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META-ANALYSIS

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Vitamin E Intake and Pancreatic Cancer Risk: A Meta-Analysis of Observational Studies

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Background: Some epidemiological studies have suggested that vitamin E intake reduces the risk of pancreatic cancer; however, this conclusion has not been supported by all the published studies. We conducted a meta-analysis to assess the relationship between vitamin E intake and the risk of pancreatic cancer by combining the results from published articles.

Material/Methods: We searched the published studies that reported the relationship between vitamin E intake and pancreatic cancer risk using the PubMed, Web of Science, and Embase databases through December 31st, 2014. Based on a fixed-effects or random-effects model, the RR and 95% CI were used to assess the combined risk.

Results: In total, 10 observational studies (6 case-control studies and 4 cohort studies) were included. The overall RR (95% CI) of pancreatic cancer for the highest *vs.* the lowest level of vitamin E intake was 0.81 (0.73, 0.89). We found little evidence of heterogeneity (I^2=19.8%, P=0.255). In the subgroup analyses, we found an inverse association between vitamin E intake and pancreatic cancer risk both in the case-control and cohort studies. Additionally, this inverse association was not modified by different populations.

Conclusions: In our meta-analysis, there was an inverse association between vitamin E intake and the risk of pancreatic cancer. A high level of vitamin E might be a protective factor for populations at risk for pancreatic cancer.

MeSH Keywords: Meta-Analysis • Pancreatic Neoplasms • Vitamin E

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Background

Pancreatic cancer is a common gastrointestinal cancer, and the incidence and mortality has been increasing in recent years. In the USA, it has been the fourth leading cause of death [1]. In 2009, approximately 42 000 new patients were diagnosed, and 35 000 Americans died of pancreatic cancer. [2]. Early diagnosis is difficult because of the lack of clinical symptoms in the early stages, and the 5-year survival rate ranges from 4% to 6% or less [3,4]. Although the incidence and mortality of pancreatic cancer are remarkably high, few treatment options are effective. The primary option is to reduce pancreatic cancer risk by taking preventive measures.

In humans, free radicals, which result from polyunsaturated fatty acids reacting with oxygen in the lipid membranes, might be essential for the occurrence of tumors [5]. Vitamin E is an effective antioxidant that prevents the occurrence of some tumors by protecting cells and DNA from free radical damage [5]. Whether vitamin E, as an antioxidant, could reduce the incidence of pancreatic cancer has been under consideration. In 2000, Heisler et al. reported the results from an *in vitro* study showing that vitamin E could inhibit pancreatic cancer cell line growth [6]. Another animal study showed that vitamin E increased the activity of superoxide dismutase (SOD) and decreased the level of thiobarbituric- acid-reactive substances (TBARS), which might be a mechanism of decreasing liver metastasis in pancreatic cancer [7].

Many epidemiological studies have assessed the relationship between vitamin E and the risk of pancreatic cancer. In the 1990s, 1 of 2 case-control studies showed that vitamin E intake was linked to a decreased risk of pancreatic cancer [8]; however, the other study showed a null association [9]. Subsequent epidemiological studies, including case-control and cohort studies, have suggested an inconsistent association between vitamin E intake and the risk of pancreatic cancer [10–17]. The sample size of each original study was smaller and original study was conducted in a single population, which might be the primary reason for the unsatisfactory results. We conducted a meta-analysis of the relevant studies by combining the results from the published observational studies to assess the relationship between vitamin E intake and the risk of pancreatic cancer. Additionally, we examined the influences of various study characteristics on the overall risk estimate. We intended to provide the best available evidence as to whether vitamin E intake has a preventive effect on pancreatic cancer.

Material and Methods

Study search and selection

The Web of Science, PubMed, and Embase databases were used to identify the observational studies that reported the association between vitamin E intake and the risk of pancreatic cancer through December 31st, 2014 with the following terms: "vitamin E intake", "dietary vitamin E" and "vitamin E" in combination with "pancreatic cancer" and "pancreatic carcinoma". The reference lists of the identified studies were searched for potential studies. If necessary, we contacted the authors of the original studies for the required data.

The studies that met the following criteria could be included: 1. the study had a case-control or cohort study design; 2. the study had been published as a full text in the English language; 3. the study reported the association between the vitamin E intake and the risk of pancreatic cancer; 4. the study reported the RR and the corresponding 95% CI for the highest *vs.* the lowest level of vitamin E intake; 5. if there were duplicate publications on the same study population, we included the most recent one.

