s Cohort Study. British journal of cancer. 2007; 96(7):1139–46. https://doi.org/10.1038/sj.bjc.6603689 PMID: 17406351.

54. Bazzano LA, He J, Ogden LG, Loria CM, Vupputuri S, Myers L, et al. Fruit and vegetable intake and risk of cardiovascular disease in US adults: the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. The American journal of clinical nutrition. 2002; 76(1):93–9. PMID: 12081821.

55. Bhupathiraju SN, Wedick NM, Pan A, Manson JE, Rexrode KM, Willett WC, et al. Quantity and variety in fruit and vegetable intake and risk of coronary heart disease. The American journal of clinical nutrition. 2013; 98(6):1514–23. https://doi.org/10.3945/ajcn.113.066381 PMID: 24088718; PubMed Central PMCID: PMCPMC2835631.

56. Buchner FL, Bueno-de-Mesquita HB, Linseisen J, Boshuizen HC, Kuenen LA, Ros MM, et al. Fruits and vegetables consumption and the risk of histological subtypes of lung cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). Cancer causes & control: CCC. 2010; 21(3):357–71. https://doi.org/10.1007/s10552-009-9468-y PMID: 19924549; PubMed Central PMCID: PMCPMC2835631.

57. Choi Y, Lee JE, Bae JM, Li ZM, Kim DH, Lee MS, et al. Vegetable intake, but not fruit intake, is associated with a reduction in the risk of cancer incidence and mortality in middle-aged Korean men. The Journal of nutrition. 2015; 145(6):1249–55. https://doi.org/10.3945/jn.114.209437 PMID: 25878208.

58. Dauchet L, Ferrieres J, Arveiler D, Yarnell JW, Gey F, Ducimetiere P, et al. Frequency of fruit and vegetable consumption and coronary heart disease in France and Northern Ireland: the PRIME study. Br J Nutr. 2004; 92(6):963–72. PMID: 15613259.

59. Dauchet L, Montaye M, Ruidavets JB, Arveiler D, Yarnell JW, Gey F, Ducimetiere P, et al. Association between the frequency of fruit and vegetable consumption and cardiovascular disease in male smokers and non-smokers. Eur J Clin Nutr. 2010; 64(6):578–86. https://doi.org/10.1038/ejcn.2010.46 PMID: 20354560.

60. Diallo A, Deschasaux M, Gaian P, Hercberg S, Zalek L, Latino-Martel P, et al. Associations between fruit, vegetable and legume intakes and prostate cancer risk: results from the prospective Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX) cohort. Br J Nutr. 2016; 115(9):1579–85. https://doi.org/10.1017/S0007114516000520 PMID: 26950824.

61. Feskanich D, Ziegler RG, Michaud DS, Giovannucci EL, Speizer FE, Willett WC, et al. Prospective study of fruit and vegetable consumption and risk of lung cancer among men and women. Journal of the National Cancer Institute. 2000; 92(22):1812–23. PMID: 11078758.

62. Genkinger JM, Platz EA, Hoffman SC, Comstock GW, Helzlsouer KJ. Fruit, vegetable, and antioxidant intake and all-cancer, cancer, and cardiovascular disease mortality in a community-dwelling population in Washington County, Maryland. American journal of epidemiology. 2004; 160(12):1223–33. https://doi.org/10.1093/aje/ PMID: 15583375.

63. Gillman MW, Cupples LA, Gagnon D, Posner BM, Ellison RC, Castelli WP, et al. Protective effect of fruits and vegetables on development of stroke in men. JAMA. 1995; 273(14):1113–7. PMID: 7707599.

64. Johnsen SP, Overvad K, Stripp C, Tjonneland A, Husted SE, Sorensen HT. Intake of fruit and vegetables and the risk of ischemic stroke in a cohort of Danish men and women. The American journal of clinical nutrition. 2003; 78(1):57–64. PMID: 12816771.

