Association between intake of antioxidants and pancreatic cancer risk: a meta-analysis

Jiamin Chen, Wuxia Jiang, Liming Shao, Dandan Zhong, Yihua Wu and Jianting Cai

Department of Gastroenterology, Second Affiliated Hospital, Zhejiang University College of Medicine, Hangzhou, China; Department of Epidemiology and Health Statistics, Zhejiang University School of Public Health, Hangzhou, China

ABSTRACT

We conducted a meta-analysis to systematically evaluate the association between antioxidants intake and pancreatic cancer risk. Relevant articles were retrieved from PUBMED and EMBASE databases and standard meta-analysis methods were applied. Finally a total of 18 studies were included. Comparing the highest with lowest categories, higher dietary intakes of selenium, vitamin C, vitamin E, \( \beta \)-carotene and \( \beta \)-cryptoxanthin were significantly associated with reduced pancreatic cancer risk (for selenium, pooled OR = 0.47, 95%CI 0.26–0.85; for vitamin C, pooled OR = 0.68, 95%CI 0.57–0.80; for vitamin E, pooled OR = 0.70, 95%CI 0.62–0.81; for \( \beta \)-carotene, pooled OR = 0.74, 95%CI 0.56–0.98; for \( \beta \)-cryptoxanthin, pooled OR = 0.70, 95%CI 0.56–0.88). Lycopene intake was marginally associated with pancreatic cancer risk (pooled OR = 0.85, 95%CI 0.73–1.00), while no significant association was observed for \( \alpha \)-carotene, lutein and zeaxanthin. In summary, higher dietary intake of selenium, vitamin C, vitamin E, \( \beta \)-carotene and \( \beta \)-cryptoxanthin was inversely associated with pancreatic cancer risk.

Introduction

Pancreatic cancer remains the 13th most commonly diagnosed cancer worldwide, and is the eighth leading cause of cancer death (Siegel et al. 2013). Early diagnostic methods for pancreatic cancer are inefficient and the prognosis is poor, with one-year survival rate of about 25% and five-year survival rate of 4–5%, and it is estimated that pancreatic cancer leads to 227,000 deaths each year (Verdecchia et al. 2007). Thus, it is an important issue to identify risk factors for pancreatic cancer and to prevent it accordingly.

Many risk factors for pancreatic cancer have been identified, including family history, smoking and type 2 diabetes (Klein et al. 2004; Huxley et al. 2005). Diet might be involved in the aetiology of pancreatic cancer, for example, vegetable and fruit consumption may decrease the risk of pancreatic cancer (Wiseman 2008). One explanation is that vegetable and fruit are rich in antioxidants, such as vitamin C, vitamin E and carotenoids, which may prevent pancreatic cancer by inactivating free radicals and reducing oxidative DNA damage (McCullough & Giovannucci 2004). This is important since DNA damage caused by heredity, smoking or other factors plays a fundamental role in pancreatic cancer development. Several studies have investigated the association between intake of antioxidants (including selenium, vitamin C, vitamin E, \( \alpha \)-carotene, \( \beta \)-carotene, \( \beta \)-cryptoxanthin, lycopene, lutein and zeaxanthin) and pancreatic cancer risk, while there is still no clear conclusion (Stolzenberg-Solomon et al. 2002, 2009; Bravi et al. 2011; Heinen et al. 2012; Banim et al. 2013; Han et al. 2013; Jansen et al. 2013). Therefore, the aim of our study is to assess the current evidence on the association between antioxidant nutrients intake and pancreatic cancer risk.

Methods

Literature search and study selection

This meta-analysis was designed, conducted and reported in adherence to the PRISMA statement (Moher et al. 2009). The literature search was conducted up to December 2014 in the PUBMED and EMBASE databases without restriction. The following terms were used in the literature search: (“antioxidant” or “vitamin” or “vitamin C” or “vitamin E” or
“carotene” or “tocopherol” or “carotenoid” or “lycopene” or “selenium” or “β-cryptoxanthin” or “lutein and zeaxanthin”) AND (“pancreatic cancer” or “pancreatic ductal adenocarcinoma” or “pancreatic adenocarcinoma”). References cited in the selected articles and relevant reviews were also manually searched for potential missing studies. For study selection, titles and abstracts of publications identified from the initial search were first scanned, and then full papers were carefully reviewed for potential eligible studies.