An article was excluded based on to the following criteria: if it were a review, case report, or animal experiment; if it were not published as a full text; or if it reported an exposure factor or endpoint that was not relevant to our study.

Data extraction and quality assessment

We conducted data extraction with a standardized data extraction form. The following information was collected from the included studies: the last name of the first author, publication year, population, number of cases and controls or total sample size, RR and the corresponding 95% CI from the most fully adjusted model for the highest *vs.* the lowest vitamin E intake, and the factors of adjustment for potential confounders. All the procedures were conducted by 2 independent authors, and any disagreements were resolved by discussion.

The key components of designs (e.g., selection of study populations, ascertainment of exposure and outcome, duration of follow-up) were used to estimate the quality of primary studies rather than reporting the aggregate scores.

Statistical analysis

The pooled relative risk (RR) and the corresponding 95% CI were used to assess the association between vitamin E intake and the risk of pancreatic cancer. A homogeneity test was conducted with I^2 and Q statistics. A fixed-effects model when low evidence of homogeneity was found or random-effects model

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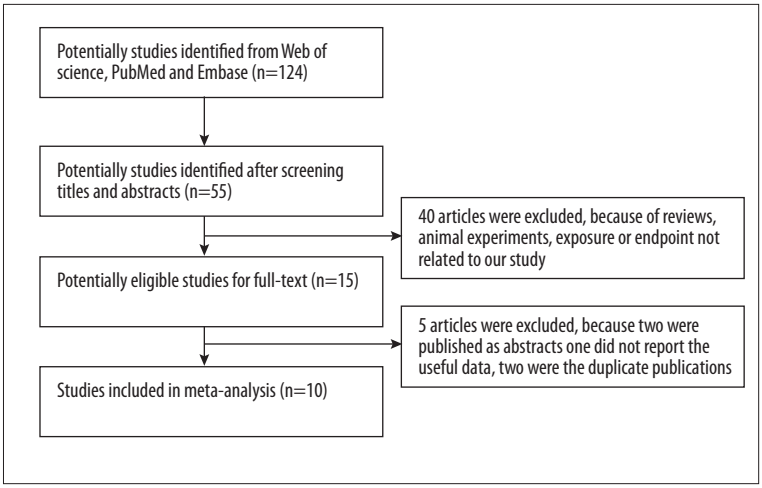

Figure 1. Flow chart of the study selection process.

when strong evidence of homogeneity was found was used to calculate the combined RR. Subgroup analysis was performed to identify the source of heterogeneity, if possible, and the effect of the potential factors on the overall risk estimate. In addition, we conducted a sensitivity analysis to investigate the influence of a single study on the overall risk estimate by omitting 1 study at a time. Begg's and Egger's tests were used to detect the evidence of a publication bias. In our study, if the P-value were less than 0.05, it was considered statistically significant. All the analyses were conducted using STATA version 12.0.

Results

Study selection and characteristics

According to the inclusion criteria, 10 observational studies involving 2976 patients and 254 393 participants or controls were included [8–17]. The study selection process is presented in Figure 1.

Table 1 shows the main characteristics of the included studies. The studies were published from 1991 to 2014. In the 10 studies, 6 were case-control studies [8–10,12,13,17], and 4 were cohort studies [11,14–16]. Four studies were conducted in USA populations [9,12,16,17], 2 in Asian populations [8,10] (Japanese [10] and Chinese [8]), and 4 in European populations [11,13–15] (Finnish [11], Italian [13], Dutch [14], and British [15]). One study [8] was conducted in females, and 3 studies were in males [8,9,11]. The other studies did not distinguish the sex. All the studies were adjusted for a wide range of potential confounders, such as age, sex, smoking, and energy intake.

Meta-analysis

In total, 11 data items from the 10 included studies were used to assess the association between vitamin E intake and the risk of pancreatic cancer. Of these, 4 results showed that vitamin E intake was linked to a reduced risk of pancreatic cancer. Overall, our study found that there was a statistically significant inverse relationship between vitamin E intake and the risk of pancreatic cancer; the summary RR and corresponding 95% CI of pancreatic cancer for the highest *vs.* the lowest level of vitamin E intake was 0.81 (0.73, 0.89). There was minimal statistically significant evidence of heterogeneity across these studies (I^2=19.8%, P=0.255). The result of the overall estimate is presented in Figure 2.

