Systematic Review and Meta-Analysis

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Vitamin intake and pancreatic cancer risk reduction

A meta-analysis of observational studies

Ying Liu, MM[a], Xiaojie Wang, MM[b], Xuejia Sun, MB[c], Shengnan Lu, MB[d], Shi Liu, PhD[e,*]

Abstract

Background: The relationship between vitamin intake and pancreatic cancer (PC) risk is disputed. We aimed to investigate the association between vitamin intake and the risk of PC via meta-analysis.

Methods: We conducted a meta-analysis of studies concerning vitamin intake and the risk of PC from EMBASE, MEDLINE, and Cochrane Library. The search yielded 25 correlative studies including 1,214,995 individuals. The relative risks (RR) were examined by a random-effect model or fixed-effect model. Subgroup analysis, dose–response analysis, sensitivity analysis, meta-regression, and publication bias analysis were used to analyze studies.

Results: The RR of PC in the highest vitamin intake group was 0.90 (95% confidence interval, 0.83–0.98) compared with that in the lowest vitamin intake in the prospective studies. Different increments of vitamin intake and the risk of PC were examined with dose–response analysis, and a decrease in the risk of PC was observed with vitamin D (25%) and vitamin B12 (27%).

Conclusions: This meta-analysis found that vitamin intake can decrease the risk of PC, particularly vitamin D and vitamin B12.

Abbreviations: CI = confidence interval, OR = odds ratio, PC = pancreatic cancer, RCT = randomized placebo-controlled trial, RR = relative risks.

Keywords: meta-analysis, pancreatic cancer, vitamin B12, vitamin D, vitamin intake

1. Introduction

Pancreatic cancer (PC) is one of the most malignant cancers with a 5-year survival rate of about 5%.[1] Almost 80% of PC patients are in the late stage at the first diagnosis in China,[2] and incidence has been increasing in recent years.[3] Therefore, efficacious preventive methods for PC, such as vitamin intake, have attracted worldwide attention. Vitamins have been suggested to prevent PC via several mechanisms.[4] The preventive effects might be via up-regulation of p21 and p27 expression,[5] increased activity of superoxide dismutase,[6] cell cycle arrest at the G1 phase,[7] suppression of NF-κB-mediated inflammatory pathways,[8] down-regulation of Her2/ErbB2 expression,[9] increased caspase-3 activity,[10] or induction of Bax expression and activation EGR-1.[11]

Vitamin intake and the risk of PC have previously been reported. However, retrospective case–control studies, cohort studies, randomized placebo-controlled trials (RCTs), and some meta-analyses[12–22] have had various results for the relationship between vitamin intake and the risk of PC. Therefore, we aimed to investigate the association between vitamin intake and the risk of PC via meta-analysis.

2. Methods

2.1. Search strategy

Studies investigating vitamin intake and PC were searched in EMBASE, MEDLINE, and Cochrane Library through March 30, 2015. Search terms were (pancreas OR pancreatic) AND (cancer OR carcinoma OR neoplasm) AND (vitamin OR food OR diet OR nutrition). References of the retrieved papers were hand-searched for potentially correlative papers. Two authors searched the studies and retrieved papers independently. Disagreements were solved by deliberation with other authors. This study was approved by the Ethics Committee of Qiqihar Medical University.

2.2. Study selection

The inclusion criteria of retrieved papers were case–control, placebo–control, or cohort design; vitamin intake as the independent variable of interest; PC as the dependent variable of interest plus reported PC incidence; and reported odds ratio (OR), relative risk (RR), or hazard ratio with the corresponding

Editor: Jianxun Ding.

Ying Liu, Shengnan Lu, and Shi Liu designed the study; Xiaojie Wang, Xuejia Sun, Shengnan Lu, and Shi Liu collected the data; Ying Liu, Shengnan Lu, and Shi Liu wrote the manuscript; all authors reviewed the manuscript.

The authors have no funding and conflicts of interest to disclose.

[a] Department of Oncology, The 3rd Affiliated Hospital, Qiqihar Medical University, Qiqihar, [b] Heilongjiang Institute of Dermatology and Sexually Transmitted Disease, Harbin, [c] Department of Radiology, The 3rd Affiliated Hospital, Qiqihar Medical University, [d] Department of Ultrasound, The 2nd Affiliated Hospital, Qiqihar Medical University, [e] Department of General Surgery, The 3rd Affiliated Hospital, Qiqihar Medical University, Qiqihar, China.

[*] Correspondence: Shi Liu, Department of General Surgery, The 3rd Affiliated Hospital, Qiqihar Medical University, Qiqihar 161099, China (e-mail: shiliu2199@163.com).