Studies would be included in this meta-analysis if they met all the following criteria: (i) study should be designed as cohort, case-control or cross-sectional study; (ii) the exposure of interest was dietary antioxidant intake, while the outcome of interest was pancreatic cancer; (iii) odds ratio (OR) or relative risk (RR) estimates with 95% confidence intervals (95%CIs) were reported or could be calculated.

Data extraction

Data of each study was independently extracted by two reviewers, and discrepancies were resolved by discussion or a third investigator. The following information was extracted from each study: first author/publication year, study design, sample size, sex and age of participants, country of origin, antioxidant kind, variables adjusted for in the study, and OR (or RR) estimates with 95%CIs for the highest versus lowest categories of dietary antioxidant intake. ORs (RRs) reflecting the greatest degree of control for potential confounders were adopted in the pooled analysis. For duplicated data, only the most detailed or recent information was extracted. We adopted the widely used Newcastle-Ottawa Scale to assess the study quality (Stang 2010).

Statistical analysis

The extent of heterogeneity was evaluated using Q test (with p value <0.1, suggesting significant heterogeneity) and I² index with I² >50%, suggesting substantial heterogeneity. Summary ORs (RRs) and 95%CIs were calculated using a random-effects model when the heterogeneity was significant, and a fixed-effects model was applied otherwise. The primary meta-analyses were conducted to evaluate the association between antioxidants intake and pancreatic cancer risk. Meta-regression, sensitivity and subgroup analyses were used for exploring source of heterogeneity with the following variables: design, country of origin and sample size. Meta-regression analyses would be applied for the meta-analyses with 10 or more studies. Besides, subgroup analyses were also applied to assess whether these variables would modify the results of meta-analysis. To evaluate the publication bias risk, funnel plots were evaluated and Begg’s and Egger’s tests were applied. However, for pooled analyses with fewer than 10 studies, we did not further conduct statistical tests for funnel plot asymmetry because of the limited test power (Sterne et al. 2011). All analyses were conducted using the Stata software (V.11.0; StataCorp, College Station, TX). p < 0.05 was considered statistically significant.

Results

Study selection and characteristics

The systematic literature search yielded 2289 articles and 1872 were assessed for eligibility after removing duplicated papers. Among them, 1828 papers were excluded through screening titles and abstracts. For the remaining studies, 26 were excluded for the following reasons: they did not report antioxidant intake and risk of pancreatic cancer (n = 10), they were review, comment or meta-analysis (n = 8), lack of sufficient data (n = 7) and duplicated reports (n = 1). The remaining 18 studies finally met the inclusion criteria and were included in this meta-analysis (Baghurst et al. 1991; Olsen et al. 1991; Zatonski et al. 1991; Howe et al. 1992; Kalapothaki et al. 1993; Shibata et al. 1994; Ji et al. 1995; Stolzenberg-Solomon et al. 2002; Lin et al. 2005; Nkondjock et al. 2005; Stolzenberg-Solomon et al. 2009; Gong et al. 2010; Bravi et al. 2011; Amaral et al. 2012; Heinen et al. 2012; Banim et al. 2013; Han et al. 2013; Jansen et al. 2013). Figure 1 shows the flow diagram of our literature search. The characteristics of the included studies are shown in Table 1 and the methodological quality assessment is shown in Supplementary Table 1.

Association between dietary selenium intake and pancreatic cancer risk

The association between dietary selenium intake and pancreatic cancer risk was assessed by six studies. The pooled OR was 0.47 (95%CI 0.26–0.85) with significant heterogeneity (I² = 82.8%, p < 0.001) (Figure 2 and Table 2), suggesting that higher selenium intake may reduce the risk of pancreatic cancer.

Association between dietary vitamin C intake and pancreatic cancer risk

A total of 15 studies evaluated the association between dietary vitamin C intake and pancreatic cancer risk.
Among the included studies, five were prospective cohort studies and 10 were case-control studies; six studies were conducted in Europe, five were in USA and four were in other countries.

