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SYSTEMATIC REVIEWS AND META-ANALYSES

Fasiha Kanwal, Section Editor

Association Between Consumption of Red and Processed Meat and Pancreatic Cancer Risk: A Systematic Review and Meta-analysis

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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e87. Learning Objective–Upon completion of this activity, successful learners will have clear recognition about the classification of red and processed meat and the different effects in different genders and geographic area.

BACKGROUND & AIMS: **The relationship between consumption of red and processed meat and pancreatic cancer risk is inconclusive. We conducted a systematic review and meta-analysis to analyze this relationship.**

METHODS: **We performed a systematic search of PubMed, EMBASE, and the Web of Science to identify studies that examined associations between consumption of different kinds of meat with pancreatic cancer and were published through February 2016. By using data from these articles, we associated level of consumption with cancer risk and performed subgroup, meta-regression, and publication bias analyses.**

RESULTS: **We collected and analyzed data from a total of 28 studies that involved 3,143,777 participants (11,325 consumers of red meat) and 2,904,866 participants (9955 consumers of processed meat). We observed statistically significant differences between consumers and non-consumers of these meats in case-control studies (red meat, $P = .02$; processed meat, $P < .01$) but not in cohort studies (red meat, $P = .09$; processed meat, $P = .18$). In cohort studies, a 100 g/day increase in red meat consumption was associated with significant increase in risk of pancreatic cancer ($P = .01$); a 50 g/day increase in processed meat consumption was not associated with significant increase in risk of pancreatic cancer ($P = .90$). In cohort studies, we observed associations in consumption of red meat by men and pancreatic cancer ($P < .01$) and consumption of processed meat by men and pancreatic cancer ($P < .01$) but no associations for women (red meat, $P = .61$; processed meat, $P = .88$).**

CONCLUSIONS: **In a systematic review and meta-analysis, we found case-control but not cohort studies to associate consumption of red and processed meat with risk of pancreatic cancer. However, in cohort studies, consumption of red and processed meat appeared to increase risk of pancreatic cancer in men but not in women.**

Keywords: Adenocarcinoma; Diet; Pancreas; PDAC; Carcinogenesis.

According to GLOBOCAN 2012, pancreatic cancer (PC) is the seventh leading cause of cancer death worldwide.[1] This cancer has moved up to fourth place for women and fifth place for men in the rankings of developed countries.[1] PC remains a highly sinister disease with an extremely poor prognosis; fewer than 5% survive for 5 years.[2] During the past 30 years, the 5-year survival rate of American patients with this disease has increased slightly from 2% to 6%.[3] Thus, identifying risk factors for PC is of great importance for public health. Processed meat consumption has been classified as "carcinogenic to humans" (Group 1) concerning colorectal cancer.[4] However, no dietary factor has yet been convincingly established for PC,[5] and the

[a]Zhanwei Zhao and Zifang Yin share co-first authorship.

Abbreviations used in this paper: CI, confidence interval; HCA, heterocyclic amine; NOC, N-nitroso compound; NOS, Newcastle-Ottawa Scale; OR, odds ratio; PAH, polycyclic aromatic hydrocarbon; PC, pancreatic cancer; RR, risk ratio.

Most current article

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associations between red and processed meat consumption and PC risk remain inconclusive.[6] To our knowledge, only 1 meta-analysis[7] on this association has been reported worldwide, in which 11 studies published up to 2011 were included but with serious questions.[8] Furthermore, many high-quality studies have appeared during the last 5 years (approximately), and an updated meta-analysis of the literature could clarify the impact of these recent studies.

Therefore, we conducted an updated systematic review and meta-analysis with the following objectives: (1) to provide an update including more sufficient epidemiologic evidence published up to February 2016 on the association between red and processed meat consumption and PC risk, (2) to further examine red and processed meat consumption in relation to PC risk according to gender, and (3) to evaluate the dose-response relationship between red and processed meat consumption and PC risk.

Methods

Selection Criteria

Selection criteria were as follows: histologic features that were not consistent with the diagnostic gold standard were excluded; data that were incomplete or that could not be combined were excluded; narrative reviews, systematic reviews, and meta-analyses, comments, case reports, editorials, and studies in which only the abstract could be obtained were excluded; we selected the most recent studies, the largest samples, and the highest quality studies when finding reports with the same patients; white meats and total meats without distinguishing red or processed meat were excluded; the language of all studies was limited to English; and the studies were limited to those involving humans.

Search Strategy

We searched PubMed, EMBASE, and the Web of Science for studies published from inception through February 2016. The following search terms were used: "meat", "beef", "pork", "lamb", "mutton", "veal", "bacon", "ham", "sausage", "salami", "hot dogs", "diet/dietary", and "food/foods" in combination with "pancreatic disease/cancer/carcinoma/adenomas/adenocarcinoma", "gastrointestinal/digestive/alimentary", and "neoplasia/carcinogenesis/tumorigenesis". The reference lists of the included studies were also searched manually to identify additional literature. Authors were contacted directly to request additional data and definitions. The 2 sets of keywords were combined individually, and the eligibility criteria were independently judged by 2 authors (Zhanwei Zhao and Zifang Yin).

Study Quality

The study quality was assessed by using the Newcastle-Ottawa Scale (NOS).[9] The NOS is judged on 3 factors including the elucidation of the exposure or outcomes of interest for case-control or cohort studies, the selection of the study populations, and the comparability of the populations. Two researchers (Zhanwei Zhao and Zifang Yin) independently assessed the quality of the studies. The range of NOS is 0–9 stars, and a high-quality study achieves 7 or more stars.[9,10]

Data Extraction

A data extraction sheet was generated for each study and included the first author, year of publication, country, study type, study population, study period, method of dietary assessment, type of dietary exposure measured, dietary exposure categories, adjusted odds ratios (ORs)/risk ratios (RRs) (95% confidence interval [CI]) (highest to lowest), adjusted variables, and NOS score (Supplementary Tables 5 and 6).

Statistical Analysis

Random-effects models were used to quantify the relationships between red and processed meat consumption and PC risk. The method described by Greenland et al[11] was used for the dose-response meta-analysis. Only studies that reported the RRs with their corresponding 95% CIs for at least 3 quantitative exposure categories were included. The median or mean level of red and processed meat consumption for each category was assigned to each corresponding RR for each study. When the data were not reported, the midpoint of the upper and lower boundaries in each category was assigned as the average consumption. When the highest category was open-ended, we assumed the open-ended interval to be the same as that of the adjacent interval.[12] If the lowest category was open-ended, we assumed the lowest boundary to be 0.[13] The best-fitting models were used to examine the potential nonlinear dose-response relationships between red and processed meat consumption and PC risk.

Heterogeneity among the studies was detected by using Q ($P < .1$ was considered representative of statistically significant heterogeneity) and I^2 statistics ($I^2 < 50\%$ was considered to indicate low heterogeneity).[14] Publication bias was assessed by using funnel plots, Begg's test, and Egger's test ($P < .1$ was considered to indicate significant publication bias).[15] Sensitivity analyses were conducted to investigate the influence of a specific study on the pooled risk estimate by removing 1 study in each turn.