Figures 3 and 4 show the results of the subgroup analyses for the influence of the study design and population on the overall risk estimate, respectively. The results showed that there was an inverse association between the vitamin E intake and pancreatic cancer risk both in the case-control and cohort studies, in which the pooled RR (95% CI) were 0.65 (0.54, 0.77) and 0.88 (0.79, 0.99), respectively. We found no evidence of heterogeneity among the case-control and cohort studies (I^2=0.0%, $P_{case\text{-}control}$=0.760 and P_{cohort}=0.868).

The inverse association between vitamin E intake and pancreatic cancer was found among people in the USA, Asians, and Europeans, for which the combined RRs (95% CIs) were 0.67 (0.55, 0.82), 0.72 (0.52, 0.99), and 0.87 (0.77, 0.98), respectively. There was minimal evidence across the 3-subgroup analyses (I^2_{USA}=0.0%, P_{USA}=0.413, I^2_{Asian}=0.0%, P_{Asian}=0.454, and $I^2_{European}$=0.0%, $P_{European}$=0.410).

By removing 1 study at a time, we conducted a sensitivity analysis to assess the influence of each included study on the pooled RR. The combined RRs were similar to each another, and none significantly modified the pooled RR. After removing the study with the highest weight [11], the pooled RR was not significantly modified.

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Table 1. Characteristics of included studies.

Study (year, population)	Study design	Age of subjects	Sample size (n) case/control (total)	Adjusted RR (95% CI) (highest *vs.* lowest)	Variables used in multivariate model
Olsen et al. (1991, American)	Case-control	40–84	212/220	Men: 0.70 [0.40, 1.30]	Age, total energy, cigarette usage, alcohol consumption, history of diabetes mellitus, educational level
Ji et al. (1995,Chinese)	Case-control	30–74	451/1552	Men: 0.57 [0.35, 0.93] Women: 0.81 [0.44, 1.50]	Age, income, smoking, green tea drinking, response status, total calories
Lin et al. (2005, Japanese)	Case-control	40–79	109/218	0.90 [0.50, 1.61]	Age, energy intake, smoking
Stolzenberg-Solomon et al. (2009, Finnish)	Cohort	50–69	306/27111	Men: 0.89 [0.78, 1.01]	Age, serum cholesterol, smoking, history of diabetes mellitus
Gong et al. (2010, American)	Case-control	21–85	532/1701	0.67 [0.49, 0.92]	Age, sex, energy intake, race, education, BMI, smoking, history of diabetes physical activity, alcohol consumption
Bravi et al. (2011, Italian)	Case-control	34–80	326/652	0.60 [0.36, 0.98]	Age, sex, center, education, year of interview, smoking, history of diabetes, BMI, energy intake
Heinen et al. (2012, Dutch)	Cohort	55–69	423/120852	0.93 [0.64, 1.36]	Age, sex, smoking, BMI, history of pancreatic cancer history of diabetes mellitus intake of energy, red meat, coffee and alcohol
Banim et al. (2013, British)	Cohort	40–74	49/23658	0.62 [0.25, 1.56]	Age, sex, smoking, diabetes, total energy intake, BMI
Han et al. (2013, American)	Cohort	50–76	184/77446	0.84 [0.57, 1.24]	Age, sex, race, education, BMI,physical activity, smoking, alcohol consumption, history of pancreatic cancer, history of diabetes, energy intake
Jansen et al. (2014,American)	Case-control	24–94	384/983	0.51 [0.33, 0.78]	Age, sex, smoking, BMI, diabetes mellitus, energy intake alcohol, fruit and vegetable consumption

Although the funnel plot shows all the included studies symmetrically distributed in the triangle area, Begg's and Egger's regression tests showed that there was a low probability of publication bias in our study (P=0.049). The funnel plot of the studies is presented in Figure 5.

Discussion

Our meta-analysis suggested a significant inverse relationship between vitamin E intake and the risk of pancreatic cancer – a high level of vitamin E was significantly linked to a decreased risk of pancreatic cancer.

Although the included studies were conducted in different populations and varied in study design, little evidence of heterogeneity was found across the studies. All the studies were published in English and had a high quality of assessment and the results from each original study were adjusted for a wide range of potential confounders, eliminating the most obvious confounding factors. These facts might partially explain the minimal evidence of heterogeneity.