Medicine (2018) 97:13(e0114)

Received: 2 October 2017 / Received in final form: 16 December 2017 / Accepted: 20 February 2018

http://dx.doi.org/10.1097/MD.0000000000010114

95% confidence interval (CI). Nonhuman studies, mechanistic research, and review articles were excluded.

2.3. Data extraction

Two authors read the retrieved papers and extracted data independently from the studies according to the selection criteria. Disagreements were solved by deliberation with other authors. The following information was extracted from each paper: first author's last name, year of publication, study design, geographic location, the age and sex of participants, follow-up period, the size of study, type and doses of vitamins, RR or OR with 95% CI for vitamin intake, and PC risk. When 2 or more papers concerned the same study, the paper with the most data was used in this study.

2.4. Quality assessment

Two authors independently evaluated the quality of retrieved studies according to the Newcastle–Ottawa scale. The retrieved papers were evaluated based on selection of cohorts (0–4 points), comparability of cohorts (0–2 points), and exposure/outcome of the participant (0–3 points). Studies with 7 to 9 points were marked as "high quality."

2.5. Statistical analysis

RRs or ORs with 95% CI and their standard errors were obtained from the studies to assess the relationship between vitamin intake and the risk of PC. The random-effect model was used to combine RRs or ORs with 95% CI concerning both intra- and inter-study variation (τ^2). I^2 was used to evaluate heterogeneity among studies including here, and I^2 values of 25%, 50%, and 75% were considered low, moderate, and high heterogeneity, respectively. A fixed-effect model was utilized if I^2 values $<50\%$, otherwise a random-effect model was selected. Meta-regression of the variables of study design, vitamin dose, and geographic area of study was employed to assess heterogeneity among all included studies. The influence of grouping on total results was evaluated by subgroup stratification analysis. Potential causes of heterogeneity were estimated by the sensitivity analysis. Publication bias was evaluated by means of funnel plots and Egger test. This meta-analysis was carried out with Rev Man 5.3 or Stata 12.1, and $P<.05$ was considered statistically significant.

3. Results

3.1. Search results and study characteristics

In this meta-analysis, we retrieved 25 studies including 1,213,821 participants published from 1991 to 2014 (Fig. 1). In the identified studies (Table 1), 10 were population-based case–control studies,[23–34] 4 were hospital-based case–control studies,[35–39] 2 were RCTs,[40–44] 9 were cohort studies,[45–56] 11 were prospective studies,[40–56] and 14 were retrospective studies.[23–39] The number of participants ranged from 305[34] to 537,218[45] and PC cases ranged from 79[44] to 2383.[45] Quality scores of included case–control and cohort studies ranged from 7 to 9 with an average score of about 8. The quality of RCTs was also estimated (data not shown).

3.2. Vitamin intake and pancreatic cancer risk

A fixed-effect model was used and the combined multivariable-adjusted RR were 0.90 (95% CI: 0.83–0.98) and 0.79 (95% CI:

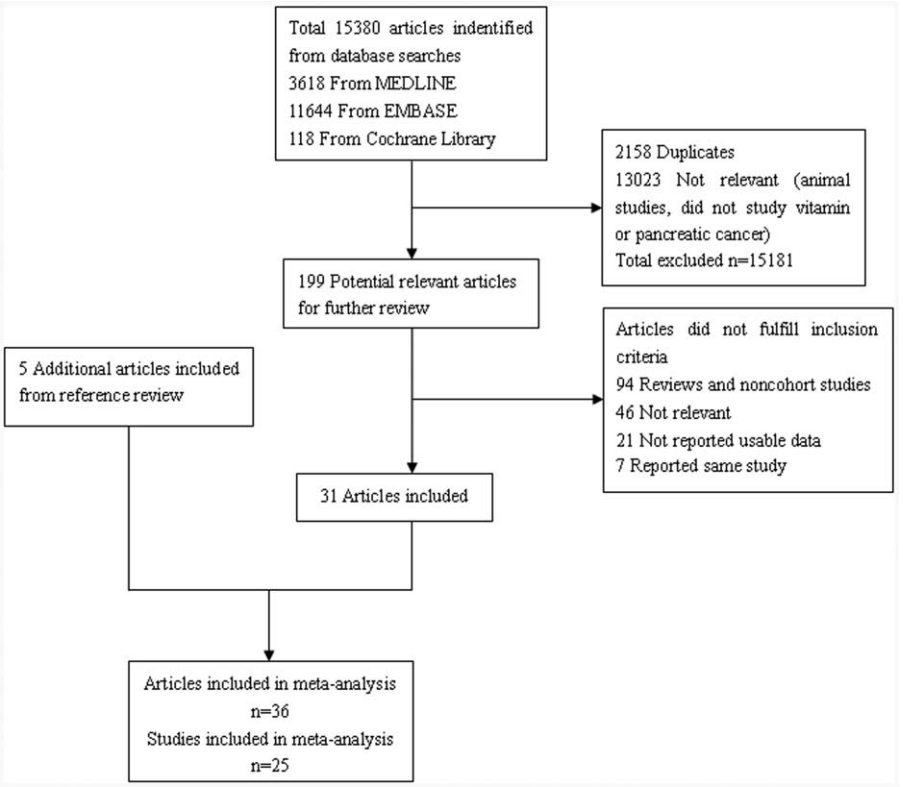

Figure 1. Flow diagram of study selection.

