Cancer Causes & Control (2023) 34:569–581
https://doi.org/10.1007/s10552-023-01698-8

ORIGINAL PAPER

The association between red, processed and white meat consumption and risk of pancreatic cancer: a meta-analysis of prospective cohort studies

Youngyo Kim[1]

Received: 25 November 2022 / Accepted: 6 April 2023 / Published online: 18 April 2023

Abstract

Purpose The association between meat consumption and the risk of pancreatic cancer has not been comprehensively investigated by different types of meat. The current study was conducted to evaluate this association.

Methods PubMed and Web of Science databases were used to search for prospective cohort studies on meat consumption and pancreatic cancer risk through May 2022. A meta-analysis was performed using random-effects models to combine study-specific relative risks (RR). The quality of the included studies was evaluated using the Newcastle–Ottawa quality assessment scale.

Results Twenty prospective cohort studies including 3,934,909 participants and 11,315 pancreatic cancer cases were identified. The pooled RR of pancreatic cancer for the highest *versus* lowest white meat intake category was 1.14 (95% CI: 1.03–1.27). There was no significant association between consumption of red meat and processed meat and pancreatic cancer risk in the highest *versus* lowest analysis. In dose–response analyses, pooled RRs were 1.14 (95% CI: 1.01–1.28) for an increase in red meat consumption of 120 g per day and 1.26 (95% CI: 1.08–1.47) for an increase in white meat consumption of 100 g per day, respectively. Processed meat consumption showed neither a linear nor a non-linear association with pancreatic cancer risk.

Conclusion Findings from this meta-analysis suggested that high consumption of red meat and white meat is associated with an increased risk of pancreatic cancer. Future prospective studies are warranted to confirm the association between meat consumption and the risk of pancreatic cancer.

Keywords Pancreatic cancer · Red meat · White meat · Processed meat · Meta-analysis · Prospective studies

Introduction

Despite its relatively low incidence (a fourteenth most common type of cancer), pancreatic cancer ranks as the seventh leading cause of cancer death worldwide in Global Cancer Statistics 2020 [1]. The incidence rates of pancreatic cancer have also increased recently [2], and such a phenomenon is observed more prominently in high-income countries, where overall rates are almost three-fold higher than middle- and low-income countries [3]. In the United States, pancreatic cancer occupied the fourth leading cause of cancer deaths with the lowest 5 year survival rate at 9% among all cancer types [4]. Because of its poor prognosis, prevention is more important than treatment for pancreatic cancer. Therefore, it is necessary to identify risk factors for pancreatic cancer and develop prevention strategies for pancreatic cancer to reduce the burden on pancreatic cancer and improve public health. According to a recent report from the World Cancer Research Fund (WCRF), being obese and being tall have been proven to increase the risk of pancreatic cancer [3]. However, there are only limited evidence for dietary factor including consumption of meat. To date, many prospective cohort studies reported the association between meat intake and risk of pancreatic cancer [5–24]. Among them, several studies found that high meat consumption was positively associated with an increased risk of pancreatic cancer [7, 13, 14, 25], but most other studies showed no significant

✉ Youngyo Kim
youngyokim@gnu.ac.kr

1 Department of Food and Nutrition/Institute of Agriculture and Life Science, Gyeongsang National University, Jinjudairo 501, Jinju 52828, South Korea

association between meat consumption and risk of pancreatic cancer [5, 6, 8–12, 15–19, 26]. Previous attempts have been made to combine results on the association between meat intake and pancreatic cancer risk, but they are mostly focused on red meat or processed meat [27, 28], with relatively little interest in white meat. Since previous results on the association between meat intake and pancreatic cancer risk were inconsistent and the nutritional composition is different by type of meat, the association between meat intake and the risk of pancreatic cancer needs to be comprehensively examined for various types of meat. There were several meta-analyses investigating the association between meat intake and pancreatic cancer [27, 29, 30], but they included only a small number of studies through 2011 [27], analyzed results from the same cohort in duplicate [30], and did not include updated results from recent studies [29], including large populations such as China Kadoorie Biobank study ($n=510{,}314$) [22] and UK Biobank study ($n=474{,}996$) [15].

Therefore, we conducted an up-to-date systematic review and meta-analysis of the association between the consumption of red meat, processed meat, and white meat and the risk of pancreatic cancer, including recent results, to better understand the association of meat consumption on the risk of pancreatic cancer and quantitatively evaluate the association by different types of meat consumption.

Materials and methods

Data sources and searches

A literature search in PubMed and ISI Web of Science databases was performed for studies published until May 2022. The search terms were as follows: "(meat OR beef OR pork OR veal OR lamb OR steak OR hamburger OR ham OR bacon OR sausage OR poultry OR chicken OR turkey OR diet OR dietary) combined with (pancreatic cancer OR pancreatic neoplasm OR pancreatic carcinoma)." A manual search was also conducted by reviewing the reference lists of retrieved articles to include further eligible studies.

Study selection

The inclusion criteria for this meta-analysis were as follows: (1) they have a prospective design; (2) the exposure of interest was intake of red meat, processed meat, or white meat; (3) the outcome of interest was incidence or mortality of pancreatic cancer; (4) they reported relative risks (RR) with related confidence intervals (CI). When more than one article was from the same cohort, the study including more subjects or providing the RRs for various types of meat was selected for meta-analysis.

The study that included fish in the white meat category was excluded.

Data extraction and quality assessment

A data extraction was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [31]. The following information was extracted from each article: last name of first author's, year of publication, geographical region or country where the study was conducted, cohort name, period of follow-up, age, sex, number of subjects and cases, categories of meat consumption, the RRs and 95% CIs for each category of meat consumption, and adjusted variables. If articles provided several RRs, we included the RRs that reflected the greatest degree of adjustment for potential confounders.