RevMan5.3 (The Cochrane Collaboration, Oxford, UK) and STATA version 12.1 (STATA Corporation, College Station, TX) software were used for data synthesis and analysis.

Results

Study Characteristics and Quality Scores

Twenty-eight studies met the eligibility criteria and provided 44 separate estimates (red meat, 24; processed meat, 20) of the relationships between red and processed meat consumption and PC risk (Figure 1). The quality scores ranged from 6 to 9.

Red Meat

Highest vs lowest consumption. Sixteen cohort studies and 8 case-control studies were included, and a random-effects model yielded the results that there were statistically significant results (RR, 1.38; 95% CI, 1.05–1.81; Supplementary Table 2, Supplementary Figure 1*A*) for case-control studies but null results (RR, 1.12; 95% CI, 0.98–1.28; Supplementary Table 1, Figure 2) for cohort studies.

Dose-response analysis. Thirteen cohort studies were included, and the results of 1.11 (1.03–1.19) suggested that PC risk increases by 11% for each 100 g/day increase in red meat consumption. Furthermore, we checked for nonlinearity of the dose-response relationship between red meat consumption and PC risk, and the evidence showed that the best-fitting model was a nonlinear model ($P = .03$ for nonlinearity; Supplementary Figure 2*A*).

Heterogeneity. There was significant heterogeneity ($P < .01$, $I^2 = 52\%$) of the included cohort studies. Subgroup analyses showed that the differences in RRs were not significant except for geographic area, quality score, and family history of PC (Supplementary Table 1). Meta-regression analyses showed that geographic area was a significant factor of the observed heterogeneity between cohort studies, potentially accounting for 19% of the heterogeneity (Supplementary Table 3).

Publication bias. The funnel plot (Supplementary Figure 3*A*), Egger's test ($P = .26$), and Begg's test ($P = .19$) of cohort studies did not suggest significant evidence. However, sensitivity analyses of cohort studies showed that the changes of recalculated RRs were significant, with a range from 1.09 (0.95–1.24) when excluding Nothlings et al[16] to 1.16 (1.02–1.31) when excluding Heinen et al.[17]

Subgroup analysis according to gender. Eight cohort studies for men and 7 cohort studies for women were included. The results (Supplementary Table 4, Figure 2) indicated that red meat consumption was associated with PC risk in men (RR, 1.21; 95% CI, 1.07–1.37) without heterogeneity ($P = .33$, $I^2 = 13\%$) but not in women (RR, 1.06; 95% CI, 0.85–1.31) without heterogeneity ($P = .16$, $I^2 = 36\%$).

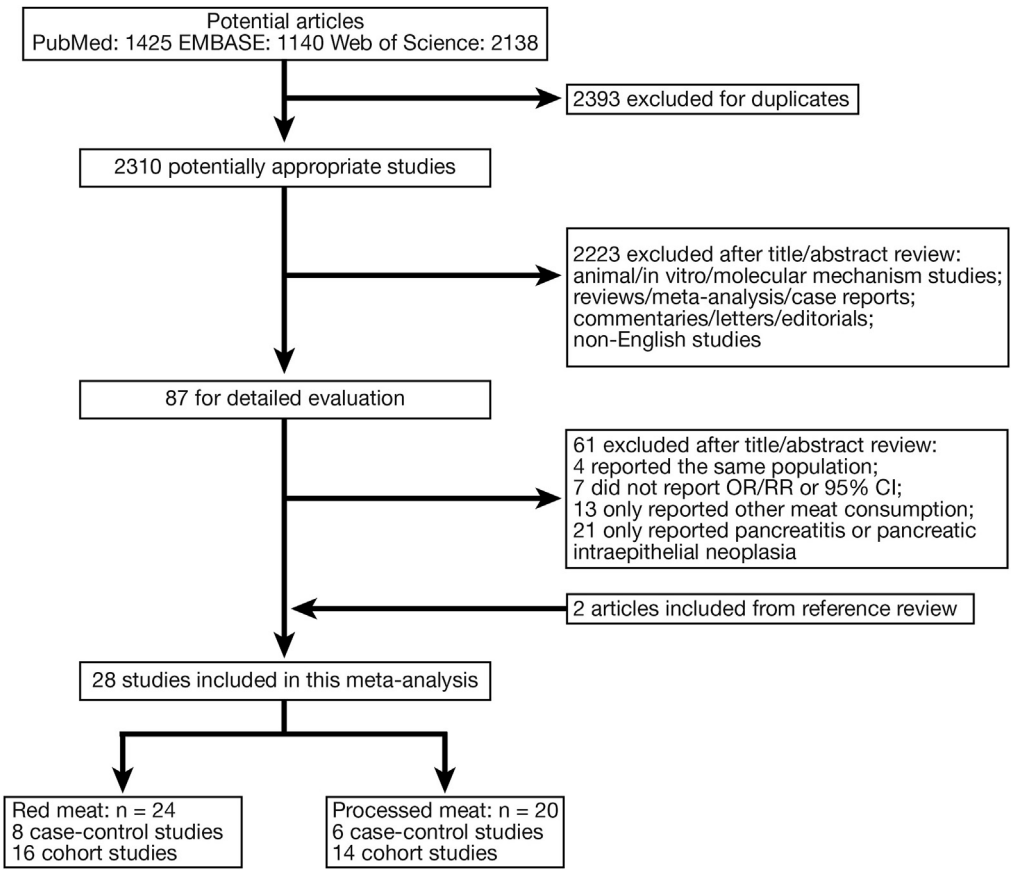

Figure 1. Flowchart of process for identification of relevant studies.