Significant heterogeneity across studies was found ($I^2 = 52.4\%$, $p = 0.009$) (Figure 3). Meta-regression analysis for study design, sample size and country of origin was used to explore source of heterogeneity, and we found that study design (regression coefficient $= 0.452$, $p = 0.013$) and sample size (regression coefficient $= 0.348$, $p = 0.041$) could partially explain the heterogeneity. Country of origin appeared not to be the source of heterogeneity (regression coefficient $= -0.092$, $p = 0.425$). We did not test the joint effect of the variables in the meta-regression analysis because of the limited number of included studies ($n = 15$). The pooled OR for pancreatic cancer comparing the highest versus lowest categories of vitamin C intake was 0.68 (95\% CI 0.57–0.80) (Figure 3 and Table 2), indicating that higher vitamin C intake significantly decreased pancreatic cancer risk. Subgroup analyses were then applied, and we found a significant association between vitamin C intake and pancreatic cancer risk in case-control studies (pooled OR $= 0.58$, 95\% CI 0.48–0.71), while there was no significant association in cohort studies (pooled OR $= 0.94$, 95\% CI 0.78–1.15). For the subgroup analyses, results for geographic region and sample size are shown in Table 3.

**Association between dietary vitamin E intake and pancreatic cancer risk**

Eleven studies were included in the analysis of the association between dietary vitamin E intake and pancreatic cancer risk. Four studies were cohort studies and the remaining were case-control designed. Most of the studies were conducted in USA ($n = 4$) or European countries ($n = 4$), while three were in other countries. Comparing the highest versus lowest categories of vitamin E intake, the pooled OR was 0.70 (95\% CI 0.62–0.81) (Figure 4 and Table 2), indicating a significant inverse association and there was no significant heterogeneity across studies ($I^2 = 0.0\%$, $p = 0.622$) (Figure 4).

As the subgroup analysis showed, the protective effect of vitamin E against pancreatic cancer differed by study design. Vitamin E intake was significantly associated with reduced pancreatic cancer risk for case-control studies (pooled OR $= 0.63$, 95\% CI 0.53–0.75) while no significant association was found for cohort studies (pooled OR $= 0.85$, 95\% CI 0.68–1.06). The subgroup analysis results for geographic region and sample size are shown in Table 3.

**Association between dietary β-carotene intake and pancreatic cancer risk**

The association between β-carotene intake and pancreatic cancer risk was assessed by nine studies. The pooled results suggested that higher β-carotene intake was associated with reduced pancreatic cancer risk (pooled OR $= 0.74$, 95\% CI 0.56–0.98) (Figure 5). Significant heterogeneity among studies was found ($I^2 = 69.6\%$, $p = 0.001$) (Figure 5). The subgroup analysis results for study design, geographic region and sample size are shown in Table 3.

**Association between β-cryptoxanthin intake and pancreatic cancer risk**

Three studies were included in this analysis. Patients with highest categories of β-cryptoxanthin intake were at a lower risk of pancreatic cancer compared with the lowest categories (pooled OR $= 0.70$, 95\% CI 0.56–0.88) (Table 2). No significant heterogeneity was observed ($I^2 = 28.4\%$, $p = 0.248$) (Table 2).

**Association between lycopene intake and pancreatic cancer risk**

Six studies were included in the pooled analysis of lycopene. The pooled OR was 0.85 (95\% CI 0.73–1.00)
Table 1. Characteristics of studies evaluating association between antioxidant vitamins intake and gastric cancer risk.