To evaluate the quality of the studies included in this meta-analysis, the Newcastle–Ottawa quality assessment scale [32] was used. The quality of each study was assessed on three factors including a selection of subjects, comparability of cohorts, and ascertainment of outcomes of interest. A high-quality study achieved a score of 10 or more (out of 13). Studies with scores of 7–9 and a score of 6 or less were considered good and low quality, respectively. The quality assessment was conducted to perform subgroup analysis by the quality score when a low quality study was included in the meta-analysis.

Statistical analysis

The pooled RRs of pancreatic cancer for the highest *versus* lowest meat intakes were synthesized using the DerSimonian and Laird [33] random-effects models, which considers both within- and between-study variations. The summary estimates were displayed as forest plots. The subgroup analysis was conducted by sex, geographical region, and adjustment for diabetes to examine the variations in the association between meat intake and pancreatic cancer by study characteristics. To test whether the results were not simply influenced by a single study, we performed sensitivity analyses by eliminating one study at a time. The methods developed by Greenland and Longnecker [34–36] were used for the linear dose–response meta-analysis. The median value of meat intake for each consumption category was assigned to each related RR for each study. If a study provided a meat intake not as grams per day but as grams per 1000 kcal, the unit was converted into grams per day to take into account the mean energy intake of the corresponding population. When meat intake was reported in 'servings', we recalculated the intake to grams per day. The standard portion size was assumed 120 g for red meat, 100 g for white meat, and 50 g for processed meat [37, 38], respectively. A potential non-linear dose–response association between meat intake

Table 1 Characteristics of Prospective Studies Included in the Meta-Analysis of meat and pancreatic caner

First author, year	Country	Cohort name	Follow-up period	Age at baseline (years)	sex	Study size		Type of meat	Meat consumption category	Adjustment for covariates
						Subjects	No. of cases			
Zheng, 1993 [17]	US	Life-insurance policy holders of the Lutheran Brotherhood Insurance Society	1966–1986	≥ 35	Male	17,633	57	Red meat White meat	Quartiles	Age, smoking, intake of alcohol and energy
Coughlin, 2000 [18]	US	Cancer Pre-vention study II	1982–1994	≥ 30	Male and female	1,102,308	3,751	Red meat	Quartiles	Age, race, years of education, family history of pancreatic cancer in a first-degree relative, history of gallstones, BMI, cigarette smoking history, alcohol consumption, total red meat consumption, consumption of citrus fruits and juices, vegetable consumption, history of diabetes
Isaksson, 2002 [19]	Sweden	Swedish Twin Registry	1961–1997	NA	Male and female	21,884	176	Red meat Processed meat	Tertiles	Age, sex, smoking, BMI
Stolzenberg-Solomon, 2002 [5]	Finland	Alpha-Tocopherol, Beta-Carotene cancer prevention study	1985–1997	50–69	Male	27,111	163	Red meat Processed meat White meat	Quartiles	Age, years of smoking, intake of energy
Michaud, 2003 [6]	US	Nurses' health study	1976–1990	30–55	Female	88,802	178	Red meat Processed meat White meat	Quintiles [a] Quartiles [b]	Age, pack-years of smoking, BMI, history of diabetes mellitus, energy intake, height, physical activity, menopausal status

Table 1 (continued)

First author, year	Country	Cohort name	Follow-up period	Age at baseline (years)	sex	Study size		Type of meat	Meat consumption category	Adjustment for covariates
						Subjects	No. of cases			
Khan, 2004 [20]	Japan	Cohort study in Hokkaido	1984–2002	≥ 40	Male and female	3,158	25	Processed meat White meat	Binary category	Age, health status, health education, health screening, smoking
Nöthlings, 2005 [7]	US	Multiethnic cohort study	1993–2001	45–75	Male and female	190,545	482	Red meat Processed meat White meat	Quintiles	Age, sex, time on study, ethnicity, history of diabetes mellitus, familial history of pancreatic cancer, smoking status, energy intake
Larsson, 2006 [24]	Sweden	The Swedish mammography cohort	1987–2004	40–76	Female	61,433	172	Red meat Processed meat White meat	Quartiles [a] Tertiles [b]	Age, education, BMI, smoking, intakes of total energy, alcohol, red meat, processed meat, fish, egg and energy-adjusted folate
Lin, 2006 [8]	Japan	Japan collaborative cohort study for evaluation of cancer risk	1988–1999	40–79	Male and female	110,792	237	Red meat Processed meat White meat	Tertiles	Age, area, pack-years of smoking
Heinen, 2009 [9]	Netherlands	The Netherlands cohort study	1986–1999	55–69	Male and female	120,852	350	Red meat Processed meat White meat	Quintiles [a] Quartiles [b]	Age, sex, energy, smoking, alcohol, history of diabetes mellitus, history of hypertension, BMI, intakes of vegetables and fruit
Inoue-Choi, 2011 [10]	US	Iowa Women's health study	1986–2007	55–69	Female	34,642	256	Red meat	Quintiles	Age, race, education, alcohol intake, smoking, physical activity

Table 1 (continued)

First author, year	Country	Cohort name	Follow-up period	Age at baseline (years)	sex	Study size		Type of meat	Meat consumption category	Adjustment for covariates
						Subjects	No. of cases			
Anderson, 2012 [11]	US	Prostate, lung, colorectal, and ovarian screening trial	1993–2007	55–74	Male and female	62,581	248	Red meat	Quintiles	Age, sex, education, race, diabetes, dietary fat intake, cigarette smoking history
Rohrmann, 2013 [23]	Europe	European prospective investigation into cancer and nutrition	1992–2008	52.7 (male), median 51 (female), median	Male and female	477,202	865	Red meat Processed meat White meat	Quartiles	Age, sex, center, height, weight, physical activity index, cigarette smoking, education, history of diabetes, total energy intake
Ghorbani, 2016 [12]	Iran	Golestan cohort study	2004–2014	40–87	Male and female	50,045	54	Red meat Processed meat White meat	Tertiles	Age, sex, history of diabetes, pack-years of cigarette smoking, years of education, alcohol consumption, opium using, BMI, total energy intake, metabolic equivalent task(MET), wealth score, residential area
Taunk, 2016 [13]	US	NIH-American association of retired persons cohort	1995–2006	50–71	Male and female	322,846	1,417	Red meat Processed meat White meat	Quintiles	Age, sex, energy, smoking, BMI, education, race, self-reported diabetes, energy-adjusted saturated fat
McCullough, 2018 [14]	US	Cancer prevention study-II nutrition cohort	1992–2013	40–92	Male and female	138,266	1,156	Red meat Processed meat White meat	Quintiles	Age, sex, BMI, history of diabetes, smoking status, ethanol intake, energy intake, saturated fat