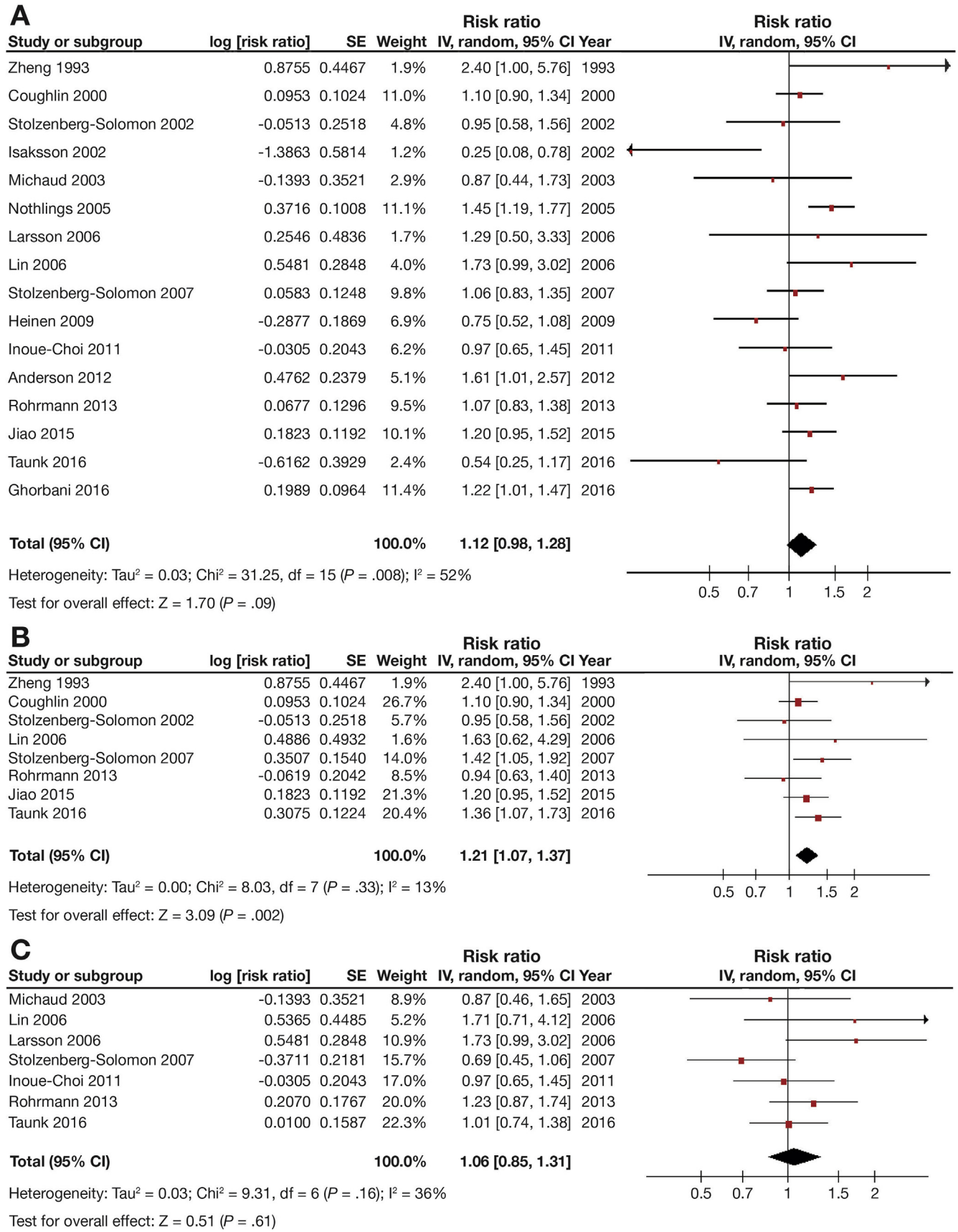

Figure 2. Forest plots of cohort studies for red meat consumption (highest vs lowest category) and PC risk (random-effects model). (*A*) Red meat consumption and PC risk. (*B*) Red meat consumption and PC risk in men. (*C*) Red meat consumption and PC risk in women. Negative relationship was found between red meat consumption and PC risk ($P = .09$). Positive relationship was found in men ($P < .01$) but not in women ($P = .61$). SE, standard error.

Processed Meat

Highest vs lowest consumption. Fourteen cohort studies and 6 case-control studies were included, and a random-effects model yielded the results that there were statistically significant results (RR, 1.62; 95% CI, 1.17–2.26; Supplementary Table 2, Supplementary Figure 1*B*) for case-control studies but null results (RR, 1.09; 95% CI, 0.96–1.23; Supplementary Table 1, Figure 3) for cohort studies.

Dose-response analysis. Eleven cohort studies were included, and the results suggested that a 50 g/day

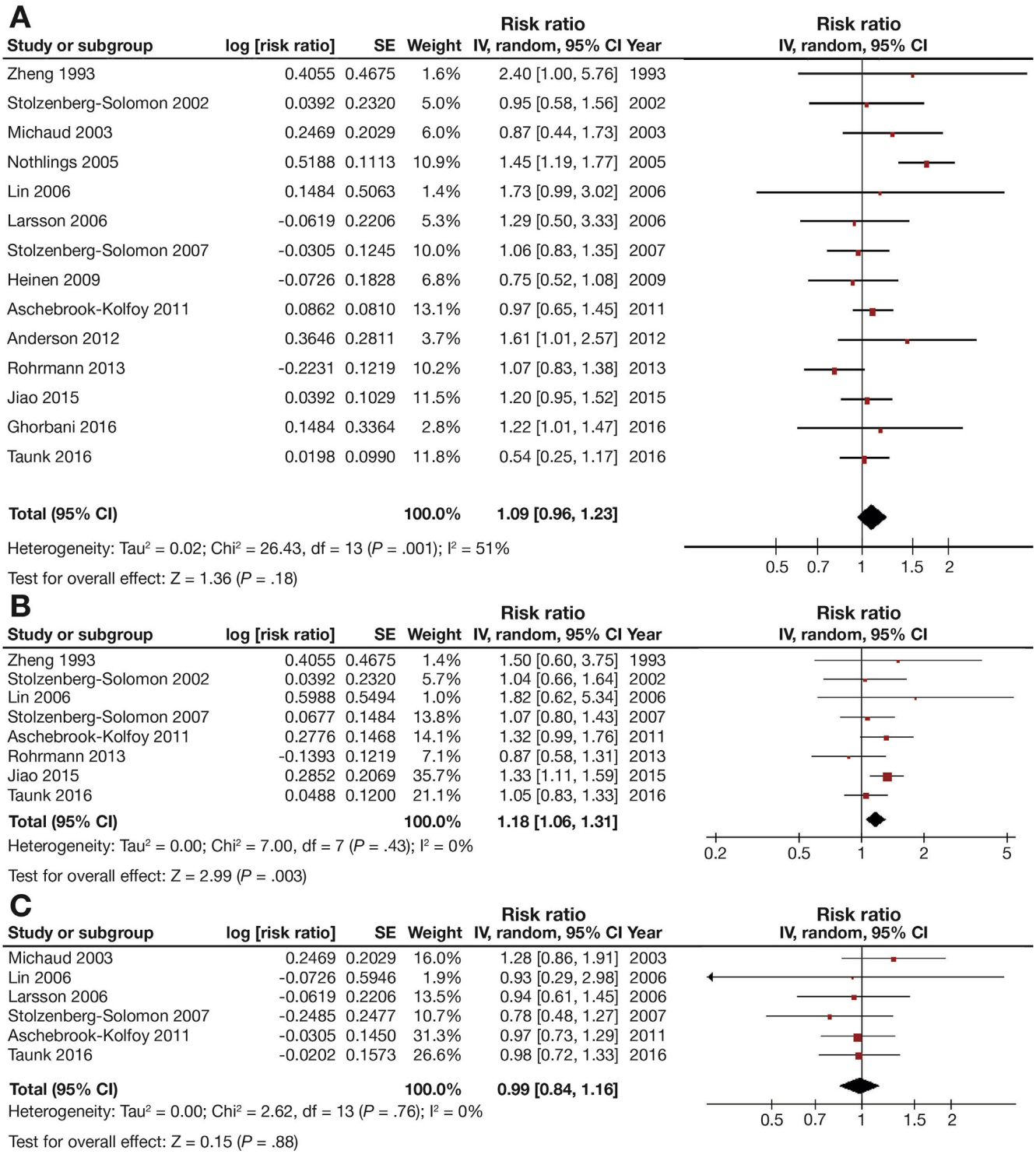

Figure 3. Forest plots of cohort studies for processed meat consumption (highest vs lowest category) and PC risk (random-effects model). (*A*) Processed meat consumption and PC risk. (*B*) Processed meat consumption and PC risk in men. (*C*) Processed meat consumption and PC risk in women. Negative relationship was found between red meat consumption and PC risk ($P = .18$). Positive relationship was found in men ($P < .01$) but not in women ($P = .88$). SE, standard error.

increase in processed meat consumption is not associated with a significant increase in PC risk ($P = .90$). In addition, we checked for nonlinearity of the dose-response relationship between processed meat consumption and PC risk, and the evidence showed that the best-fitting model was nonlinear ($P = .01$ for nonlinearity; Supplementary Figure 2*B*).