| Author and publication year | Study design | Sample size (no. of cancer cases) | Gender (male/female) | Age (year) | Country | Antioxidant kind | Adjusted variables |
|-----------------------------|--------------|----------------------------------|----------------------|------------|---------|-----------------|-------------------|
| (Jansen et al. 2013)        | Case-control | 1367 (384)                       | 704/663              | Case: 67.0 Control: 65.8 | USA     | Selenium, α-carotene, β-carotene, β-cryptoxanthin, lycopene, vitamin C, vitamin E, lutein and zeaxanthin | Age, gender, energy, smoking, BMI and drinks of alcohol per week |
| (Han et al. 2013)           | Cohort       | 77,446 (162)                     | 37,221/40,225        | 62.0       | USA     | Selenium, β-carotene, lycopene, vitamin C, vitamin E, lutein and zeaxanthin | Age, gender, ethnicity, education, BMI, physical activity, smoking, alcohol consumption, family history of pancreatic cancer, history of diabetes and total energy intake |
| (Banim et al. 2013)         | Case-cohort  | 4019 (49)                        | 1767/2252            | Nr         | UK      | Selenium, vitamin C and vitamin E | Age, gender, smoking, diabetes, total energy intake and BMI |
| (Heinen et al. 2012)        | Cohort       | 120,852 (423)                    | 58,279/62,573        | 55–69      | Netherlands | α-Carotene, β-carotene, β-cryptoxanthin, lycopene, vitamin C, vitamin E, lutein and zeaxanthin | Age, gender, smoking, BMI, family history of pancreatic cancer, history of diabetes mellitus, intake of energy, red meat, coffee and alcohol |
| (Amaral et al. 2012)        | Case-control | 517 (118)                        | 421/96               | Case: 66.1 Control: 63.8 | Spain   | Selenium | Age, gender, region and smoking |
| (Bravi et al. 2011)         | Case-control | 978 (326)                        | 522/456              | Nr         | Italy   | α-Carotene, β-carotene, β-cryptoxanthin, lycopene, vitamin C, vitamin E, lutein and zeaxanthin | Age, gender, centre, year of interview, education, smoking, history of diabetes, BMI and total energy intake |
| (Gong et al. 2010)          | Case-control | 2233 (532)                       | 1174/1059            | Nr         | USA     | Vitamin C and vitamin E | Age, gender, total energy intake, race, education, BMI, history of diabetes, smoking, physical activity and alcohol consumption |
| (Stolzenberg-Solomon et al. 2009) | Cohort | 29,092 (318) | 29,092/0 | 50–69 | Finland | Vitamin E | Age, serum cholesterol, smoking and history of diabetes mellitus |
| (Nkondjock et al. 2005)     | Case-control | 5183 (462)                       | 2589/2594            | Nr         | Canada  | α-Carotene, β-carotene, lycopene, lutein and zeaxanthin | Age, province, smoking, educational attainment, BMI, folate and total energy intake |
| (Lin et al. 2005)           | Case-control | 327 (109)                        | Nr                   | Case: 64.7 Control: 65.1 | Japan   | Vitamin C and vitamin E | Age, smoking and energy intake |
| (Stolzenberg-Solomon et al. 2002) | Cohort | 27,111 (163) | 27,111/0 | 50–69 | Finland | Selenium, β-carotene, lycopene and vitamin C | Age, years of smoking and energy intake |

(continued)
| Author and publication year | Study design | Sample size (no. of cancer cases) | Gender (male/female) | Age (year) | Country | Antioxidant kind | Adjusted variables |
|-----------------------------|--------------|----------------------------------|----------------------|------------|---------|-----------------|--------------------|
| (Ji et al. 1995)            | Case-control | 2003 (451)                       | Nr                   | NR         | China   | Vitamin C and vitamin E | Age, income, smoking, green tea drinking, response status and total calories |
| (Shibata et al. 1994)       | Cohort       | 13,979 (65)                      | Nr                   | Males: 75.0 Females: 73.8 | USA | β-Carotene and vitamin C | Age, gender and smoking |
| (Kalapothaki et al. 1993)   | Case-control | 543 (181)                        | Nr                   | NR         | Greece | Vitamin C | Age, gender, hospital, past residence, years of schooling, cigarette smoking, diabetes mellitus and energy intake |
| (Howe et al. 1992)          | Case-control | 2471 (802)                       | 1170/1301            | 28–87      | Australia | Vitamin C | All nutrient variables (categorical) and smoking |
| (Zatonski et al. 1991)      | Case-control | 305 (110)                        | 157/148              | NR         | Poland | Vitamin C | Cigarette lifetime consumption and calories |
| (Olsen et al. 1991)         | Case-control | 432 (212)                        | 432/0                | 40–84      | USA     | β-Carotene, vitamin C and vitamin E | Age, total energy, smoking, alcohol consumption, history of diabetes mellitus and educational level |
| (Baghurst et al. 1991)      | Case-control | 357 (104)                        | 194/163              | NR         | Australia | Selenium, β-carotene, vitamin C and vitamin E | Total energy, smoking and alcohol consumption |

Nr: not reported; BMI: body mass index.

Figure 2. The association between selenium intake and pancreatic cancer risk.
with no significant heterogeneity ($I^2 = 0\%$, $p = 0.701$) (Table 2), indicating a borderline significant inverse association.