Table 1 (continued)

First author, year	Country	Cohort name	Follow-up period	Age at baseline (years)	sex	Study size		Type of meat	Meat consumption category	Adjustment for covariates
						Subjects	No. of cases			
Pang, 2018 [22]	China	China Kadoorie biobank study	9 years	30–79	Male and female	510,314	688	Red meat White meat	Quartiles	Age at baseline, age-at-risk, sex, area, education, smoking, alcohol, BMI, total physical activity, other food intake (fresh fruit, soybean products, fish, poultry, and dairy products), diabetes
Knuppel, 2020 [15]	UK	UK biobank study	6.9 years	37–73	Male and female	474,996	606	Red meat Processed meat White meat	Per 50 g/day [c] Per 20 g/day [d] Per 30 g/day [b]	Age, ethnicity, deprivation, qualification, employment, living with a spouse or partner, height, smoking, physical activity, alcohol intake, total fruit and vegetable intake, estimated cereal fibre intake, BMI, menopausal status, parity, hormone replacement therapy and oral contraceptive pill use (in women)
Petrick, 2020 [16]	US	BlackWomen's health study	1995–2018	21–69	Female	52,706	168	Red meat Processed meat	Quartiles	Age, cigarette smoking, total energy intake

Table 1 (continued)

First author, year	Country	Cohort name	Follow-up period	Age at baseline (years)	sex	Study size		Type of meat	Meat consumption category	Adjustment for covariates
						Subjects	No. of cases			
Huang, 2021 [21]	US	Southern Community Cohort Study	10.6 years	51.9, mean	Male and Female	66,793	266	Red meat	Quartiles	Age at enrollment, ethnicity, sex, BMI, smoking status, pack years of smoking, pre-existing diabetes, family history of pancreatic cancer, total calories

BMI: body mass index, NA: not available, UK: United Kingdom, US: United States

[a]In case of red meat and processed meat

[b]In case of white meat

[c]In case of red meat

[d]In case of processed meat

and pancreatic cancer was also examined through restricted cubic splines with three knots at fixed percentiles (10, 50, and 90%) of the aggregated exposure [39]. The non-linear *P* value was obtained by testing the null hypothesis that the coefficient of the second spline is equal to zero.

The *Q* [40] and I^2 statistics [41] were used to investigate heterogeneity among the studies and to quantify inconsistency. Publication bias was examined with Begg's [42] and Egger's regression test [43]. The *P*-values were two-tailed, and it was assumed that there is a significant difference when $P < 0.05$. All statistical analyses were performed using Stata version 14.2 software (StataCorp, TX, USA).

Results

Study characteristics

Twenty prospective cohort studies including 3,934,909 participants and 11,315 cases were eligible for the current meta-analysis [5–22, 25, 26]. Table 1 shows the general characteristics of prospective cohort studies included in this meta-analysis. Eleven studies reported RRs of pancreatic cancer for all three type of meat (red, processed, and white meat) [5–9, 12–15, 25, 26]. Five studies provided RRs of pancreatic cancer for two different types of meat [16, 17, 19, 20, 22], and four studies provided RRs for red meat only [10, 11, 18, 21]. Regarding geographic region, ten studies were conducted in the United States [6, 7, 10, 11, 13, 14, 16–18, 21], six studies in Europe [5, 9, 15, 19, 25, 26], and four studies in Asia [8, 12, 20, 22]. The shortest follow-up duration was 6.9 years. All studies adjusted for age and smoking, and most studies also controlled for energy intake ($n = 13$) or BMI ($n = 12$). Other fewer studies adjusted for diabetes ($n = 11$) or alcohol consumption ($n = 9$). The scores of the quality assessment ranged from 9 to 12, with a mean score of 10.8.

Red meat intake

Nineteen prospective cohort studies involving 3,931,751 participants and 11,290 cases evaluated the association between intake of red meat and risk of pancreatic cancer [5–19, 21, 25, 26]. The pooled RR for pancreatic cancer comparing the highest *versus* lowest intakes of red meat was 1.09 (95% CI: 0.97–1.21) showing significant heterogeneity among studies ($I^2 = 60.1\%$, $P < 0.001$) (Fig. 1). By sex, a significant positive association was observed for men (RR: 1.22, 95% CI: 1.02–1.47) unlike for women (RR: 1.02, 95% CI: 0.89–1.16). We did not find any significant variances by adjustment for history of diabetes (*P* for difference = 0.48), and geographical region (*P* for difference > 0.1 in all comparisons) in subgroup analysis (Table 2).