Heterogeneity. There was significant heterogeneity ($P = .02$, $I^2 = 51\%$) among the included cohort studies. Subgroup analyses showed that the differences in RRs were not significant except for geographic area. Meta-regression analyses also showed that geographic area was a significant factor of the observed heterogeneity between cohort studies, potentially accounting for 35% of the heterogeneity (Supplementary Table 3).

Publication bias. The funnel plot (Supplementary Figure 3*B*), Egger's test ($P = .51$), and Begg's test ($P = .32$) of cohort studies did not suggest significant evidence. Sensitivity analyses of cohort studies showed that the change of the null effect in recalculated RRs was significant, with a range from 1.02 (0.94–1.11) when excluding Nothlings et al[16] to 1.13 (1.00–1.26) when excluding Rohrmann et al.[18]

Subgroup analysis according to gender. Eight cohort studies for men and 6 cohort studies for women were included. The results (Supplementary Table 4, Figure 3) indicated that processed meat consumption was associated with PC risk in men (RR, 1.18; 95% CI, 1.06–1.31) without heterogeneity ($P = .43$, $I^2 = 0\%$) but not in women (RR, 0.99; 95% CI, 0.84–1.16) without heterogeneity ($P = .76$, $I^2 = 0\%$).

Discussion

The continuous update report of the World Cancer Research Fund 2012 on PC stated that the evidence about the role of red meat and processed meat was judged as "limited" of an increased risk because of the inconsistent evidence. Our results that are based on more sufficient epidemiologic evidence provided more detailed evidence that high consumption of red and processed meat increases PC risk in case-control studies, whereas no overall association is observed in cohort studies. Furthermore, our findings are consistent with current dietary guidelines and reinforce the adverse role that high consumption of red and processed meat increases PC risk in men but not in women in cohort studies. Overall, the detailed findings further highlight the relationships between red meat and processed meat consumption and the risk of PC.

Several potential mechanisms may contribute to the effects. First, the positive relationships between red and processed meat consumption and PC risk in case-control studies and in men may be biologically plausible. Heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) are considered carcinogens[10] and are believed to play an important role in the etiology of PC.[4] Red and processed meat is a major dietary source of carcinogens such as HCAs (DiMeIQx, MeIQx, and PhIP) and PAHs (BaP), especially when barbecuing, frying, and grilling.[16] In addition, lower absolute intake of meat and meat-derived carcinogens in women than in men[19] and men preferring to consume fried, barbecued, or grilled meat more than women[18] may contribute to the different results according to gender. Dietary N-nitroso compounds (NOCs), which are considered a risk factor for cancers,[20] also form during red and processed meat cooking and preserving processes.[17] However, tobacco smoking is the main route of human exposure to NOCs.[7] Thus, we further performed subgroup analyses according to smoking status adjusted or not to explore the relationships. Commendably, all the included cohort studies and most of case-control studies modified this adjustment, and subgroup analyses suggested that the relationships between red and processed meat consumption and PC risk were positive in case-control studies but negative in cohort studies. Second, genetically controlled differences may contribute to the relationships. Mutations in the BRCA2 gene have been reported to be associated with PC susceptibility, accounting for 6% of PC families.[21] Notably, family history of PC is among the main risk factors for this disease.[22] Thus, we further explored the adjustment of family history of PC by using subgroup analyses, and the results suggested that the relationship was positive for red meat consumption but negative for processed meat consumption. Finally, evidence associated with hormones has found possible mechanisms. High red meat consumption increases diabetes risk,[23,24] which may be linked to insulin sensitivity[25]; furthermore, diabetes has been considered one of the main risk factors for PC.[26,27] Thus, we conducted subgroup analyses to exclude the influence of diabetes, and the results of cohort studies indicated that red and processed meat consumption did not contribute to the increased PC risk.

Study Strengths and Limitations

Our study has several strengths. The first strength was the large and substantial sample size, which provided the most reliable and robust evidence to date and increased the statistical power of the analysis. Second, we estimated the separated effects according to study design and gender and performed subgroup analyses according to potential confounding factors of the included studies and the main adjustments of PC. These independent detailed data increased the significant power of the analysis and provided more detailed evidence of reference significance for dietary guidelines concerning PC worldwide. Third, studies were identified from 16 countries in America, Europe, and Asia, which increased the statistical generalizability. Fourth, a dose-response analysis was conducted to assess these associations rather than simply performing categorical comparisons. Finally, the authors of the

articles were contacted directly to request additional data and definitions, somewhat reducing publication bias.

However, several limitations of the present meta-analysis must be considered. First, the included studies were observational, and residual confounding and unmeasured factors cannot be excluded. Nevertheless, most included studies were adjusted for potential confounders including sex, age, energy intake, body mass index, physical activity, smoking, alcohol use, and family history of diabetes mellitus. Furthermore, we performed subgroup analyses that were based on the main adjustment for confounders. Generally, our findings were similar to the overall pooled estimates and were consistent for each of the subgroup analyses. Yet, most of the included studies in relation to PC lacked information concerning family history of PC. In addition, red and processed meat consumption is often associated with a higher fat intake, a fact that should not be ignored. Furthermore, production methods, storage conditions, and the cooking and preparation of red and processed meat might have differed between the included studies. Therefore, our results should be interpreted carefully because of these potential confounding factors.

Second, our analyses showed significant heterogeneity among the studies, which may be related to the study design, publication year, number of cases, geographic region, method of exposure measurement, quality score of the study, classification of meat consumption, and other confounders. Part of our data derived from case-control studies, and many included case-control studies provided exposure information obtained after cancer diagnosis, which may be subject to inaccurate measurements of dietary consumption and recall bias. Thus, the overall results of cohort studies and case-control studies could not be combined, and we provided the separated estimates according to study design. Furthermore, we performed subgroup analyses to avoid the influence of confounders and used meta-regression analyses to explore sources of heterogeneity. However, the range from the lowest to highest categories varied, and the consumption levels of red and processed meat between the lowest and highest categories differed between the included studies. Heterogeneity was observed mainly in the overall analysis comparing the highest versus lowest consumption of red and processed meat, which can be explained, at least in part, by the different categories of meat consumption. Thus, we used random-effects models to account for heterogeneity.