In the subgroup analyses, the summary risk estimate of 6 case-control studies and 4 cohort studies showed an inverse association between vitamin E intake and a risk of pancreatic cancer. It is well known that a higher level of statistical evidence is detected in cohort studies than in case-control studies, thus,

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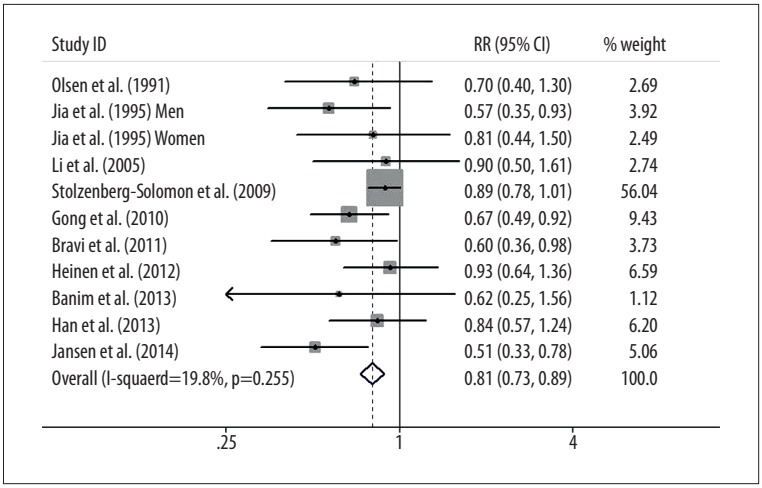

Figure 2. Meta-analysis of 12 studies that assess vitamin E intake and pancreatic cancer risk.

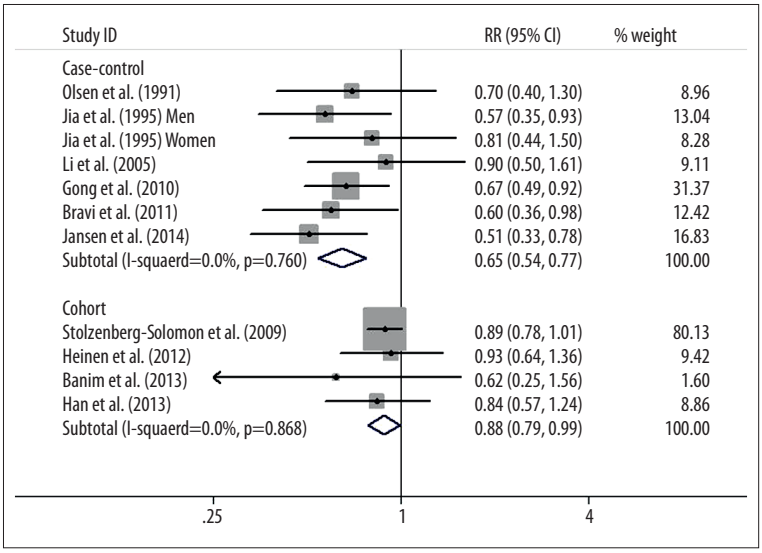

Figure 3. Subgroup analysis of vitamin E intake and pancreatic cancer risk in different study designs.

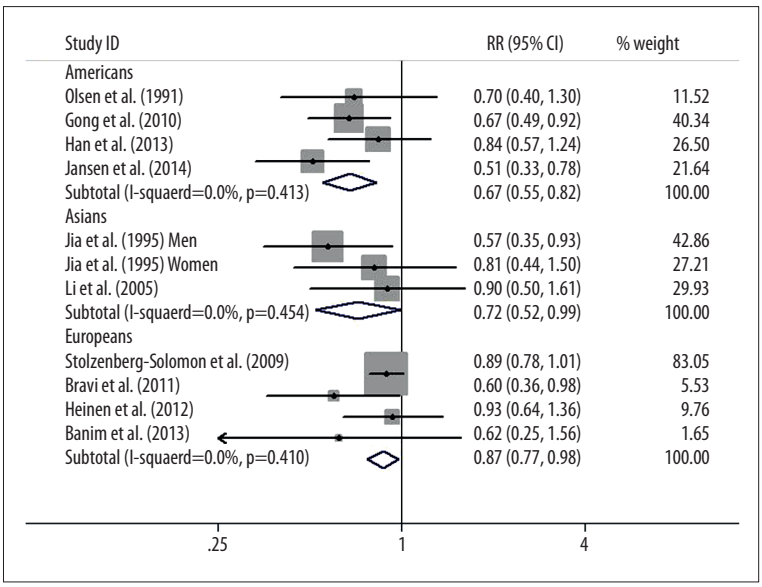

Figure 4. Subgroup analysis of vitamin E intake and pancreatic cancer risk in different populations.