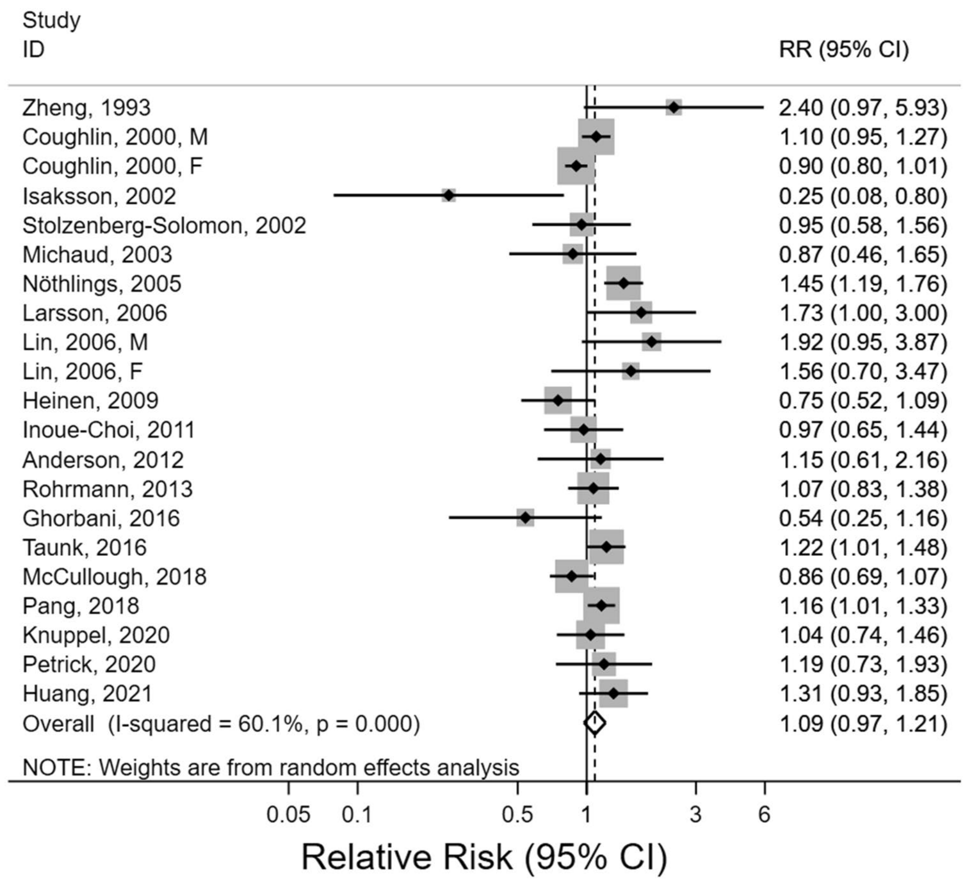

Fig. 1 Forest plot of prospective studies of pancreatic cancer for the highest *versus* lowest category of red meat consumption, using random-effects model

In a dose–response meta-analysis, the pooled RR for 120 g per day increase of red meat intake was 1.14 (95% CI: 1.01–1.28) suggesting a borderline significant association between red meat intake and pancreatic cancer (*P* for linearity = 0.04) (Table 2). There was no significant non-linear association between red meat intake and pancreatic cancer (*P* for non-linearity = 0.44).

Processed meat intake

Fourteen prospective cohort studies including 2,140,638 participants and 6,049 cases examined the association between intake of processed meat and risk of pancreatic cancer [5–9, 12–16, 19, 20, 25, 26]. The pooled RR for pancreatic cancer comparing the highest *versus* lowest intakes of processed meat was 1.00 (95% CI: 0.85–1.18) with significant heterogeneity among studies (I^2 = 59.9%, *P* = 0.001) (Fig. 2). Any significant variances were not observed by sex (*P* for difference = 0.90), adjustment for history of diabetes (*P* for difference = 0.43), and geographical region (*P* for difference > 0.2 in all comparisons) in subgroup analysis (Table 2). In the dose–response meta-analysis of processed meat intake and pancreatic cancer, no significant non-linear association was observed (*P* for non-linearity = 0.35) (Table 2). The pooled RR for an increase of 50 g per day of processed meat intake was 0.99 (95% CI: 0.78–1.25).

White meat intake

Fourteen prospective cohort studies involving 2,593,995 participants and 6,450 cases evaluated the association between intakes of white meat and risk of pancreatic cancer [5–9, 12–15, 17, 20, 22, 25, 26]. The pooled RR for pancreatic cancer comparing the highest *versus* lowest intakes of white meat was 1.14 (95% CI: 1.03–1.27) (Fig. 3). There was no significant evidence of heterogeneity among studies (I^2 = 24.9%, *P* = 0.17). The positive association between white meat intake and pancreatic cancer was stronger in studies adjusted for history of diabetes (RR: 1.17, 95% CI: 1.07–1.28) than in studies unadjusted for history of diabetes (RR: 1.04, 95% CI: 0.74–1.46). However, the variance was not significant (*P* for difference = 0.18) (Table 2). For geographic region, stronger associations were found in Asia (RR: 1.48, 95% CI: 1.05–2.07) and US (RR: 1.16, 95% CI: 1.04–1.28) than Europe (RR: 1.04, 95% CI: 0.84–1.28) (*P* for Asia or US *versus*. Europe = 0.14 and 0.41, respectively). In a dose–response meta-analysis, we found a positive association between intakes of white meat and risk of

Table 2 Summary of pooled relative risks for meat consumption and risk of pancreatic cancer

Factor	No. of studies	Relative risk	95% CIs	*P* for difference
Red meat				
All studies	19	1.09	0.97–1.21	
Stratified by sex				
Male	7	1.22	1.02–1.47	0.17
Female	9	1.02	0.89–1.16	
Stratified by geographical region				
Europe	5	0.90	0.70–1.16	
US	11	1.13	0.99–1.30	0.18[a]
Asia	3	1.18	0.79–1.76	0.24[a]
Adjusted for history of diabetes				
Yes	11	1.06	0.94–1.19	0.48
No	8	1.19	0.91–1.55	
Increment of 120 g/day				
All studies	12	1.14	1.01–1.28	
Processed meat				
All studies	14	1.00	0.85–1.18	
Stratified by sex				
Male	5	0.97	0.80–1.16	0.90
Female	7	0.95	0.81–1.12	
Stratified by geographical region				
Europe	6	0.89	0.76–1.03	
US	5	1.09	0.81–1.46	0.24[b]
Asia	3	1.12	0.72–1.75	0.46[b]
Adjusted for history of diabetes				
Yes	7	1.06	0.83–1.33	0.43
No	7	0.94	0.77–1.14	
Increment of 50 g/day				
All studies	9	0.99	0.78–1.25	
White meat				
All studies	14	1.14	1.03–1.27	
Stratified by sex				
Male	7	1.21	0.97–1.53	0.41
Female	7	1.27	0.98–1.64	
Stratified by geographical region				
Europe	5	1.04	0.84–1.28	
US	5	1.16	1.04–1.28	0.41[C]
Asia	4	1.48	1.05–2.07	0.14[C]
Adjusted for history of diabetes				
Yes	8	1.17	1.07–1.28	0.18
No	6	1.04	0.74–1.46	
Increment of 100 g/day				
All studies	9	1.26	1.08–1.47	