**Association between intake of α-carotene and pancreatic cancer risk**

The association between α-carotene and pancreatic cancer risk was evaluated by four studies. We observed no significant association (pooled OR = 0.86, 95%CI 0.56–1.33).

**Association between lutein and zeaxanthin intake and pancreatic cancer risk**

Lutein and zeaxanthin were jointly investigated by five studies and no significant association was found (pooled OR = 0.82, 95%CI 0.58–1.15).

**Publication bias**

We did not find significant asymmetry of the funnel plots in the current study, and statistical tests for funnel plot asymmetry revealed no significant publication bias for the analysis of vitamin C ($p = 0.235$ for Begg’s test and 0.053 for Egger’s test) and vitamin E ($p = 0.640$ for Begg’s test and 0.596 for Egger’s test). The funnel plots are shown in the supplementary file.

**Discussion**

Diet has been reported to be involved in the etiology of pancreatic cancer, and vegetable and fruit consumption might be inversely associated with pancreatic cancer risk, though the evidence seemed to be limited and the protective effect was observed mainly in case-control studies (Wiseman 2008). Antioxidants were thought to be strong protective dietary components, and observational studies provided evidence for the relation between dietary antioxidants intake and pancreatic cancer risk. This meta-analysis included 18 eligible studies and evaluated the association between eight kinds of antioxidants intake and pancreatic cancer risk, including selenium, vitamin C, vitamin E, α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein and zeaxanthin. Among them, selenium, vitamin C, vitamin E, β-carotene and β-cryptoxanthin were found to be inversely associated with pancreatic cancer risk.
Subgroup analyses were then applied according to study design, geographical region, and sample size for vitamin C, vitamin E and β-carotene. Of note, inverse association was found in case-control studies while no association was found in cohort studies for these antioxidants. It is easier to conduct a case-control study than cohort study, and there were more case-control studies included in this analysis. However, case-control studies are retrospectively designed and rely on recall for antioxidant intake measurement, thus there would be more selection and recall bias. Compared with case-control studies, cohort studies could measure antioxidant intake more precisely and are better in evaluating causal relationships. Thus, more prospective cohort studies are warranted to further clarify this issue and the conclusion should be taken cautiously.

Blood levels of antioxidants can better represent the actual bioavailability and thus is an important method to assess the association between intake of micronutrients and pancreatic cancer risk. Several studies have also investigated the relation between blood antioxidant levels and risk of pancreatic cancer (Burney et al. 1989; Stolzenberg-Solomon et al. 2009; Jeurnink et al. 2014). In a small nested case-control study with 22 pancreatic cancer patients and 44 controls, pre-diagnostic serum levels of selenium and lycopene were higher among controls than cases (Burney et al. 1989). A large cohort with 29,133 male Finnish smokers examined the relation between serum α-tocopherol concentration and

| Table 3. Subgroup analyses of the association between vitamin C, vitamin E and β-carotene and pancreatic cancer risk. |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| **Factor**                                      | **Vitamin C intake**                            | **Vitamin E intake**                            | **β-carotene intake**                           |
|                                                 | No. of studies | Pooled OR (95%CI) | I² | No. of studies | Pooled OR (95%CI) | I² | No. of studies | Pooled OR (95%CI) | I² |
| Design                                          |              |                   |    |              |                   |    |              |                   |    |
| Cohort                                          | 5            | 0.94 (0.78, 1.15) | 0.0| 4             | 0.85 (0.68, 1.06) | 0.0| 4             | 0.91 (0.65, 1.28) | 53.2|
| Case-control                                    | 10           | 0.58 (0.48, 0.71) | 50.3| 7             | 0.63 (0.53, 0.75) | 0.0| 5             | 0.62 (0.41, 0.95) | 74.6|
| Region of origin                                |              |                   |    |              |                   |    |              |                   |    |
| USA                                             | 5            | 0.66 (0.55, 0.80) | 18.7| 4             | 0.63 (0.51, 0.78) | 0.0| 5             | 0.68 (0.47, 0.99) | 72.0|
| Europe                                          | 6            | 0.80 (0.61, 1.05) | 56.2| 4             | 0.83 (0.67, 1.04) | 0.0| 3             | 0.95 (0.63, 1.45) | 60.6|
| Others                                          | 4            | 0.54 (0.43, 0.68) | 0.0 | 3             | 0.65 (0.48, 0.87) | 36.1| 1             | 0.45 (0.22, 0.92) | – |
| Sample sizea                                    |              |                   |    |              |                   |    |              |                   |    |
| Large sample size                               | 6            | 0.83 (0.70, 0.98) | 35.8| 4             | 0.85 (0.68, 1.06) | 0.0| 5             | 0.99 (0.83, 1.19) | 42.3|
| Small                                           | 9            | 0.58 (0.47, 0.73) | 53.5| 7             | 0.63 (0.53, 0.75) | 0.0| 4             | 0.51 (0.39, 0.66) | 0.0|