Table 1

Characteristics of the included studies.

Study/year	Design	Country	Age/sex	Study period	Total subjects	Total events
Anderson 2009[23]	PCC	Canada	≤79 M/F	2003–2007	734	422
Arem 2013[45]	Cohort	United States	50–71 M/F	1995–2006	537,218	2383
ATBC 2001, 2002, 2006, 2009[40–43]	RCT	Finland	50–69 M	1985–2004	27,111	306
Baghurst 1991[24]	PCC	Australia	M/F	1984–1987	357	104
Banim 2013[46]	Cohort	United Kingdom	40–74 M/F	1993–2010	23,658	86
Bravi 2011[35]	HCC	Italy	34–80 M/F	1991–2008	978	326
Ghadirian 1991[25]	PCC	Canada	35–79 M/F	1984–1988	508	179
Gong 2009, 2010, Zablotska 2011[26–28]	PCC	United States	21–85 M/F	1995–1999	2233	532
Han 2013[47]	Cohort	United States	50–76 M/F	2000–2008	69,517	155
Heinen 2012[48]	Cohort	The Netherlands	55–69 M/F	1986–2002	120,852	423
Howe 1990[29]	PCC	Canada	35–79 M/F	1983–1986	754	249
Inoue-Choi 2011[49]	Cohort	United States	55–69 F	1986–2007	34,642	256
Jansen 2013, 2014[36,37]	HCC	United States	24–94 M/F	2004–2009	1367	384
Ji 1995[30]	PCC	China	30–74 M/F	1990–1993	2003	451
Kalapothaki 1993[38]	HCC	Greece	M/F	1991–1992	362	181
Keszei 2009[50]	Cohort	The Netherlands	55–69 M/F	1986–1999	120,852	363
Larsson 2006, 2007[51,52]	Cohort	Sweden	45–83 M/F	1997–2005	81,922	147
Lin 2005[31]	PCC	Japan	40–79 M/F	2000–2002	327	109
NHS and HPFS 2004, 2006, 2010[53–55]	Cohort	United States	30–75 M/F	1984–2004	118,597	575
Oaks 2010[56]	Cohort	United States	55–74 M	1998–2006	51,988	162
Olsen 1991[32]	PCC	United States	40–84 M	1980–1983	432	212
Soler 1998[39]	HCC	Italy	≤75 M/F	1983–1992	1914	362
Stolzenberg-Solomon 2009[33]	PCC	United States	55–74 M/F	1994–2006	552	184
Wang 2014[44]	RCT	United States	≥50 M	1997–2011	14,638	79
Zatonski 1991[34]	PCC	Poland	62.2–63.2 M/F	1985–1988	305	110

F = female, HCC = hospital-based case–control, M = male, PCC = population-based case–control, RCT = randomized placebo-controlled trial.

0.73–0.85) for the highest vitamin intake group compared with the lowest intake group in the prospective studies and retrospective ones, respectively (Fig. 2). Among the 25 studies, an opposite association between vitamin intake and PC risk was observed in 19 studies[23–28,30–32,34–38,45–49,51–56] and was statistically significant in 7 studies.[23,30,34–38,45] No significant heterogeneity was observed among included studies ($P < .00001$, $I^2 = 36\%$ among retrospective studies; $P < .05$, $I^2 = 11\%$ among