Third, we did not perform analyses for subtypes of red and processed meat. In addition, because our results are based on the diagnosis of PC only, the available data should not be used inattentively to analyze other pancreatic lesions such as pancreatic intraepithelial neoplasia and pancreatic benign tumors.

Finally, despite meeting the eligibility criteria, the quality of several of the included studies was not high, and the sample size of several studies regarding our topic was not large (Supplementary Table 3). However, the subgroup analyses of quality score and sample size addressed these issues.

Conclusions

The present analysis provided evidence that red and processed meat consumption was positively associated with PC risk in case-control studies, whereas no overall association was observed in cohort studies. Notably, red and processed meat consumption may increase PC risk in men but not in women.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2016.09.143.

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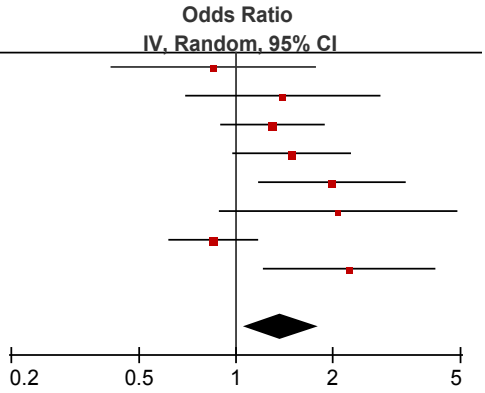
Conflicts of interest
The authors disclose no conflicts.

A

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
La Vecchia 1990	-0.1625	0.372	8.8%	0.85 [0.41, 1.76]	1990
Anderson 2002	0.3365	0.3537	9.4%	1.40 [0.70, 2.80]	2002
Chan 2007	0.2624	0.1876	16.9%	1.30 [0.90, 1.88]	2007
Anderson 2009	0.3988	0.2138	15.5%	1.49 [0.98, 2.27]	2009
Polesel 2010	0.6881	0.2666	12.8%	1.99 [1.18, 3.36]	2010
Ghadirian 2010	0.7324	0.4331	7.2%	2.08 [0.89, 4.86]	2010
Jansen 2013	-0.1625	0.161	18.4%	0.85 [0.62, 1.17]	2013
Ghorbani 2015	0.8109	0.3123	10.9%	2.25 [1.22, 4.15]	2015
Total (95% CI)			**100.0%**	**1.38 [1.05, 1.81]**	

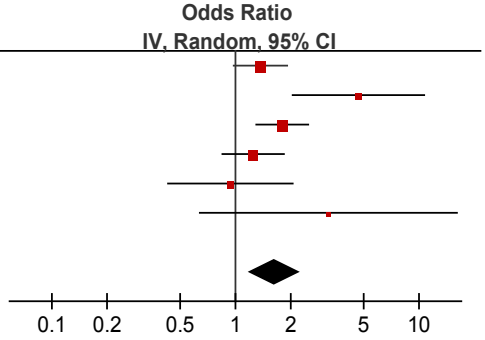
Heterogeneity: Tau² = 0.08; Chi² = 15.51, df = 7 (P = 0.03); I² = 55%
Test for overall effect: Z = 2.34 (P = 0.02)



B

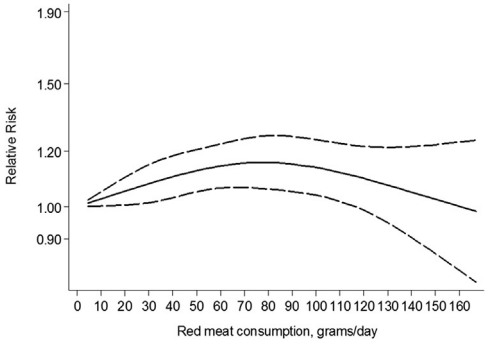
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
La Vecchia 1990	0.3148	0.1709	25.1%	1.37 [0.98, 1.92]	1990
Ghadirian 1995	1.5433	0.4212	10.9%	4.68 [2.05, 10.68]	1995
Chan 2007	0.5878	0.166	25.5%	1.80 [1.30, 2.49]	2007
Polesel 2010	0.2231	0.1968	23.1%	1.25 [0.85, 1.84]	2010
Ghadirian 2010	-0.0619	0.399	11.7%	0.94 [0.43, 2.05]	2010
Liu 2014	1.1663	0.8227	3.7%	3.21 [0.64, 16.10]	2014
Total (95% CI)			**100.0%**	**1.62 [1.17, 2.26]**	

Heterogeneity: Tau² = 0.08; Chi² = 11.77, df = 5 (P = 0.04); I² = 58%
Test for overall effect: Z = 2.87 (P = 0.004)



Supplementary Figure 1. Forest plots of case-control studies for red and processed meat consumption (highest vs lowest category) and PC risk (random-effects model). (*A*) Red meat; (*B*) processed meat. SE, standard error.

A



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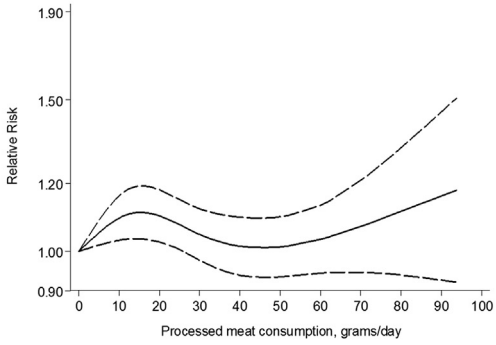
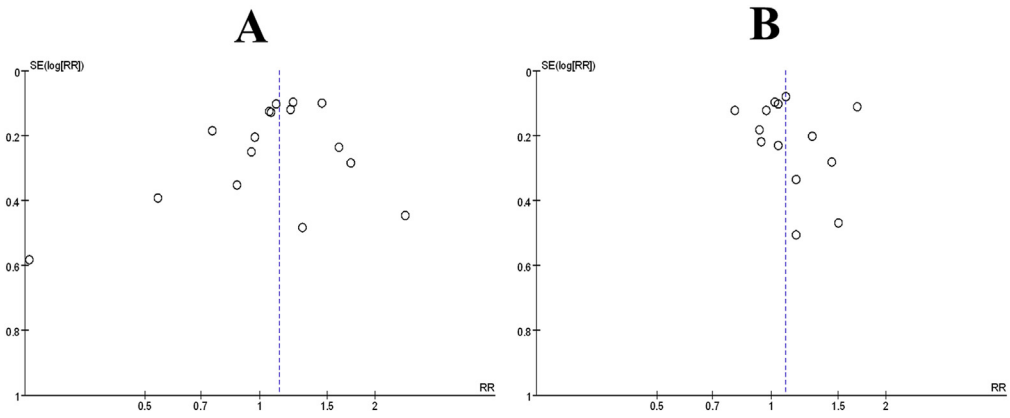


Supplementary Figure 2. Nonlinear associations between (*A*) red meat consumption and (*B*) processed meat consumption and PC risk.



Supplementary Figure 3. Funnel plots of cohort studies evaluating publication bias of (*A*) red meat and (*B*) processed meat consumption and PC risk. SE, standard error.