*Large sample size means the sample size ≥2400 while small sample size means the sample size <2400.

Figure 4. The association between vitamin E intake and pancreatic cancer risk.
risk of exocrine pancreatic cancer, and a significant inverse association was found (Q5 versus Q1, adjusted HR = 0.52, 95% CI 0.34–0.80) (Stolzenberg-Solomon et al. 2009). Besides, Jeurnink et al. conducted a nested case-control study within the European Prospective Investigation into Cancer and Nutrition (EPIC), and found that higher plasma levels of α-tocopherol, β-carotene and zeaxanthin might be associated with reduced pancreatic cancer risk (Jeurnink et al. 2014). These studies further support the protective effects of certain antioxidants against pancreatic cancer.

The mechanisms of selenium, vitamin C, vitamin E and carotenoids against pancreatic cancer are not fully understood, one explanation is their antioxidant property (McCann et al. 2005). Reactive oxygen species (ROS) are considered to be important risk factors for pancreatic cancer (Chiera et al. 2008), while antioxidants provide important defense against free-radical damage to DNA (Maritim et al. 2003). Besides, vitamin C and carotenoids were shown to have immune-enhancing role (McCullough & Giovannucci 2004). Further, experimental work indicated that the induction of apoptosis by carotenoids may be an important role of antioxidants in cancer prevention (Muller et al. 2002). Another mechanism for antioxidants is the effect against inflammatory process, while chronic inflammation may play a role in carcinogenesis (Algul et al. 2007). Variations of genes regulating antioxidant pathways were reported to be associated with risk of pancreatic cancer (Wheatley-Price et al. 2008), and the inconsistence in reported association between dietary antioxidant intake and pancreatic cancer might be explained by unmeasured variation in inflammation genes or antioxidant metabolism genes (Jansen et al. 2013).

In the current study, we applied meta-regression and subgroup analyses to explore the potential source of heterogeneity. For vitamin C, meta-regression analysis suggested that study design and sample size of the included studies could partially explain the heterogeneity across studies. Other factors, including age and sex of the participants, may also be the source of heterogeneity. However, we were unable to evaluate these factors because of insufficient data. Therefore, further individual patient data (IPD) analysis would be helpful if data is available. We also observed significant heterogeneity in the analysis of selenium and β-carotene. Meta-regression analyses were not applied for the concern of limited number of studies and the heterogeneity could not be fully explained. Interestingly, we found that intake of vitamin C, vitamin E and β-carotene was not significant associated with pancreatic cancer risk in European countries, while an inverse association was observed in other geographic area (Table 3). It should be noted that most of the cohort studies reported a null association between antioxidant intake and pancreatic cancer risk, while most of them (four out of six) were conducted in European countries, which might be the reason. Besides, in the current study, Begg’s funnel plot and Egger’s test did not suggest significant publication bias in the pooled analysis of vitamin C and vitamin E. For the remaining
meta-analyses, funnel plot showed no significant asymmetry, while no statistical tests for funnel plot asymmetry were conducted because of the possible insufficient test power. Thus, because of the limited number of the included studies, whether the publication bias exists in the current meta-analysis is still difficult to confirm.

The current analysis comprehensively assessed the association between antioxidants intake and pancreatic cancer risk, and suggested that intake of several antioxidants might be inversely associated with pancreatic risk. We applied standard meta-analysis methods and conducted the study in accordance with the PRISMA checklist, which may improve the quality of our study. Besides, most of the included studies were of high or moderate methodological quality and have relatively large sample size.