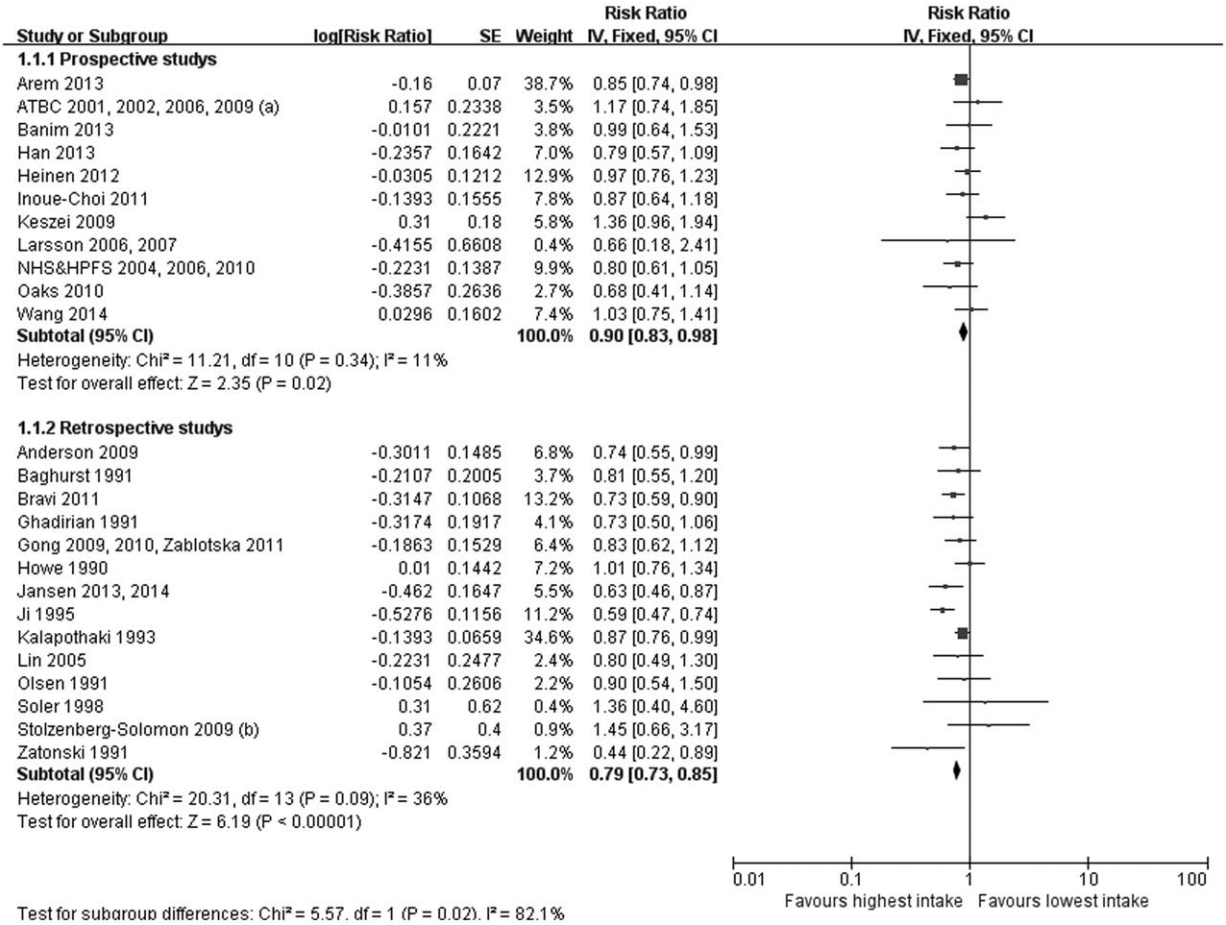

Figure 2. Forest plot of vitamin intake and risk of pancreatic cancer. Squares or diamonds to the left of the solid vertical line indicate benefit with vitamin intake.