Supplementary Table 1. Subgroup Analyses of Cohort Studies for Red and Processed Meat Consumption and PC Risk

	Red meat							Processed meat						
Subgroups	n	RR (95% CI)	P_o	P_s	I_s^2 (%)	P_h	I_h^2 (%)	n	RR (95% CI)	P_o	P_s	I_s^2 (%)	P_h	I_h^2 (%)
All studies	16	1.12 (0.98–1.28)	.09	<.01	52			14	1.09 (0.96–1.23)	.18	.02	51		
Geographic area														
Europe	5	0.93 (0.65–1.34)	.71	.02	67			4	0.88 (0.74–1.04)	.13	.73	0		
America	9	**1.21 (1.08–1.35)**	**<.01**	.20	28			8	**1.17 (1.01–1.36)**	**.04**	.01	60		
Asia	2	0.80 (0.34–1.86)	.60	.16	49	.27	23.8	2	1.16 (0.67–2.01)	.60	1	0	.04	68.8
Sample size														
<200	7	1.15 (1.02–1.29)	.02	.07	45			6	1.12 (0.90–1.39)	.31	.90	0		
≥200	9	0.99 (0.63–1.56)	.95	.01	63	.52	0	8	1.08 (0.92–1.26)	.36	<.01	72	.77	0
Publication year														
Before 2010	10	1.10 (0.89–1.36)	.38	<.01	63			8	1.15 (0.93–1.42)	.19	.03	56		
2010 or later	6	1.14 (0.98–1.33)	.08	.21	31	.77	0	6	1.02 (0.91–1.15)	.73	.28	21	.32	0
Quality score														
<7 stars	3	0.71 (0.20–2.46)	.59	<.01	82			1	1.50 (0.60–3.75)	.39	—	—		
≥7 stars	13	**1.15 (1.04–1.28)**	**<.01**	.12	33	.45	0	13	1.08 (0.96–1.22)	.21	.01	54	.49	0
Adjustments														
Smoking														
Yes	16	1.12 (0.98–1.28)	.09	<.01	52			12	1.09 (0.96–1.23)	.18	.02	51		
No	0	—	—	—	—	—	—	2	2.38 (0.72–7.90)	.16	<.01	86	.20	38.8
Alcohol														
Yes	7	1.08 (0.86–1.35)	.51	.03	57			5	1.02 (0.87–1.19)	.79	.87	0		
No	9	1.16 (0.98–1.36)	.09	.04	50	.62	0	9	1.12 (0.94–1.32)	.20	<.01	67	.45	0
BMI														
Yes	10	1.05 (0.90–1.22)	.53	.03	52			9	1.01 (0.93–1.10)	.81	.58	0		
No	6	1.31 (1.05–1.63)	.02	.20	31	.10	62	5	1.51 (1.26–1.81)	<.01	.43	0	<.01	93.7
Energy intake														
Yes	10	1.14 (0.98–1.34)	.09	.01	56			12	1.07 (0.95–1.22)	.27	<.01	57		
No	6	1.05 (0.80–1.38)	.72	.08	49	.59	0	2	1.37 (0.85–2.22)	.20	.71	0	.34	0
Diabetes														
Yes	10	1.13 (0.99–1.28)	.07	.03	51			10	1.09 (0.95–1.26)	.22	<.01	65		
No	6	1.11 (0.72–1.71)	.64	.02	61	.94	0	4	1.04 (0.78–1.38)	.78	.83	0	.76	0
Family history Of PC														
Yes	3	**1.24 (1.05–1.47)**	**.01**	.15	48			3	1.23 (0.93–1.62)	.14	<.01	84		
No	13	1.06 (0.89–1.26)	.05	.02	51	.20	40.1	11	0.99 (0.89–1.10)	.86	.64	0	.15	52.3

NOTE. Boldface indicates statistical significance.

BMI, body mass index; I_h^2, I^2 value for heterogeneity between subgroups; I_s^2, I^2 value for heterogeneity within each subgroup; P_h, P value for heterogeneity between subgroups; P_o, test for over effect; P_s, P value for heterogeneity within each subgroup.

Supplementary Table 2. Subgroup Analyses of Case-control Studies for Red and Processed Meat Consumption and PC Risk

	Red meat							Processed meat						
Subgroups	n	OR (95% CI)	P_o	P_s	I_s^2 (%)	P_h	I_h^2 (%)	n	OR (95% CI)	P_o	P_s	I_s^2 (%)	P_h	I_h^2 (%)
All studies	8	**1.38 (1.05–1.81)**	**.01**	.03	55			6	**1.62 (1.17–2.26)**	**<.01**	.04	58		
Geographic area														
Europe	2	1.35 (0.59–3.10)	.48	.06	71			2	**1.32 (1.02–1.70)**	**.03**	.72	0		
America	5	1.25 (0.94–1.67)	.13	.11	47			3	1.95 (0.95–4.01)	.07	.02	74		
Asia	1	2.22 (1.22–4.15)	<.01	—	—	.23	31.4	1	3.21 (0.64–16.10)	.16	—	—	.36	2.5
Sample size														
<200	2	1.64 (0.96–2.81)	.07	.48	0			2	2.09 (0.43–10.05)	.36	<.01	87		
≥200	6	1.34 (0.97–1.84)	.07	.01	65	.52	0	4	**1.50 (1.22–1.84)**	**.03**	.36	6	.68	0
Publication year														
Before 2010	4	1.31 (1.03–1.67)	.03	.63	0			3	1.96 (1.20–3.20)	<.01	.02	73		
2010 or later	4	1.60 (0.90–2.84)	.11	<.01	78	.53	0	3	1.24 (0.88–1.73)	.22	.40	0	.13	57.1
Quality score														
<7 stars	4	1.56 (1.07–2.28)	.02	.21	34			5	1.61 (1.03–2.51)	.04	.03	62		
≥7 stars	4	1.27 (0.87–1.85)	.21	.04	65	.45	0	1	1.80 (1.30–2.49)	<.01	—	—	.69	0
Adjustments														
Smoking														
Yes	6	**1.46 (1.03–2.07)**	**.03**	.02	64			4	**1.47 (1.07–2.02)**	**.02**	.23	30		
No	2	1.22 (0.72–2.07)	.45	.19	42	.58	0	2	2.38 (0.72–7.90)	.16	<.01	86	.44	0
Alcohol														
Yes	2	**2.10 (1.41–3.12)**	**<.01**	.76	0			1	1.25 (0.85–1.84)	.26	—	—		
No	6	1.19 (0.92–1.55)	.18	.14	39	.02	81.4	5	1.78 (1.17–2.70)	<.01	.04	61	.22	32.7
BMI														
Yes	4	1.42 (0.91–2.21)	.12	<.01	76			2	**1.52 (1.07–2.17)**	**.02**	.16	50		
No	4	1.40 (1.03–1.89)	.03	.44	0	.95	0	4	1.88 (0.94–3.75)	.07	.02	69	.59	0
Energy intake														
Yes	2	**2.01 (1.29–3.14)**	**<.01**	.93	0			2	1.18 (0.84–1.67)	.34	.52	0		
No	6	1.25 (0.94–1.67)	.13	.05	54	.08	67.5	4	2.01 (1.28–3.16)	<.01	.04	63	.07	70.3
Diabetes														
Yes	6	**1.46 (1.03–2.07)**	**.03**	.02	64			4	**1.47 (1.07–2.02)**	**.02**	.23	30		
No	2	1.22 (0.72–2.07)	.45	.19	42	.58	0	2	2.38 (0.72–7.90)	.16	<.01	86	.44	0
Family history Of PC														
Yes	0	—	—	—	—			0	—	—	—	—		
No	8	1.38 (1.05–1.81)	.01	.03	55	—	—	6	1.62 (1.17–2.26)	<.01	<.04	58	—	—

NOTE. Boldface indicates statistical significance.
BMI, body mass index; I_h^2, I^2 value for heterogeneity between subgroups; I_s^2, I^2 value for heterogeneity within each subgroup; P_h, P value for heterogeneity between subgroups; P_o, test for over effect. P_s, P value for heterogeneity within each subgroup.