The current analysis also has some limitations. First, number of studies included in this analysis was not large enough, thus some of the subgroup analyses were hard to conduct and less reliable. Second, most of the involved studies were case-control studies which were prone to bias. Besides, the included studies were mainly from Europe, USA and Asia, therefore the conclusions should be taken cautiously for other ethnic populations.

**Conclusions**

In summary, higher dietary intake of antioxidants including selenium, vitamin C, vitamin E, β-carotene and β-cryptoxanthin, was inversely associated with pancreatic cancer risk. More studies, especially prospective cohort studies are warranted to further clarify this issue.

**Disclosure statement**

The authors have declared no conflicts of interest.

**Funding information**

This work was supported by the Major Science and Technology Projects of Zhejiang province (grant number 2014C030411-1).

**References**

Algil H, Treiber M, Lesina M, Schmid RM. 2007. Mechanisms of disease: chronic inflammation and cancer in the pancreas – a potential role for pancreatic stellate cells? Nat Clin Pract Gastroenterol Hepatol. 4:454–462.

Amaral AF, Porta M, Silverman DT, Milne RL, Kogevinas M, Rothman N, Cantor KP, Jackson BP, Pumarega JA, Lopez T, et al. 2012. Pancreatic cancer risk and levels of trace elements. Gut. 61:1583–1588.

Baghurst PA, McMichael AJ, Slavotinek AH, Baghurst KI, Boyle P, Walker AM. 1991. A case-control study of diet and cancer of the pancreas. Am J Epidemiol. 134:167–179.

Banim PJ, Luben R, McTaggart A, Welch A, Wareham N, Khaw KT, Hart AR. 2013. Dietary antioxidants and the aetiology of pancreatic cancer: a cohort study using data from food diaries and biomarkers. Gut. 62:1489–1496.

Bravi F, Polesel J, Bosetti C, Talamini R, Negri E, Dal Maso L, Serraino D, La Vecchia C. 2011. Dietary intake of selected micronutrients and the risk of pancreatic cancer: an Italian case-control study. Ann Oncol. 22:202–206.

Burney PG, Comstock GW, Morris JS. 1989. Serologic precursors of cancer: serum micronutrients and the subsequent risk of pancreatic cancer. Am J Clin Nutr. 49:895–900.

Chiera F, Meccia E, Degan P, Aquilina G, Pietraforte D, Minetti M, Lambeth D, Bignami M. 2008. Overexpression of human NOX1 complex induces genome instability in mammalian cells. Free Radic Biol Med. 44:332–342.

Gong Z, Holly EA, Wang F, Chan JM, Bracci PM. 2010. Intake of fatty acids and antioxidants and pancreatic cancer in a large population-based case-control study in the San Francisco Bay Area. Int J Cancer. 127:1893–1904.

Han X, Li J, Brasky TM, Xun P, Stevens J, White E, Gammon MD, He K. 2013. Antioxidant intake and pancreatic cancer risk: the Vitamins and Lifestyle (VITAL) Study. Cancer. 119:1314–1320.

Heinen MM, Verhage BA, Goldbohm RA, van den Brandt PA. 2012. Intake of vegetables, fruits, carotenoids and vitamins C and E and pancreatic cancer risk in The Netherlands Cohort Study. Int J Cancer. 130:147–158.

Howe GR, Ghadirian P, Bueno de Mesquita HB, Zatonski WA, Baghurst PA, Miller AB, Simard A, Baillargeon J, de Waard F, Przewozniak K, et al. 1992. A collaborative case-control study of nutrient intake and pancreatic cancer within the search programme. Int J Cancer. 51:365–372.

Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M. 2005. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer. 92:2076–2083.

Jansen RJ, Robinson DP, Stolzenberg-Solomon RZ, Bamlet WR, de Andrade M, Oberg AL, Rabe KG, Anderson KE, Olson JE, Sinha R, et al. 2013. Nutrients from fruit and vegetable consumption reduce the risk of pancreatic cancer. J Gastrointest Cancer. 44:152–161.

Jeurnink SM, Ros MM, Leenders M, van Duijnhoven FJ, Siersema PD, Jansen EH, van Gils CH, Bakker MF, Overvad K, Roswall N, et al. 2014. Plasma carotenoids, vitamin C, retinol and tocopherols levels and pancreatic cancer risk within the European Prospective Investigation into Cancer and Nutrition: a nested case-control study: plasma micronutrients and pancreatic cancer risk. Int J Cancer. 136:E665–E676.