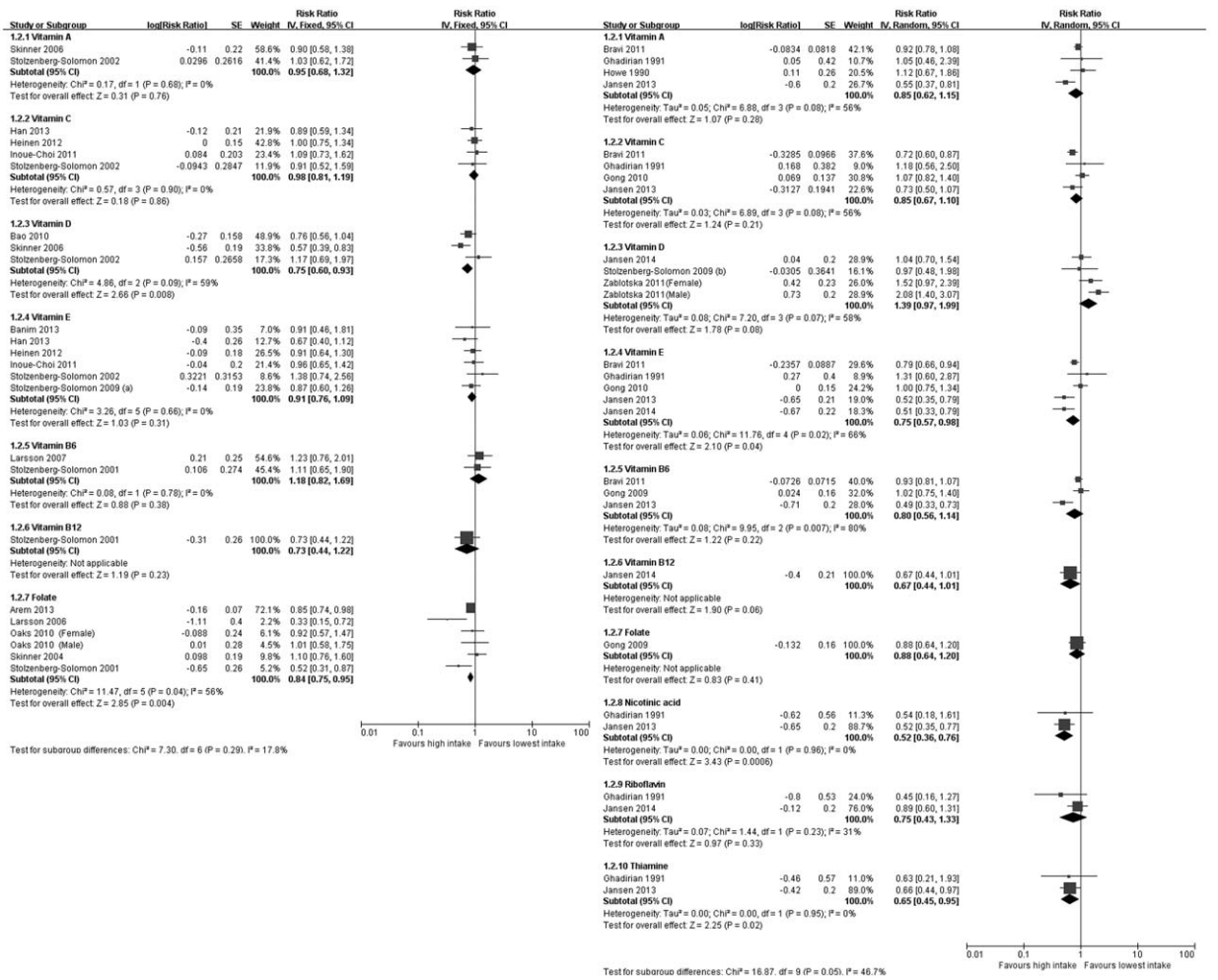

Figure 3. Forest plot of dose–response meta-analysis. Squares or diamonds to the left of the solid vertical line indicate benefit with vitamin intake. Left forest plot indicates prospective studies and the right one indicates retrospective studies.

prospective studies). These results demonstrate that moderate vitamin consumption can reduce the risk of PC.

3.3. Dose–response meta-analysis

In prospective studies, the multivariable-adjusted RR of vitamin D (10 μg/d) intake was 0.75 (95% CI: 0.60–0.93) with moderate heterogeneity ($P = .008$, $I^2 = 59\%$) in the 3 included studies. The multivariable-adjusted RR of vitamin B12 (10 μg/d) intake was 0.73 (95% CI: 0.44–1.22) in 1 included study. Figure 3 details the dose–response meta-analysis data.

In retrospective study, the multivariable-adjusted RR of vitamin E (10 mg/d) intake was 0.75 (95% CI: 0.57–0.98) with moderate heterogeneity ($P = .04$, $I^2 = 66\%$) in the 5 included studies. The multivariable-adjusted RR of vitamin B12 (10 μg/d) intake was 0.67 (95% CI: 0.44–1.01) in 1 included study. The multivariable-adjusted RR of nicotinic acid (30 mg/d) intake was 0.52 (95% CI: 0.36–0.76) without heterogeneity ($P = .0006$, $I^2 = 0\%$) in the 2 included studies. The multivariable-adjusted RR of riboflavin (3 mg/d) intake was 0.75 (95% CI: 0.43–1.33) without significant heterogeneity ($P = .33$, $I^2 = 31\%$) in the 2 included studies. The multivariable-adjusted RR of the thiamine (2 mg/d) intake was 0.65 (95% CI: 0.45–0.95) without heterogeneity ($P = .02$, $I^2 = 0\%$) in the 2 included studies. Figure 3 details the dose–response meta-analysis data.

3.4. Subgroup analysis

3.4.1. Study design. The multivariable-adjusted RR of the prospective studies was 0.90 (95% CI: 0.83–0.98), which demonstrated that vitamin intake can moderately reduce the risk of PC. The multivariable-adjusted RR of the retrospective studies was 0.79 (95% CI: 0.73–0.85), which suggested that vitamin intake can significantly reduce the risk of PC. Details of the subgroup analysis are shown in Table 2.

3.4.2. Geographic area. The combined RR was 0.84 (95% CI: 0.77–0.90) for research carried out in North America,[23,25–29,32,33,36,37,44,45,47,49,53–56] 0.89 (95% CI: 0.81–0.97) for research carried out in Europe,[34,35,38–43,46,48,50–52] 0.62 (95% CI: 0.51–0.77) for research carried out in East Asia,[30,31] and 0.81 (95% CI: 0.55–1.20) for research carried out in Australia.[24] These results demonstrated that vitamin intake can moderately decrease the risk of PC (Table 2).