65. Kunzmann AT, Coleman HG, Huang WY, Cantwell MM, Kitahara CM, Berndt SI. Fruit and vegetable intakes and risk of colorectal cancer and incident and recurrent adenomas in the PLCO cancer screening trial. International journal of cancer Journal international du cancer. 2016; 138(8):1851–61. https://doi.org/10.1002/ijc.29922 PMID: 26559156.
66. Kurotani K, Nanri A, Goto A, Mizoue T, Noda M, Kato M, et al. Vegetable and fruit intake and risk of type 2 diabetes: Japan Public Health Center-based Prospective Study. Br J Nutr. 2013; 109(4):709–17. https://doi.org/10.1017/S0007114512001705 PMID: 22571826.

67. Larsson SC, Bergkvist L, Wolk A. Fruit and vegetable consumption and incidence of gastric cancer: a prospective study. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2006; 15(10):1998–2001. https://doi.org/10.1158/1055-9965.EPI-06-0402 PMID: 17035412.

68. Larsson SC, Virtamo J, Wolk A. Total and specific fruit and vegetable consumption and risk of stroke: a prospective study. Atherosclerosis. 2013; 227(1):147–52. https://doi.org/10.1016/j.atherosclerosis.2012.12.022 PMID: 23294925.

69. Leenders M, Boshuizen HC, Ferrari P, Siersma PD, Overvad K, Tjonneland A, et al. Fruit and vegetables and all-cause mortality: evidence from a large Australian cohort study. Int J Behav Nutr Phys Act. 2016; 13:9. https://doi.org/10.1186/s12966-016-0334-5 PMID: 26810760; PubMed Central PMCID: PMCPMC4727264.

70. Nunez-Cordoba JM, Alonso A, Beunza JJ, Palma S, Gomez-Graiceria E, Martinez-Gonzalez MA, Role of vegetables and fruits in Mediterranean diets to prevent hypertension. Eur J Clin Nutr. 2009; 63 (5):605–12. https://doi.org/10.1038/ejcn.2008.22 PMID: 18301434.

71. Okuda N, Miura K, Okayama A, Okamura T, Abbott RD, Nishi N, et al. Fruit and vegetable intake and mortality from cardiovascular disease in Japan: a 24-year follow-up of the NIPPON DATA80 Study. Eur J Clin Nutr. 2015; 69(4):482–8. https://doi.org/10.1038/ejcn.2014.276 PMID: 25585600.

72. Oude Griep LM, Geleijnse JM, Kromhout D, Ocke MC, Verschuren WM. Raw and processed fruit and vegetable consumption and 10-year coronary heart disease incidence in a population-based cohort study in the Netherlands. PLoS One. 2010; 5(10):e13609. https://doi.org/10.1371/journal.pone.0013609 PMID: 21049053; PubMed Central PMCID: PMCPMC2963618.

73. Oyebode O, Gordon-Dseagu V, Walker A, Mindell JS. Fruit and vegetable consumption and all-cause mortality: analysis of Health Survey for England data. J Epidemiol Community Health. 2014; 68(8):856–62. https://doi.org/10.1136/jech-2013-203500 PMID: 24687909; PubMed Central PMCID: PMCPMC4145465.

74. Park Y, Subar AF, Kipnis V, Thompson FE, Mouw T, Hollenbeck A, et al. Fruit and vegetable intakes and risk of colorectal cancer in the NIH-AARP diet and health study. American journal of epidemiology. 2007; 166(2):170–80. https://doi.org/10.1093/aje/kwm067 PMID: 17485731.

75. Rautiainen S, Levitan EB, Mittleman MA, Wolk A. Fruit and vegetable intake and rate of heart failure: a population-based prospective cohort of women. Eur J Heart Fail. 2015; 17(1):20–6. https://doi.org/10.1002/ejhf.191 PMID: 25382356.

76. Rissannen TH, Voutilainen S, Virtanen JK, Venho B, Vanharanta M, Mursu J, et al. Low intake of fruits, berries and vegetables is associated with excess mortality in men: the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study. The Journal of nutrition. 2003; 133(1):199–204. PMID: 12514290.