[a]*P* value for difference in RRs of red meat consumption for US vs. Europe ($P=0.18$) and Asia vs. Europe ($P=0.24$)

[b]*P* value for difference in RRs of processed meat consumption for US vs. Europe ($P=0.24$) and Asia vs. Europe ($P=0.46$)

[C]*P* value for difference in RRs of white meat consumption for US vs. Europe ($P=0.41$) and Asia vs. Europe ($P=0.14$)

pancreatic cancer. The pooled RR of pancreatic cancer for a 100 g per day increase in intakes of white meat was 1.26 (95% CI: 1.08–1.47) (*P* for linearity = 0.004) (Table 2). There was no evidence of a non-linear association between intakes of white meat and risk of pancreatic cancer (*P* for non-linearity = 0.82).

Publication bias

There was no indication of publication bias for the meta-analysis of red meat (Begg's $p=0.98$; Egger's $p=0.74$), processed meat (Begg's $p=0.89$; Egger's $p=0.50$), and white meat (Begg's $p=0.62$; Egger's $p=0.78$).

Discussion

The findings based on 20 prospective studies involving 3,934,909 subjects and 11,315 cases indicated a positive association between intakes of white meat and red meat and risk of pancreatic cancer. People in the highest intake group of white meat had a 14% higher risk of pancreatic cancer compared to those in the lowest intake group of white meat. Results from dose–response meta-analysis showed that white meat and red meat intakes are associated with pancreatic cancer in a positive linear fashion. Processed meat intake showed no significant association with the risk of pancreatic cancer in the highest *versus* lowest meta-analysis and dose–response meta-analysis.

Regard for red meat, the risk of pancreatic cancer increased by 14% for every 120 g increase in daily intake. Although the evidence of the association between red meat consumption and risk of pancreatic cancer was categorized as "limited-suggestive for increased risk" in the WCRF/American Institute for Cancer Research (AICR) report [3], red meat intake has been reported to increase the risk of other types of cancer. A recent huge meta-analysis including 148 published articles showed that high red meat intake was associated with increased risks of lung cancer, endometrial cancer, liver cancer, colorectal cancer, and breast cancer [44]. Suspected carcinogens such as heterocyclic aromatic amines (HAA) and polycyclic aromatic hydrocarbons (PAH) can be produced when red meat was cooked at high temperature [45], and these have been observed to be mutagens related to pancreatic cancer in a previous study which was excluded from this meta-analysis due to overlapping population [46]. The NIH-AARP Diet and Health Study cohort reported increased risks of pancreatic cancer for high-temperature cooked meat, grilled/barbequed meat, and well/very well done meat by 21, 24, and 32%, respectively [13]. Further studies are needed to identify the effect of cooking methods on the association between red meat intake and the risk of pancreatic cancer. In subgroup analysis

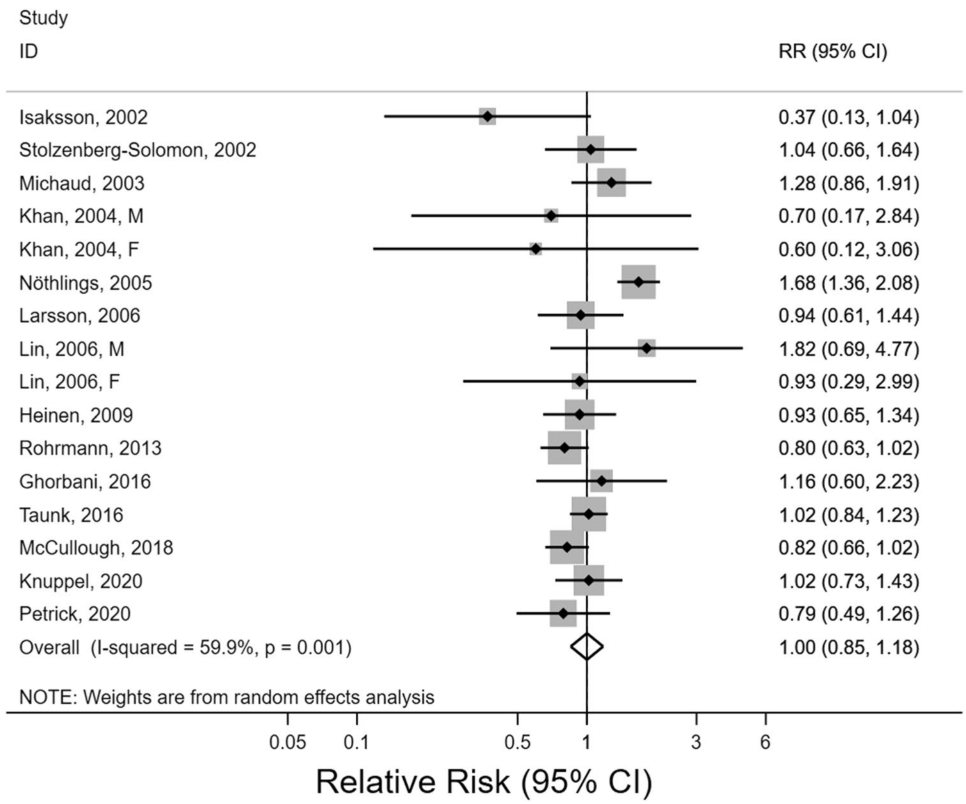

Fig. 2 Forest plot of prospective studies of pancreatic cancer for the highest *versus* lowest category of processed meat consumption, using random-effects model