3.4.3. Vitamin dose. In prospective studies, there was no significant difference in PC risk in the high-dose group compared with the low-dose (Fig. 4; Table 2). The combined RR was 0.93

Table 2

Subgroup analyses of vitamin intake and pancreatic cancer risk.

Groups	No. of reports	RR (95%)	Heterogeneity test		
			χ^2	*P*	I^2, %
Study design					
Prospective	11	0.90 (0.83, 0.98)	11.21	.02	11
Retrospective	14	0.79 (0.73, 0.85)	20.31	<.00001	36
Vitamin type (PS)					
Vitamin A	2	1.02 (0.73, 1.41)	0.78	.93	0
Vitamin B	9	0.89 (0.71, 1.11)	21.85	.31	63
Vitamin C	6	0.93 (0.78, 1.12)	0.34	.46	0
Vitamin D	3	0.74 (0.52, 1.06)	4.44	.10	55
Vitamin E	6	0.91 (0.77, 1.08)	4.11	.29	0
Vitamin type (RS)					
Vitamin A	12	0.87 (0.69, 1.08)	25.26	.21	56
Vitamin B	27	0.77 (0.67, 0.89)	52.56	.0002	51
Vitamin C	13	0.65 (0.55, 0.77)	21.91	<.00001	45
Vitamin D	5	1.21 (0.97, 1.51)	1.31	.09	0
Vitamin E	10	0.67 (0.56, 0.80)	12.52	<.0001	28
Vitamin dose (PS)					
High dose	6	0.93 (0.78, 1.11)	6.52	.43	23
Low dose	5	0.86 (0.64, 1.16)	13.89	.33	71
Vitamin dose (RS)					
High dose	5	0.79 (0.62, 1.01)	10.02	.06	60
Low dose	1	0.82 (0.50, 1.34)	—	.43	—
Geographic area					
East Asia	2	0.62 (0.51, 0.77)	1.24	<.00001	19
Europe	9	0.89 (0.81, 0.97)	15.8	.01	49
North America	13	0.84 (0.77, 0.90)	10.5	<.00001	0
Australia	1	0.81 (0.55, 1.20)		.29	
Publication year					
<2000	8	0.78 (0.66, 0.93)	15.09	.007	54
≥2000	17	0.86 (0.78, 0.94)	21.4	.0008	25
Sample size					
<1000	10	0.82 (0.74, 0.91)	10.06	.0001	10
≥1000	15	0.85 (0.76, 0.96)	29.96	.008	48

PS = prospective studies, RR = relative risks, RS = retrospective studies.

(95% CI: 0.78–1.11) in participants who were given 2 or more times the vitamin dosage than the standard vitamin intake level in 6 studies (high-dose group). The combined RR was 0.86 (95% CI: 0.64–1.16) in participants who were given doses under the standard vitamin intake level in 5 studies (low-dose group).

In retrospective studies, there was no significant difference in PC risk in the high-dose group compared with the low-dose (Fig. 4; Table 2). The combined RR was 0.79 (95% CI: 0.62–1.01) in participants who were given 2 or more times the vitamin dosage than the standard vitamin intake level in 5 studies (high-dose group). The RR was 0.82 (95% CI: 0.50–1.34) in participants who were given doses under the standard vitamin intake level in 1 study (low-dose group).

3.4.4. Vitamin type. In prospective studies, the combined RR of vitamin A or retinol intake and PC risk was 1.02 (95% CI: 0.73–1.41).[41,54] The combined RR of B family vitamin intake and PC risk was 0.89 (95% CI: 0.71–1.11).[40,45,50–53,56] The combined RR of vitamin C intake and PC risk was 0.93 (95% CI: 0.78–1.12).[41,44,46–49] The combined RR of vitamin D intake and PC

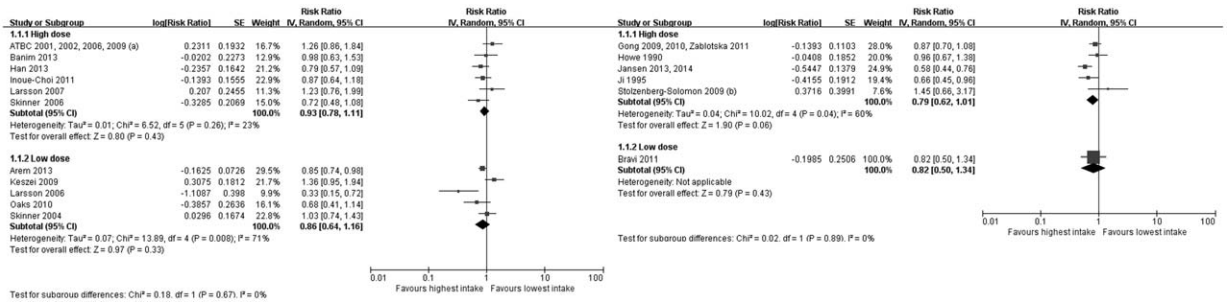

Figure 4. Forest plot of high-dose versus low-dose vitamin intake and risk of pancreatic cancer. Squares or diamonds to the left of the solid vertical line indicate benefit with vitamin intake. Left forest plot indicates prospective studies and the right one indicates retrospective studies.