77. Shigihara M, Obara T, Nagai M, Sugawara Y, Watanabe T, Kakizaki M, et al. Consumption of fruits, vegetables, and seaweeds (sea vegetables) and pancreatic cancer risk: the Ohsaki Cohort Study. Cancer epidemiology. 2014; 38(2):129–36. https://doi.org/10.1016/j.canep.2014.01.001 PMID: 24522236.

78. Steffen LM, Jacobs DR Jr., Stevens J, Shahar E, Carithers T, Folsom AR. Associations of whole-grain, refined-grain, and fruit and vegetable consumption with risks of all-cause mortality and incident...
coronary artery disease and ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study. The American journal of clinical nutrition. 2003; 78(3):383–90. PMID: 12936919.

83. Stefler D, Pikhart H, Kubinova R, Pajak A, Stepaniak U, Malyutina S, et al. Fruit and vegetable consumption and mortality in Eastern Europe: Longitudinal results from the Health, Alcohol and Psychosocial Factors in Eastern Europe study. Eur J Prev Cardiol. 2016; 23(5):493–501. https://doi.org/10.1177/2047487315588230 PMID: 25903971; PubMed Central PMCID: PMCPMC4767146.

84. Takachi R, Inoue M, Ishihara J, Kurahashi N, Iwasaki M, Sasazuki S, et al. Fruit and vegetable intake and risk of total cancer and cardiovascular disease: Japan Public Health Center-Based Prospective Study. American journal of epidemiology. 2008; 167(1):59–70. https://doi.org/10.1093/aje/kwm263 PMID: 17928402.

85. Thompson CA, Habermann TM, Wang AH, Vierkant RA, Folsom AR, Ross JA, et al. Antioxidant intake from fruits, vegetables and other sources and risk of non-Hodgkin’s lymphoma: the Iowa Women’s Health Study. International journal of cancer Journal international du cancer. 2010; 126(4):992–1003. https://doi.org/10.1002/ijc.24830 PMID: 19685491; PubMed Central PMCID: PMCPMC2798902.

86. van Duijnhoven FJ, Bueno-De-Mesquita HB, Ferrari P, Jenab M, Boshuizen HC, Ros MM, et al. Fruit, vegetables, and colorectal cancer risk: the European Prospective Investigation into Cancer and Nutrion. The American journal of clinical nutrition. 2009; 89(5):1441–52. https://doi.org/10.3945/ajcn.2008.27120 PMID: 19393931.

87. Wright ME, Park Y, Subar AF, Freedman ND, Albanes D, Hollenbeck A, et al. Intakes of fruit, vegetables, and specific botanical groups in relation to lung cancer risk in the NIH-AARP Diet and Health Study. American journal of epidemiology. 2006; 168(9):1024–34. https://doi.org/10.1093/aje/kwm212 PMID: 18791192; PubMed Central PMCID: PMCPMC2631557.

88. Yu D, Zhang X, Gao YT, Li H, Yang G, Huang J, et al. Fruit and vegetable intake and risk of CHD: results from prospective cohort studies of Chinese adults in Shanghai. Br J Nutr. 2014; 111(2):353–62. https://doi.org/10.1017/S0007114513002328 PMID: 23866086; PubMed Central PMCID: PMCPMC3947047.

89. Zhang X, Shu XO, Xiang YB, Yang G, Li H, Gao J, et al. Cruciferous vegetable consumption is associated with a reduced risk of total and cardiovascular disease mortality. The American journal of clinical nutrition. 2011; 94(1):240–6. https://doi.org/10.3945/ajcn.110.009340 PMID: 21593509; PubMed Central PMCID: PMCPMC3127519.

90. Bamia C, Lagiou P, Jenab M, Aleksandrova K, Fedirko V, Trichopoulos D, et al. Fruit and vegetable consumption in relation to hepatocellular carcinoma in a multi-centre, European cohort study. British journal of cancer. 2015; 112(7):1273–82. https://doi.org/10.1038/bjc.2014.654 PMID: 25742480; PubMed Central PMCID: PMCPMC4385950.