Supplementary Table 3. Meta-regression Analyses of Cohort Studies for Red and Processed Meat Consumption and PC Risk

Variable	Coefficient	Standard error	P value	95% CI
Red meat				
Geographic area	0.3832338	0.1407418	**.021**	0.0696415–0.6968261
Sample size	−0.0001205	0.0001182	.332	−0.0003838 to 0.0001429
Publication year	−0.0717394	0.0782376	.381	−0.2460636 to 0.1025847
Quality score	0.1738007	0.0896026	.081	−0.2584650 to 0.3734478
Processed meat				
Geographic area	0.3628519	0.1166296	**.012**	0.0990174–0.6266863
Sample size	−0.0000574	0.0001228	.651	−0.0003352 to 0.0002204
Publication year	−0.0220412	0.0145886	.165	−0.0550429 to 0.0109605
Quality score	0.1809876	0.0926502	.083	−0.0860170 to 0.3905768

NOTE. Boldface indicates statistical significance.

Supplementary Table 4. Subgroup Analyses of Cohort Studies for PC According to Gender

Subgroups	N	RR (95% CI)	P_o	P_h	I^2 (%)
Red meat					
Male	8	**1.21 (1.07–1.37)**	**<.01**	.33	13
Female	7	1.06 (0.85–1.31)	.61	.16	36
Processed meat					
Male	8	**1.18 (1.06–1.31)**	**<.01**	.43	0
Female	6	0.99 (0.84–1.16)	.88	.76	0

NOTE. Boldface indicates statistical significance.
I^2, I^2 value for heterogeneity within each subgroup; P_h, P value for heterogeneity between subgroups; P_o, test for over effect.

Supplementary Table 5. Baseline Characteristics of Included Studies of Red Meat Consumption and PC Risk

First author	Year	Country	Study type	Case/control (cohort, n)	Study population	Study period	Method	Type of meat	Exposure categories	RR/OR, 95% CI	Controlled variables	Quality score
La Vecchia[1]	1990	Italy	cc	247/1089	Men & women	1983–1988	FFQ-14	Liver	Tertile	0.85 (0.41–1.77)	Age and sex	6
Zheng[2]	1993	USA	co	57/17,818	Men	1966–1986	FFQ-185	Red meat	Quartile	2.40 (1.00–6.10)	Age, smoking, alcohol, and total calories	6
Coughlin[3]	2000	USA	co	1967/483,109	Men	1982–1994	FFQ-NS	Red meat	Quartile	1.10 (0.90–1.20)	Age, race, education, family history of PC, history of cholecystectomy, BMI, smoking, alcohol, citrus fruit juices, vegetable, and history of diabetes	8
Anderson[4]	2002	USA	cc	193/674	Men & women	1994–1998	FFQ-151	Fried red meat	Quintile	1.40 (0.70–2.60)	Age, sex, smoking, education, race, diabetes, white meat, red meat not fried, and other red meat	8
Isaksson[5]	2002	Sweden	co	176/21,884	Men & women	1969–1997	FFQ-NS	Pork	Quartile	0.25 (0.08–0.81)	Age, sex, BMI, and smoking	6
Stolzenberg-Solomon[6]	2002	Finland	co	163/27,111	Men	1985–1997	FFQ-200	Red meat	Quintile	0.95 (0.58–1.56)	Energy intake, age, and smoking	9
Michaud[7]	2003	USA	co	178/88,802	Women	1976–1990	FFQ-130	Red meat	Quintile	0.87 (0.46–1.65)	Smoking, BMI, history of diabetes, energy intake, physical activity, menopausal status, and glycemic load intake	8
Nothlings[8]	2005	USA	co	482/190,545	Men & women	1993–2003	FFQ-NS	Beef, pork, lamb	Quintile	1.45 (1.19–1.76)	Sex, age at cohort entry, ethnicity, history of diabetes, familial history of PC, smoking, and energy intake	9
Larsson[9]	2006	Sweden	co	172/61,433	Women	1987–2004	FFQ-350	Red meat	Quartile	1.73 (0.99–2.98)	Age, education, BMI, smoking, total energy, and alcohol	8
Lin[10]	2006	Japan	co	107/110,792	Men & women	1990–1999	FFQ-33	Pork	Tertile	1.29 (0.50–3.32)	Age, area, and smoking	7
Chan[11]	2007	USA	cc	532/1701	Men & women	1995–1999	FFQ-131	All red meat	Quartile	1.30 (0.90–1.80)	Age, sex, BMI, race, education, smoking, and history of diabetes	8
Stolzenberg-Solomon[12]	2007	USA	co	836/537,302	Men & women	1995–2001	FFQ-124	Red meat	Quintile	1.06 (0.83–1.35)	Age, energy, smoking, BMI, education, race, self-reported diabetes, and energy-adjusted saturated fat	8

Anderson[13]	2009	Canada	cc	422/312	Men & women	2003–2007	PHQ CPQ FHQ	Red meat	Tertile	1.49 (0.98–2.28)	Age	6
Heinen[14]	2009	Netherlands	co	350/120,852	Men & women	1986–1999	FFQ-150	Red meat	Quintile	0.75 (0.52–1.09)	Gender, age, energy, smoking, alcohol, history of diabetes, history of hypertension, BMI, vegetables, and fruit	8
Ghadirian[15]	2010	Canada	cc	179/239	Men & women	NR	FFQ-200	Pork	Quartile	2.08 (0.89–4.84)	Age, smoking, diabetes status, proxy use, gender, and total energy intake	6
Polesel[16]	2010	Italy	cc	326/652	Men & women	1991–2008	FFQ-78	Red meat	Quintile	1.99 (1.18–3.36)	Center, gender, age, year of interview, education, smoking, alcohol, self-reported history of diabetes, BMI, and total energy	7
Inoue-Choi[17]	2011	USA	co	256/34,642	Women	1986–2007	FFQ-42	Red meat	Quintile	0.97 (0.65–1.44)	Age, race, education, alcohol, smoking, and physical activity	7
Anderson[18]	2012	USA	co	248/62,581	Men & women	1993–2007	FFQ-170	Red meat	Quintile	1.61 (1.01–2.54)	Age, sex, education, race, diabetes, dietary fat intake, and smoking	8
Jansen[19]	2013	USA	cc	384/983	Men & women	2004–2009	FFQ-144	Red meat	Quartile	0.85 (0.62–1.15)	BMI, smoking, history of diabetes, education, race, total white meat, and total red meat not grilled/barbecued	8
Rohrmann[20]	2013	Europe	co	865/477,202	Men & women	1992–2008	FFQ-NS	Red meat	Quartile	1.07 (0.83–1.38)	BMI, physical activity, smoking, education, history of diabetes, and energy intake	9
Ghorbani[21]	2015	Iran	cc	307/322	Men & women	2011–2014	FFQ-NS	Red meat	Quartile	2.25 (1.22–4.14)	Gender, age, BMI, education, diabetes, alcohol, smoking, and opium use	6
Jiao[22]	2015	USA	co	1407/528,251	Men	1995–2006	FFQ-170	Red meat	Quintile	1.20 (0.95–1.53)	Race, education, diabetes, smoking, family history of cancer, BMI, alcohol, age, energy and carbohydrate intake, saturated fat, and N-(carboxymethyl)lysine advanced glycation end products	9