Ji BT, Chow WH, Gridley G, McLaughlin JK, Dai Q, Wacholder S, Hatch MC, Gao YT, Fraumeni JF, Jr. 1995. Dietary factors and the risk of pancreatic cancer: a case-control study in San Francisco Bay Area. Cancer Epidemiol Biomarkers Prev. 4:885–893.

Kalapothaki V, Tzonou A, Hsieh CC, Karakatsani A, Trichopoulou A, Toupadaki N, Trichopoulos D. 1993.
Nutrient intake and cancer of the pancreas: a case-control study in Athens, Greece. Cancer Causes Control. 4:383–389.

Klein AP, Brune KA, Petersen GM, Goggins M, Tersmette AC, Offerhaus GJ, Griffin C, Cameron JL, Yeo CJ, Kern S, et al. 2004. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res. 64:2634–2638.

Lin Y, Tamakoshi A, Hayakawa T, Naruse S, Kitagawa M, Ohno Y. 2005. Nutritional factors and risk of pancreatic cancer: a population-based case-control study based on direct interview in Japan. J Gastroenterol. 40:297–301.

Maritim AC, Sanders RA, Watkins JB, 3rd. 2003. Diabetes, oxidative stress, and antioxidants: a review. J Biochem Mol Toxicol. 17:24–38.

McCann SE, Ambrosone CB, Moysich KB, Brasure J, Marshall JR, Freudenheim JL, Wilkinson GS, Graham S. 2005. Intakes of selected nutrients, foods, and phytochemicals and prostate cancer risk in western New York. Nutr Cancer. 53:33–41.

McCullough ML, Giovannucci EL. 2004. Diet and cancer prevention. Oncogene. 23:6349–6364.

Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 151:264–269. W64.

Muller K, Carpenter KL, Challis IR, Skepper JN, Arends MJ. 2002. Carotenoids induce apoptosis in the T-lymphoblast cell line Jurkat E6.1. Free Radic Res. 36:791–802.

Nkondjock A, Ghadirian P, Johnson KC, Krewski D. 2005. Dietary intake of lycopene is associated with reduced pancreatic cancer risk. J Nutr. 135:592–597.

Olsen GW, Mandel JS, Gibson RW, Wattenberg LW, Schuman LM. 1991. Nutrients and pancreatic cancer: a population-based case-control study. Cancer Causes Control. 2:291–297.

Shibata A, Mack TM, Paganini-Hill A, Ross RK, Henderson BE. 1994. A prospective study of pancreatic cancer in the elderly. Int J Cancer. 58:46–49.

Siegel R, Naishadham D, Jemal A. 2013. Cancer statistics, 2013. CA Cancer J Clin. 63:11–30.

Stang A. 2010. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 25:603–605.

Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, Carpenter J, Rucker G, Harbord RM, Schmid CH, et al. 2011. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 343:d4002.

Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, Albanes D. 2002. Prospective study of diet and pancreatic cancer in male smokers. Am J Epidemiol. 155:783–792.

Stolzenberg-Solomon RZ, Sheffler-Collins S, Weinstein S, Garabrant DH, Mannisto S, Taylor P, Virtamo J, Albanes D. 2009. Vitamin E intake, alpha-tocopherol status, and pancreatic cancer in a cohort of male smokers. Am J Clin Nutr. 89:584–591.

Verdecchia A, Francischi S, Brenner H, Gatta G, Micheli A, Mangone L, Kunkler I, Group E-W. 2007. Recent cancer survival in Europe: a 2000–02 period analysis of EUROCARE-4 data. Lancet Oncol. 8:784–796.

Wheatley-Price P, Asomaning K, Reid A, Zhai R, Su L, Zhou W, Zhu A, Ryan DP, Christiani DC, Liu G. 2008. Myeloperoxidase and superoxide dismutase polymorphisms are associated with an increased risk of developing pancreatic adenocarcinoma. Cancer. 112:1037–1042.

Wiseman M. 2008. 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. Proc Nutr Soc. 67:253–256.

Zatonski W, Przewozniak K, Howe GR, Maisonneuve P, Walker AM, Boyle P. 1991. Nutritional factors and pancreatic cancer: a case-control study from south-west Poland. Int J Cancer. 48:390–394.