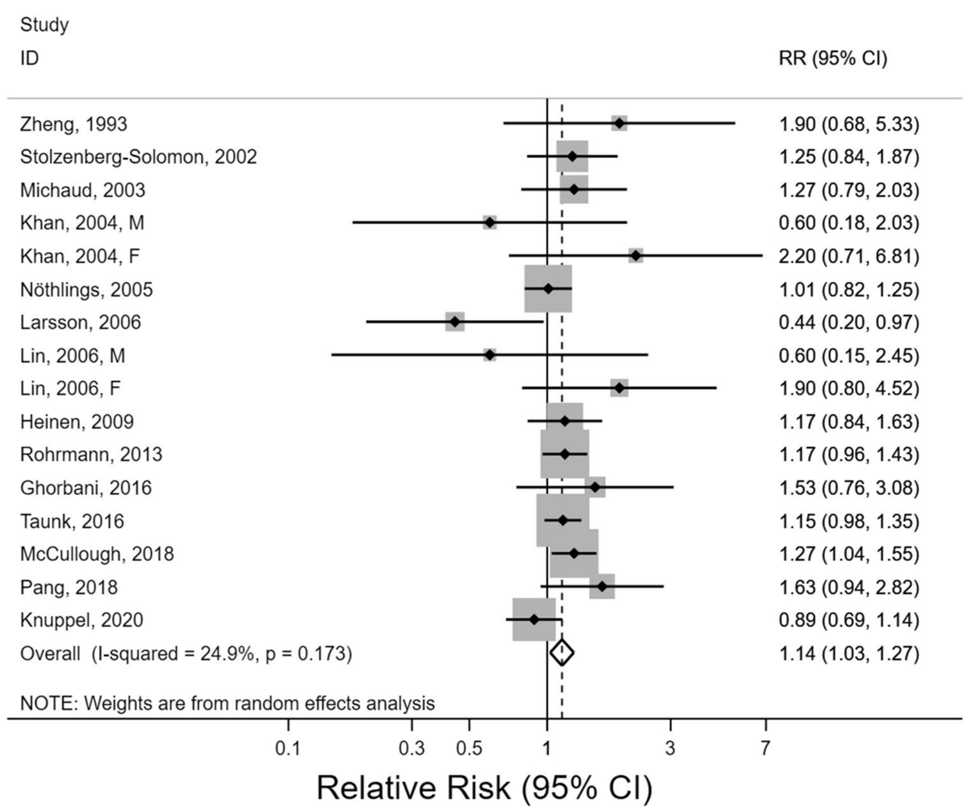

Fig. 3 Forest plot of prospective studies of pancreatic cancer for the highest *versus* lowest category of white meat consumption, using random-effects model

stratified by sex, men showed a stronger positive association of red meat and pancreatic cancer risk than women. Several studies reporting different intake categorization criteria for men and women have found that men ate more red meat than women [13, 14], which may have influenced the association between red meat consumption and risk of pancreatic cancer. Another possible explanation for variation by sex could be heme iron rich in red meat. Because of usual iron loss during menstruation, women generally do not have as high iron stores as men throughout their lives. The level of iron storage in the body can affect serum iron levels and transferrin saturation, and the positive association between serum iron and iron saturation and risk of pancreatic cancer was observed in previous study [14, 47]. A large cohort including 322,846 participants also showed heme iron from red meat increased pancreatic cancer risk by 21% [13]. Relatively higher iron storage of men might have increased the pancreatic cancer risk by upregulating the level of serum iron.

For white meat, a positive association between white meat intake and risk of pancreatic cancer was found both in the highest *versus* lowest analysis and dose–response analysis, which is a rather unexpected result. Compared to red meat, white meat was generally considered to be beneficial to health because it contains more polyunsaturated fatty acids which can reduce blood pressure and inflammation through eicosanoid production [48, 49]. Among 14 prospective studies that investigated the association between white meat intake and pancreatic cancer risk, 10 studies reported point estimates greater than 1, indicating the raised risk of pancreatic cancer with increased consumption of white meat [5–7, 9, 12–14, 17, 22, 23]. One of the studies included in this meta-analysis speculated that roxarsone might be responsible for an increased risk of pancreatic cancer [14]. Roxarsone has long been used in poultry production to promote growth and fight against parasites [50]. When roxarsone is metabolized in the body of chickens, inorganic arsenic can be produced [50, 51]. A previous study of the US population observed that poultry consumption was positively associated with arsenic exposure [52]. Arsenic has been reported to be associated with the development of skin, bladder, and lung cancer [53], and a possible association with the development of pancreatic cancer has also been found [54]. Further studies are needed to determine the link between arsenic exposure and pancreatic cancer risk.

Given that both red and white meat consumption was positively associated with pancreatic cancer risk in this meta-analysis, another potential mechanism can be speculated. The human body's acid–base balance is affected by dietary intake, and animal products such as meat increase an acid load [55]. Diet-induced acidosis can raise plasma cortisol [56], which was reported to increase insulin resistance [57]. In addition, acidosis induced by a high-protein diet was found to be associated with upregulated serum insulin-like growth factor 1[58]. Previous studies have found that higher insulin resistance and insulin-like growth factor 1 can promote the development of pancreatic cancer [59, 60]. Meanwhile, acidosis can decrease adiponectin production by inhibiting the gene transcription of adiponectin [61]. Low serum adiponectin levels have been reported to be associated with a raised risk of developing cancer by causing tumor growth [62]. Therefore, hyper carnivorous acidosis caused by high meat consumption may have increased the risk of pancreatic cancer due to high insulin resistance, high insulin-like growth factor 1, and low serum adiponectin levels.