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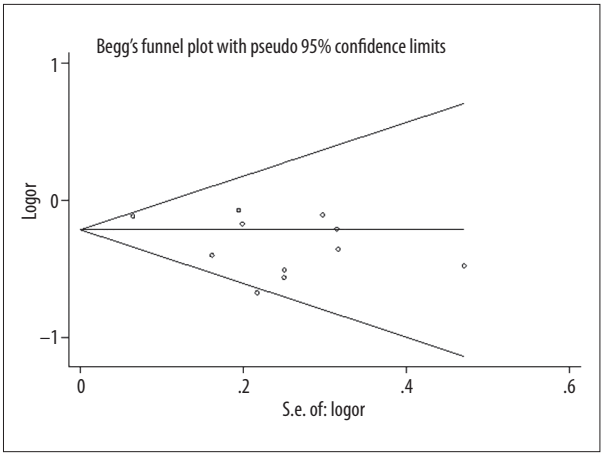

Figure 5. Funnel plot of vitamin E intake and pancreatic cancer risk.

our results were credible, but more cohort studies are needed. Additionally, our subgroup analyses showed that this inverse association was not modified by different populations, including Asians, Europeans, and people in the USA. The subgroup analyses added additional evidence for the association between vitamin E intake and risk of pancreatic cancer.

Although there is evidence of an association of vitamin E intake with a decreased risk of many cancers [18–20], the mechanisms are not well understood. However, some potential explanations have gradually been accepted by researchers. The primary mechanism of vitamin E might be as an antioxidant, preventing DNA damage by scavenging lipid peroxyl radicals and terminating the lipid peroxidation chain reaction [21] while increasing the activity of superoxide dismutase (SOD) and decreasing the level of thiobarbituric-acid-reactive substances (TBARS) [7]. Other potential mechanisms are based on the possibility that vitamin E might decease the activity of the protein kinase C (PKC) pathway [22], enhance the immune response of the body [23], suppress cancer cell growth by down-regulation of the phosphoinositide 3-kinase pathway [24], and increase the expression of anti-oncogene p27 [25].

Early-stage diagnosis is difficult, and the mortality associated with pancreatic cancer is remarkably high; there are few effective treatment options to overcome this fatal cancer. The primary option is to prevent the occurrence of pancreatic cancer. Our study, which included 10 observational studies with 2976 patients and 254 393 participants or controls, significantly improved the statistical power and found a more reliable association between vitamin E intake and a pancreatic cancer risk. We provided evidence that vitamin E intake is related to a decreased risk of pancreatic cancer, and that vitamin E intake might effectively prevent pancreatic cancer. This result has important significance for public health.

Some limitations of our study should be considered. First, 10 studies with relatively larger sample sizes were included in our studies; however, many of the studies were case-control studies, and recall bias and selection bias were inevitable. Although 4 cohort studies were included, the following factors limited the statistical evidence: a smaller number of sample cases and a lack of groups of patients of different ages. Second, most of the included studies did not respectively report the risk among males and/or females, and hormonal factors might lead to the male-to-female differential in the incidence of pancreatic cancer [26]. In general, a high level of estrogen exposure via estrogen-only therapy could significantly reduce the risk of pancreatic cancer [27]. Third, vitamin E is a mixture of 8 structurally related and naturally occurring components, including tocopherols (α, β, δ, ϒ) and tocotrienols (α, β, δ, ϒ) [28]. However, only 1 component is naturally contained in food, and determining the diverse biological activities between the dietary intake and supplementation is challenging. In the included studies, 1 study reported the RRs associated with the intake of various vitamin E isoforms and the risk of pancreatic cancer [11]. Most studies did not report the source of vitamin E. Fourth, the pooled risk estimate was predominantly based on USA and European populations; 2 Asian populations and no other populations were included in the studies, and additional studies that include other populations are needed.

Conclusions

This study showed a significant inverse relationship between vitamin E intake and the risk of pancreatic cancer. Vitamin E might effectively prevent pancreatic cancer.

Competing interests

The authors declare no competing financial interests.

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