risk was 0.74 (95% CI: 0.52–1.06).[42,54,55] The combined RR of vitamin E intake and PC risk was 0.91 (95% CI: 0.77–1.08).[43,44,46–49] These findings are summarized in Table 2.

In retrospective studies, the combined RR of vitamin A or retinol intake and PC risk was 0.87 (95% CI: 0.69–1.08).[24,25,28–32,34–36,38,39] The combined RR of B family vitamin intake and PC risk was 0.77 (95% CI: 0.67–0.89).[23–26,32,35–38] The combined RR of vitamin C intake and PC risk was 0.65 (95% CI: 0.55–0.77).[23–25,27,29–32,34–36,38] The combined RR of vitamin D intake and PC risk was 1.21 (95% CI: 0.97–1.51).[24,28,33,35,37] The combined RR of vitamin E intake and PC risk was 0.67 (95% CI: 0.56–0.80).[24,25,27,29–32,35–37] These findings are summarized in Table 2.

3.5. Sensitivity analyses and meta-regression

In prospective study group, the combined RR was 0.91 (95% CI: 0.82–1.00) after 3 studies[44,49,55] were excluded owing to not adjusting for dietary factors or total energy intake with a moderate level of heterogeneity ($P = .06$, $I^2 = 28\%$). The combined RR was 0.89 (95% CI: 0.82–0.98) among 10 studies adjusted for smoking with a moderate level of heterogeneity ($P = .01$, $I^2 = 14\%$).[40–43,45–56] The combined RRs were 0.88 (95% CI: 0.81–0.96) to 0.94 (95% CI: 0.84–1.04) after any single study was excluded, which did not affect the final result.

In retrospective study group, the combined RR was 0.79 (95% CI: 0.73–0.85) after 1 study[39] was excluded owing to not adjusting for dietary factors or total energy intake with a moderate level of heterogeneity ($P < .00001$, $I^2 = 39\%$). The combined RR was 0.78 (95% CI: 0.72–0.84) among 13 studies adjusted for smoking with a moderate level of heterogeneity ($P < .00001$, $I^2 = 33\%$).[23–32,34–39] The combined RRs were 0.75 (95% CI: 0.68–0.82) to 0.82 (95% CI: 0.75–0.88) after any single study was excluded, which did not affect the final result.

Meta-regression analysis demonstrated that study design ($P = .005$) included significant sources of heterogeneity. Study design alone explained 44.52% of the τ^2 in the meta-regression analyses.

3.6. Publication bias

No unambiguous asymmetry was detected in the funnel plot (Fig. 5) and no publication bias was observed in the Egger test ($P = .764$).

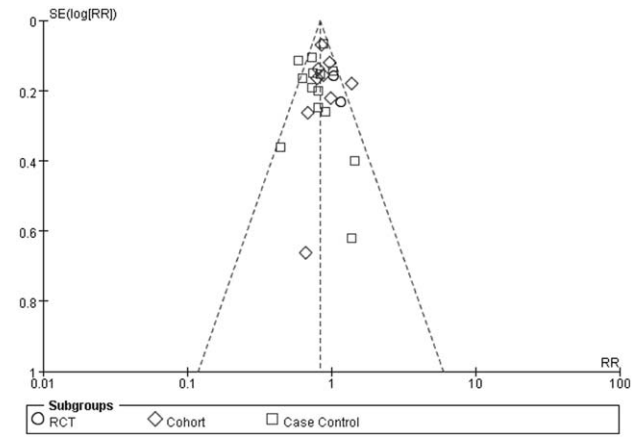

Figure 5. Funnel plot of relative risk of studies.

4. Discussion

This meta-analysis included more than 1.2 million human participants and 8000 PC cases. We found that vitamin consumption can moderately decrease the risk of PC. Daily consumption of 10 μg/d of vitamin B12 or vitamin D can dramatically reduce the incidence of PC, 27% for vitamin B12 and 25% for vitamin D in the dose–response meta-analysis.