This meta-analysis provided updated results by including a recent study that performed both a highest *versus* lowest meta-analysis and a dose–response meta-analysis and did not include duplicate cohort results through validation. In addition, the large number of subjects and cases made it possible to perform subgroup analyses to identify differences by sex, geographical region, and adjustment for history of diabetes. The current study has some limitations to be acknowledged. Since the included studies were observational, residual or confounding factors cannot be ruled out. However, all included studies had controlled for age and smoking, and many of the studies had adjusted for potential confounders such as energy intake, BMI, or history of diabetes mellitus. Another limitation is measurement error which can happen in the dietary assessments such as food frequency questionnaires. Measurement error may cause misclassification in the consumption of meat. However, misclassification tends to bias the RR values toward the null value, underestimating the association between meat consumption and pancreatic cancer risk. Lastly, subgroup analysis by cooking methods could not be performed because of the small body of data.

In conclusion, the results from this meta-analysis indicated that high consumption of white meat and red meat was associated with an increased risk of pancreatic cancer. Further extensive prospective cohort studies are needed to investigate the association between meat consumption and the risk of pancreatic cancer by cooking methods.

Author contributions YK: developed study concept and design and contributed to critical revision of the manuscript for important intellectual content; YK: wrote the manuscript; YK: researched data, conducted the statistical analysis; YK: contributed to discussion and reviewed/edited the manuscript.

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability Not applicable.

Declarations

Competing interests The author has no conflicts of interest to declare that are relevant to the content of this article.

Ethical approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

References

1. Sung H, Ferlay J, Siegel RL et al (2021) Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71:209–249
2. Ward EM, Sherman RL, Henley SJ et al (2019) Annual report to the nation on the status of cancer, featuring cancer in men and women age 20–49 years. J Natl Cancer Inst 111:1279–1297
3. WCRF/AICR. (2018) Diet, Nutrition, Physical Activity and cancer: a Global Perspective. Continous Update Project Expert Report 2018. World Cancer Research Fund/American Institute for Cancer Research.
4. Siegel RL, Miller KD, Jemal A (2020) Cancer statistics, 2020. CA Cancer J Clin 70:7–30
5. 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
6. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS (2003) Dietary meat, dairy products, fat, and cholesterol and pancreatic cancer risk in a prospective study. Am J Epidemiol 157:1115–1125
7. Nöthlings U, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Kolonel LN (2005) Meat and fat intake as risk factors for pancreatic cancer: the multiethnic cohort study. J Natl Cancer Inst 97:1458–1465
8. Lin Y, Kikuchi S, Tamakoshi A et al (2006) Dietary habits and pancreatic cancer risk in a cohort of middle-aged and elderly Japanese. Nutr Cancer 56:40–49
9. Heinen MM, Verhage BA, Goldbohm RA, van den Brandt PA (2009) Meat and fat intake and pancreatic cancer risk in the Netherlands cohort study. Int J Cancer 125:1118–1126
10. Inoue-Choi M, Flood A, Robien K, Anderson K (2011) Nutrients, food groups, dietary patterns, and risk of pancreatic cancer in postmenopausal women. Cancer Epidemiol Biomarkers Prev 20:711–714
11. Anderson KE, Mongin SJ, Sinha R et al (2012) Pancreatic cancer risk: associations with meat-derived carcinogen intake in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) cohort. Mol Carcinog 51:128–137
12. Ghorbani Z, Pourshams A, Fazeltabar Malekshah A, Sharafkhah M, Poustchi H, Hekmatdoost A (2016) Major dietary protein sources in relation to pancreatic cancer: a large prospective study. Arch Iran Med 19:248–256
13. Taunk P, Hecht E, Stolzenberg-Solomon R (2016) Are meat and heme iron intake associated with pancreatic cancer? Results from the NIH-AARP diet and health cohort. Int J Cancer 138:2172–2189
14. McCullough ML, Jacobs EJ, Shah R et al (2018) Meat consumption and pancreatic cancer risk among men and women in the cancer prevention study-ii nutrition cohort. Cancer causes & control : CCC 29:125–133
15. Knuppel A, Papier K, Fensom GK et al (2020) Meat intake and cancer risk: prospective analyses in UK Biobank. Int J Epidemiol 49:1540–1552
16. Petrick JL, Castro-Webb N, Gerlovin H et al (2020) A prospective analysis of intake of red and processed meat in relation to pancreatic cancer among African American women. Cancer Epidemiol Biomarkers Prev 29:1775–1783
17. Zheng W, McLaughlin JK, Gridley G et al (1993) A cohort study of smoking, alcohol consumption, and dietary factors for pancreatic cancer (United States). Cancer causes & control 4:477–482
18. Coughlin SS, Calle EE, Patel AV, Thun MJ (2000) Predictors of pancreatic cancer mortality among a large cohort of United States adults. Cancer causes & control 11:915–923
19. Isaksson B, Jonsson F, Pedersen NL, Larsson J, Feychting M, Permert J (2002) Lifestyle factors and pancreatic cancer risk: a cohort study from the Swedish Twin Registry. Int J Cancer 98:480–482
20. Khan MM, Goto R, Kobayashi K et al (2004) Dietary habits and cancer mortality among middle aged and older Japanese living in hokkaido, Japan by cancer site and sex. Asian Pacific J cancer prevent 5:58–65
21. Huang BZ, Wang SR, Bogumil D et al (2021) Red meat consumption, cooking mutagens, NAT1/2 genotypes and pancreatic cancer risk in two ethnically diverse prospective cohorts. Int J Cancer 149:811–819
22. Pang YJ, Holmes MV, Guo Y et al (2018) Smoking, alcohol, and diet in relation to risk of pancreatic cancer in China: a prospective study of 0.5 million people. Cancer Med 7:229–239
23. Rohrmann S, Linseisen J, Nöthlings U et al (2013) Meat and fish consumption and risk of pancreatic cancer: results from the European prospective investigation into cancer and nutrition. Int J Cancer 132:617–624
24. Larsson SC, Håkanson N, Permert J, Wolk A (2006) Meat, fish, poultry and egg consumption in relation to risk of pancreatic cancer: a prospective study. Int J Cancer 118:2866–2870
25. Larsson SC, Hakanson N, Permert J, Wolk A (2006) Meat, fish, poultry and egg consumption in relation to risk of pancreatic cancer: a prospective study. Int J Cancer 118:2866–2870
26. Rohrmann S, Linseisen J, Nothlings U et al (2013) Meat and fish consumption and risk of pancreatic cancer: results from the European prospective investigation into cancer and nutrition. Int J Cancer 132:617–624
27. Larsson SC, Wolk A (2012) Red and processed meat consumption and risk of pancreatic cancer: meta-analysis of prospective studies. Br J Cancer 106:603–607
28. Zhao Z, Yin Z, Pu Z, Zhao Q (2017) Association between consumption of red and processed meat and pancreatic cancer risk: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 15:486-493.e410
29. Gao Y, Ma Y, Yu M et al (2021) Poultry and fish intake and pancreatic cancer risk: a systematic review and meta-analysis. Nutr Cancer 74:1–13
30. Zhao ZW, Yin ZF, Pu ZS, Zhao QC (2017) Association between consumption of red and processed meat and pancreatic cancer risk: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 15:486
31. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS med 6:e1000097
32. Wells GA SB, O'Connell D. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
33. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188