91. Boggs DA, Palmer JR, Wise LA, Spiegelman D, Stampfer MJ, Adams-Campbell LL, et al. Fruit and vegetable intake in relation to risk of breast cancer in the Black Women’s Health Study. American journal of epidemiology. 2010; 172(11):1268–79. https://doi.org/10.1093/aje/kwq293 PMID: 20937636; PubMed Central PMCID: PMCPMC3025632.

92. Breslow RA, Graubard BI, Sinha R, Subar AF. Diet and lung cancer mortality: a 1987 National Health Interview Survey cohort study. Cancer causes & control: CCC. 2000; 11(5):419–31. PMID: 10877335.

93. Farvid MS, Chen WY, Michels KB, Cho E, Willett WC, Eliassen AH. Fruit and vegetable consumption in adolescence and early adulthood and risk of breast cancer: population based cohort study. Bmj. 2016; 353:i2343. https://doi.org/10.1136/bmj.i2343 PMID: 27170029; PubMed Central PMCID: PMCPMC5068921 http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

94. Flood A, Velie EM, Chatterjee N, Subar AF, Thompson FE, Lacey JV Jr., et al. Fruit and vegetable intakes and the risk of colorectal cancer in the Breast Cancer Detection Demonstration Project follow-up cohort. The American journal of clinical nutrition. 2002; 75(5):936–43. PMID: 11976170.

95. Joshipura KJ, Ascherio A, Manson JE, Stampfer MJ, Rimm EB, Speizer FE, et al. Fruit and vegetable intake in relation to risk of ischemic stroke. JAMA. 1999; 282(13):1233–9. PMID: 10517425.

96. Kirsh VA, Peters U, Mayne ST, Subar AF, Chatterjee N, Johnson CC, et al. Prospective study of fruit and vegetable intake and risk of prostate cancer. Journal of the National Cancer Institute. 2007; 99(15):1200–9. https://doi.org/10.1093/jnci/djm095 PMID: 17652278.

97. Kobylecki CJ, Afzal S, Davey Smith G, Nordestgaard BG. Genetically high plasma vitamin C, intake of fruit and vegetables, and risk of ischemic heart disease and all-cause mortality: a Mendelian randomization study. The American journal of clinical nutrition. 2015; 101(6):1135–43. https://doi.org/10.3945/ajcn.114.104497 PMID: 25948669.
98. Lai HT, Threapleton DE, Day AJ, Williamson G, Cade JE, Burley VJ. Fruit intake and cardiovascular disease mortality in the UK Women’s Cohort Study. Eur J Epidemiol. 2015; 30(9):1035–48. https://doi.org/10.1007/s10654-015-0505-5 PMID: 26076918.

99. Lin J, Zhang SM, Cook NR, Rexrode KM, Liu S, Manson JE, et al. Dietary intakes of fruit, vegetables, and fiber, and risk of colorectal cancer in a prospective cohort of women (United States). Cancer causes & control: CCC. 2005; 16(3):225–33. https://doi.org/10.1007/s10552-004-4025-1 PMID: 15947874.

100. Liu S, Manson JE, Lee IM, Cole SR, Hennekens CH, Willett WC, et al. Fruit, vegetable and bean intake and risk of cardiovascular disease: the Women’s Health Study. The American journal of clinical nutrition. 2000; 72(4):922–8. PMID: 11019332.

101. McCullough ML, Robertson AS, Chao A, Jacobs EJ, Stampfer MJ, Jacobs DR, et al. A prospective study of whole grains, fruits, vegetables and colon cancer risk. Cancer causes & control: CCC. 2003; 14(10):959–70. PMID: 14750535.

102. Michels KB, Edward G, Joshipura KJ, Rosner BA, Stampfer MJ, Fuchs CS, et al. Prospective study of fruit and vegetable consumption and incidence of colon and rectal cancer. Journal of the National Cancer Institute. 2000; 92(21):1740–52. PMID: 11058617.

103. Michels KB, Giovannucci E, Chan AT, Singhania R, Fuchs CS, Willett WC. Fruit and vegetable consumption and colorectal adenomas in the Nurses’ Health Study. Cancer Res. 2006; 66(7):3942–53. https://doi.org/10.1158/0008-5472.CAN-05-3637 PMID: 16585224.