Several RCTs and observational studies have explored the association of vitamin consumption and the risk of PC. Some studies reported that vitamin consumption may be correlated with PC incidence.[26,27,30–32,34–37,40,43,51,54,56] However, others found that vitamin consumption had no influence on the incidence of PC.[38,44,48,50,53] Vitamin intake may also have a negative effect on the prevention of PC.[28,39,42] The discrepancy of study design, type and dosage of vitamin intake, method used to estimate vitamin intake, and the time of follow-up may contribute to the different results among the studies.

Some meta-analyses have reported a preventive effect of vitamins on PC.[12–22] The results of some of them suggested that vitamin intake can reduce the risk of PC,[13,17,19–21] which echo this study. Nevertheless, several other studies reported that vitamins cannot decrease the risk of PC and may increase the risk.[12,14–16,18,22] Differences in vitamin dosages used in the latter studies, inclusion of retrospective case–control studies, and inclusion of high-risk individuals, such as long-time chronic smokers, may contribute to discrepancies between their conclusions and ours.

Many studies[23–26,28,32,33,35–38,40,42,45,50–56] have found that nonantioxidant vitamins may help prevent PC. However, some studies[23–25,27–32,34–39,41,43,44,46–49,54] have suggested that antioxidant vitamins, such as vitamins A, C, and E, may influence the prevention of PC. Nevertheless, it is difficult to separate antioxidant vitamins from nonantioxidant vitamins in the daily diet. Therefore, we combined antioxidant and nonantioxidant vitamins together in this meta-analysis.

This meta-analysis demonstrated that vitamins can moderately reduce the incidence of PC. We found that the RR was 0.79 (95% CI: 0.73–0.85) in retrospective studies; however, it was 0.90 (95% CI: 0.83–0.98) in the prospective ones. It suggested that vitamin consumption can moderately decrease the risk of PC. In retrospective study, the RR of vitamin E intake was 0.75 (95% CI: 0.57–0.98), the RR of vitamin B12 intake was 0.67 (95% CI: 0.44–1.01), the RR of nicotinic acid intake was 0.52 (95% CI: 0.36–0.76), the RR of riboflavin intake was 0.75 (95% CI: 0.43–1.33), and the RR of the thiamine intake was 0.65 (95% CI: 0.45–0.95). Nevertheless, the prospective studies suggested that the consumption of vitamin D (10 μg/d; RR: 0.75; 95% CI: 0.60–0.93) and vitamin B12 (10 μg/d; RR: 0.73; 95% CI: 0.44–1.22) can decrease the risk of PC. These dose–response meta-analysis data recommended that daily consumption of 10 μg/d of vitamin B12 or vitamin D can dramatically reduce the incidence of PC, 27% for vitamin B12 and 25% for vitamin D. Some in vitro studies have suggested that nicotinic acid, thiamine, and vitamin B12 can prevent PC. Pour and Lawson[57] suggested that nicotinic acid can inhibit pancreatic carcinogenesis in a hamster model. Zhang et al[58] reported that nicotinamide prohibits proliferation and enhances chemosensitivity in PC cells; and Hanberry et al[10] reported that high-dose vitamin B1 reduces proliferation in Panc-1 PC cell lines. However, whether or not the consumption of vitamin E, vitamin B12, nicotinic acid, riboflavin, and thiamine can reduce the incidence of PC need more evidence from prospective studies.

Several studies have investigated the mechanism of how vitamins might inhibit PC. Vitamin D can up-regulate p21 and p27 during growth inhibition of PC cell lines.[5] Vitamins A, C, and E can increase the activity of superoxide dismutase to decrease the incidence of PC in hamsters.[6] Vitamin E can induce cell cycle arrest at the G1 phase, induce apoptosis in human PC cells,[7] induce Bax expression, and activate EGR-1 in PC cells.[11] Another study found that vitamin E can inhibit the growth of human PC cells by suppressing NF-κB-mediated inflammatory pathways.[8] Vitamin E can also induce apoptosis in PC cells by suppressing signaling pathways such as the PI3K/AKT and ERK/MAPK pathways via down-regulation of Her2/ErbB2,[9] and inhibit the proliferation of PC cells dependent on p27 (Kip1) induction.[59] Vitamin K can inhibit PC cell survival via a caspase-dependent pathway.[60] Thiamine can increase caspase-3 activity and reduce proliferation in PC cell lines.[10] Nevertheless, the mechanisms of vitamins reducing the risk of PC needs further investigation.

5. Conclusion

In conclusion, this meta-analysis suggested that vitamin intake can moderately reduce the risk of PC, particularly the consumption of vitamin D and vitamin B12.

Author contributions

Data curation: S. Lu, X. Sun.
Funding acquisition: X. Wang.
Investigation: S. Liu, X. Wang, Y. Liu.
Methodology: X. Sun.
Software: S. Lu, X. Sun.
Supervision: Y. Liu.
Writing – original draft: S. Liu.
Writing – review & editing: S. Liu.

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