34. Greenland S, Longnecker MP (1992) Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 135:1301–1309
35. Berlin JA, Longnecker MP, Greenland S (1993) Meta-analysis of epidemiologic dose-response data. Epidemiology 4:218–228
36. Orsini N, Bellocco R, Greenland S (2006) Generalized least squares for trend estimation of summarized dose-response data. Stata J 6:40–57
37. Norat T, Lukanova A, Ferrari P, Riboli E (2002) Meat consumption and colorectal cancer risk: an estimate of attributable and preventable fractions. IARC Sci Publ 156:223–225
38. Shi Y, Yu PW, Zeng DZ (2015) Dose-response meta-analysis of poultry intake and colorectal cancer incidence and mortality. Eur J Nutr 54:243–250
39. Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D (2012) Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am J Epidemiol 175:66–73
40. Cochran WG (1954) The combination of estimates from different experiments. Biometrics 10:101–129
41. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327:557–560
42. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50:1088–1101
43. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315:629–634
44. Farvid MS, Sidahmed E, Spence ND, Mante Angua K, Rosner BA, Barnett JB (2021) Consumption of red meat and processed meat and cancer incidence: a systematic review and meta-analysis of prospective studies. Eur J Epidemiol 36:937–951
45. Bouvard V, Loomis D, Guyton KZ et al (2015) Carcinogenicity of consumption of red and processed meat. Lancet Oncol 16:1599–1600
46. Stolzenberg-Solomon RZ, Cross AJ, Silverman DT et al (2007) Meat and meat-mutagen intake and pancreatic cancer risk in the NIH-AARP cohort. Cancer Epidemiol Biomarkers Prev 16:2664–2675
47. Friedman GD, van den Eeden SK (1993) Risk factors for pancreatic cancer: an exploratory study. Int J Epidemiol 22:30–37
48. Miller PE, Van Elswyk M, Alexander DD (2014) Long-chain omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid and blood pressure: a meta-analysis of randomized controlled trials. Am J Hypertens 27:885–896
49. Mozaffarian D, Wu JH (2011) Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol 58:2047–2067
50. Konkel L (2016) Organoarsenic drugs over time: the pharmacokinetics of roxarsone in chicken meat. Environ Health Perspect 124:A150
51. Nachman KE, Baron PA, Raber G, Francesconi KA, Navas-Acien A, Love DC (2013) Roxarsone, inorganic arsenic, and other arsenic species in chicken: a U.S.-based market basket sample. Environ Health Perspect 121:818–824
52. Nigra AE, Nachman KE, Love DC, Grau-Perez M, Navas-Acien A (2017) Poultry consumption and arsenic exposure in the U.S. Population Environ Health Perspect 125:370–377
53. Humans IWGotEoCRt (2012) Arsenic, metals, fibres, and dusts. IARC Monogr Eval Carcinog Risks Hum 100:11–465
54. Liu-Mares W, Mackinnon JA, Sherman R et al (2013) Pancreatic cancer clusters and arsenic-contaminated drinking water wells in Florida. BMC Cancer 13:111
55. Adeva MM, Souto G (2011) Diet-induced metabolic acidosis. Clin Nutr 30:416–421
56. Espino L, Suarez ML, Santamarina G, Goicoa A, Fidalgo LE (2005) Effects of dietary cation-anion difference on blood cortisol and ACTH levels in reproducing ewes. J Vet Med A Physiol Pathol Clin Med 52:8–12
57. Rizza RA, Mandarino LJ, Gerich JE (1982) Cortisol-induced insulin resistance in man: impaired suppression of glucose production and stimulation of glucose utilization due to a postreceptor detect of insulin action. J Clin Endocrinol Metab 54:131–138
58. Robey IF (2012) Examining the relationship between diet-induced acidosis and cancer. Nutr Metab (Lond) 9:72
59. Thomas D, Radhakrishnan P (2020) Role of tumor and stroma-derived IGF/IGFBPs in pancreatic cancer. Cancers (Basel) 12:1228
60. Stolzenberg-Solomon RZ, Graubard BI, Chari S et al (2005) Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. JAMA 294:2872–2878
61. Disthabanchong S, Niticharoenpong K, Radinahamed P, Stitchantrakul W, Ongphiphadhanakul B, Hongeng S (2011) Metabolic acidosis lowers circulating adiponectin through inhibition of adiponectin gene transcription. Nephrol Dial Transplant 26:592–598
62. Hursting SD, Berger NA (2010) Energy balance, host-related factors, and cancer progression. J Clin Oncol 28:4058–4065

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.