104. Nagura J, Iso H, Watanabe Y, Maruyama K, Date C, Toyoshima H, et al. Fruit, vegetable and bean intake and mortality from cardiovascular disease among Japanese men and women: the JACC Study. Br J Nutr. 2009; 102(2):285–92. https://doi.org/10.1017/S0140-6736(08)60269-X PMID: 19138438.

105. Nakamura K, Nagata C, Oba S, Takatsuka N, Shimizu H. Fruit and vegetable intake and mortality from cardiovascul ar disease among Japanese men and women: the JACC Study. Br J Nutr. 2009; 102(2):285–92. https://doi.org/10.1017/S0140-6736(08)60269-X PMID: 19138438.

106. Sauvaget C, Nagano J, Hayashi M, Spencer E, Shimizu Y, Allen N. Vegetables and fruit intake and cancer risk: the Hiroshima/Nagasaki Life Span Study. British journal of cancer. 2003; 88(5):689–94. https://doi.org/10.1038/sj.bjc.6600775 PMID: 12618875; PubMed Central PMCID: PMC2376354.

107. Strandhagen E, Hansson PO, Bosaeus I, Isaksson B, Eriksson H. High fruit intake may reduce mortality among middle-aged and elderly men. The Study of Men Born in 1913. Eur J Clin Nutr. 2000; 54(4):337–41. PMID: 10745285.

108. Suzuki R, Iwasaki M, Harra A, Inoue M, Sasazuki S, Sawada N, et al. Fruit and vegetable intake and breast cancer risk defined by estrogen and progesterone receptor status: the Japan Public Health Center-based Prospective Study. Cancer causes & control: CCC. 2013; 24(12):2117–28. https://doi.org/10.1007/s10552-013-0289-7 PMID: 24091793.

109. Villegas R, Shu XO, Gao YT, Yang G, Elsayed T, Li H, et al. Vegetable but not fruit consumption reduces the risk of type 2 diabetes in women. The Journal of nutrition. 2008; 138(9):574–80. PMID: 18287369; PubMed Central PMCID: PMC2615491.

110. Bendinelli B, Masala G, Saieva C, Salvini S, Calonico C, Sacerdote C, et al. Fruit, vegetables, and olive oil and risk of coronary heart disease in Italian women: the EPICOR Study. The American journal of clinical nutrition. 2011; 93(2):275–83. https://doi.org/10.3945/ajcn.110.00521 PMID: 21177799.

111. Liu Y, Sobue T, Otani T, Tsugane S. Vegetables, fruit consumption and risk of lung cancer among middle-aged Japanese men and women: JPHC study. Cancer causes & control: CCC. 2004; 15(4):349–57. https://doi.org/10.1023/B:CACO.0000027507.22124.26 PMID: 15141136.

112. Nothlings U, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Kolonel LN. Vegetable intake and pancreatic cancer risk: the multiethnic cohort study. American journal of epidemiology. 2007; 165(2):138–47. https://doi.org/10.1093/aje/kw336 PMID: 17088894.

113. Pham TM, Fujino Y, Ide R, Kudo T, Shirane K, Tokui N, et al. Prospective study of vegetable consumption and liver cancer in Japan. International journal of cancer. Journal international du cancer. 2006; 119(10):2408–11. https://doi.org/10.1002/ijc.22122 PMID: 16894561.

114. Takachi R, Inoue M, Sawada N, Iwasaki M, Sasazuki S, Ishihara J, et al. Fruits and vegetables in relation to prostate cancer in Japanese men: the Japan Public Health Center-Based Prospective Study. Nutrition and cancer. 2010; 62(1):30–9. https://doi.org/10.1080/01608580903191502 PMID: 20043257.

115. Katzke VA, Kaaks R, Kuhn T. Lifestyle and cancer risk. Cancer journal. 2015; 21(2):104–10. Epub 2015/03/31. https://doi.org/10.1097/PPO.0000000000000101 PMID: 25815850.

116. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008; 371(9612):569–78. Epub 2008/02/19. https://doi.org/10.1016/S0140-6736(08)60269-X PMID: 18280327.
117. Keum N, Greenwood DC, Lee DH, Kim R, Aune D, Ju W, et al. Adult weight gain and adiposity-related cancers: a dose-response meta-analysis of prospective observational studies. Journal of the National Cancer Institute. 2015; 107(2). Epub 2015/03/12. https://doi.org/10.1093/jnci/djv088 PMID: 25757865.

118. Giovannucci E, Michaud D. The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. Gastroenterology. 2007; 132(6):2208–25. Epub 2007/05/15. https://doi.org/10.1053/j.gastro.2007.03.050 PMID: 17498513.

119. Gandini S, Botteri E, Iodice S, Boniol M, Lowenfels AB, Maisonneuve P, et al. Tobacco smoking and cancer: a meta-analysis. International journal of cancer Journal international du cancer. 2008; 122 (1):155–64. Epub 2007/09/26. https://doi.org/10.1002/ijc.23033 PMID: 17893872.

120. Dallongeville J, Marecaux N, Fruchart JC, Amouyel P. Cigarette smoking is associated with unhealthy patterns of nutrient intake: a meta-analysis. The Journal of nutrition. 1998; 128(9):1450–7. Epub 1998/09/10. PMID: 9732304.

121. Conway DI, Brenner DR, McMahon AD, Macpherson LM, Agudo A, Ahrens W, et al. Estimating and explaining the effect of education and income on head and neck cancer risk: INHANCE consortium pooled analysis of 31 case-control studies from 27 countries. International journal of cancer Journal international du cancer. 2015; 136(5):1125–39. Epub 2014/07/06. https://doi.org/10.1002/ijc.29063 PMID: 24998155; PubMed Central PMCID: PMC4531373.

122. Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. British journal of cancer. 2015; 112(3):580–93. Epub 2014/11/26. https://doi.org/10.1038/bjc.2014.579 PMID: 25422909; PubMed Central PMCID: PMC4453639.

123. Larsson SC, Orsini N, Wolk A. Processed meat consumption and stomach cancer risk: a meta-analysis. Journal of the National Cancer Institute. 2006; 98(15):1078–87. Epub 2006/08/03. https://doi.org/10.1093/jnci/djj301 PMID: 16882945.

124. Wu K, Spiegelman D, Hou T, Albanes D, Allen NE, Berndt SI, et al. Associations between unprocessed red and processed meat, poultry, seafood and egg intake and the risk of prostate cancer: A pooled analysis of 15 prospective cohort studies. International journal of cancer Journal international du cancer. 2016; 138(10):2368–82. https://doi.org/10.1002/ijc.29973 PMID: 26685908; PubMed Central PMCID: PMC4837898.

125. Domingo JL, Nadal M. Carcinogenicity of consumption of red and processed meat: What about environmental contaminants? Environmental research. 2016; 145:109–15. Epub 2015/12/15. https://doi.org/10.1016/j.envres.2015.11.031 PMID: 26656511.

126. Figueiredo JC, Hsu L, Hutter CM, Lin Y, Campbell PT, Baron JA, et al. Genome-wide diet-gene interaction analyses for risk of colorectal cancer. PLoS genetics. 2014; 10(4):e1004228. https://doi.org/10.1371/journal.pgen.1004228 PMID: 24743840; PubMed Central PMCID: PMC3990510.

127. Skjelbred CF, Saebo M, Hjartaker A, Grotmol T, Hansteen IL, Tveit KM, et al. Meat, vegetables and genetic polymorphisms and the risk of colorectal carcinomas and adenomas. BMC cancer, 2007; 7:228. https://doi.org/10.1186/1471-2407-7-228 PMID: 18093316; PubMed Central PMCID: PMC2228310.

128. Turner F, Smith G, Sachse C, Lightfoot T, Garner RC, Wolf CR, et al. Vegetable, fruit and meat consumption and potential risk modifying genes in relation to colorectal cancer. International journal of cancer Journal international du cancer. 2004; 112(2):259–64. https://doi.org/10.1002/ijc.20404 PMID: 15352038.