Supplementary Table 5. Continued

First author	Year	Country	Study type	Case/control (cohort, n)	Study population	Study period	Method	Type of meat	Exposure categories	RR/OR, 95% CI	Controlled variables	Quality score
Ghorbani[23]	2016	Iran	co	54/50,045	Men & women	2004–2015	FFQ-116	Red meat	Tertile	0.54 (0.25–1.16)	History of diabetes, smoking, education, alcohol, opium, BMI, age, total energy intake, gender, MET, wealth score, and area	6
Taunk[24]	2016	USA	co	1417/322,846	Men & women	1995–2005	FFQ-124	Red meat	Quintile	1.22 (1.01–1.48)	Age, energy, smoking, BMI, education, race, self-reported diabetes, and energy-adjusted saturated fat	9

BMI, body mass index; cc, case-control; co, cohort; CPQ, clinical patient questionnaire; FFQ, food frequency questionnaire; FHQ, family history questionnaire; MET, metabolic equivalent task; NR, not reported; NS, not specified; PHQ, personal history (epidemiology) questionnaire.

Supplementary Table 6. Baseline Characteristics of Included Studies of Processed Meat Consumption and PC Risk

Author	Year	Country	Study type	Case/ control (cohort, n)	Study population	Study period	Method	Type of meat exposure	Exposure categories	RR/OR, 95% CI	Controlled variables	Quality score
La Vecchia[1]	1990	Italy	cc	247/1089	Men & women	1983–1988	FFQ-14	Ham	Tertile	1.37 (0.98–1.92)	Age and sex	6
Zheng[2]	1993	USA	co	57/17,818	Men	1966–1986	FFQ-185	Salted/smoked	Quartile	1.50 (0.60–3.40)	Age, smoking, alcohol, and total calories	6
Ghadirian[25]	1995	Canada	cc	179/239	Men & women	1984–1988	FFQ-20	Smoked meat	Quartile	4.68 (2.05–10.69)	Age and sex	6
Stolzenberg-Solomon[6]	2002	Finland	co	163/27,111	Men	1985–1997	FFQ-200	Processed meat	Quintile	1.04 (0.66–1.65)	Energy intake by the residual method (except coffee and tea) and adjusted for age, and years of smoking	9
Michaud[7]	2003	USA	co	178/88,802	Women	1976–1990	FFQ-130	Processed meat	Quintile	1.28 (0.86–1.92)	Smoking, BMI, history of diabetes, energy intake, physical activity, menopausal status, and glycemic load intake	8
Nothlings[8]	2005	USA	co	482/190,545	Men & women	1993–2003	FFQ-NS	Processed meat	Quintile	1.68 (1.35–2.07)	Sex, age at cohort entry, ethnicity, history of diabetes, familial history of PC, smoking, and energy intake	9
Larsson[26]	2006	Sweden	co	172/61,433	Women	1987–2004	FFQ-350	Processed meat	Quartile	0.94 (0.61–1.44)	Age, education, BMI, smoking, total energy, and alcohol	8
Lin[10]	2006	Japan	co	135/110,792	Men & women	1990–1999	FFQ-33	Ham and sausage	Tertile	1.16 (0.43–3.19)	Age, area, smoking	7
Chan[11]	2007	USA	cc	526/1701	Men & women	1995–1999	FFQ-131	Sausage, kielbasa, etc	Quartile	1.80 (1.30–2.60)	Age, sex, BMI, race, education, smoking, and history of diabetes	8
Stolzenberg-Solomon[12]	2007	USA	co	836/537,302	Men & women	1995–2001	FFQ-124	Processed meat	Quintile	0.97 (0.76–1.23)	Age, energy, smoking, BMI, education, race, self-reported diabetes, and energy-adjusted saturated fat	8
Heinen[14]	2009	Netherlands	co	350/120,852	Men & women	1986–1999	FFQ-150	Processed meat	Quintile	0.93 (0.65–1.35)	Gender, age, energy, smoking, alcohol, history of diabetes, history of hypertension, BMI, vegetables, and fruit	8
Ghadirian[15]	2010	Canada	cc	179/239	Men & women	NR	FFQ-200	Sausage, luncheon meat	Quartile	0.94 (0.43–2.03)	Age, smoking, diabetes status, proxy use, gender, and total energy intake	6

Supplementary Table 6. Continued

Author	Year	Country	Study type	Case/ control (cohort, n)	Study population	Study period	Method	Type of meat exposure	Exposure categories	RR/OR, 95% CI	Controlled variables	Quality score
Polesel[16]	2010	Italy	cc	326/652	Men & women	1991–2008	FFQ-78	Processed meat	Tertile	1.25 (0.85–1.84)	Center, gender, age, year of interview, education, smoking, alcohol, self-reported history of diabetes, BMI, and total energy	6
Aschebrook-Kilfoy[27]	2011	USA	co	1728/303,156	Men & women	1995–2006	FFQ-124	Processed meat	Quintile	1.09 (0.93–1.29)	Age, race, total energy intake, smoking, family history of cancer and diabetes, BMI, intakes of saturated fat, folate, and vitamin C	8
Anderson[18]	2012	USA	co	248/62,581	Men & women	1993–2007	FFQ-170	Bacon and sausage	Tertile	1.44 (0.83–2.51)	Age, sex, education, race, diabetes, dietary fat intake, and smoking	8
Rohrmann[20]	2013	Europe	co	865/477,202	Men & women	1992–2008	FFQ-NS	Processed meat	Quartile	0.80 (0.63–1.02)	BMI, physical activity, smoking, education, history of diabetes, and total energy intake	9
Liu[28]	2014	China	cc	323/323	Men & women	2011–2013	FFQ-NS	Bacon	Tertile	3.21 (0.64–16.11)	Center, sex, and age, smoking, and history of diabetes	6
Jiao[22]	2015	USA	co	1407/528,251	Men	1995–2006	FFQ-170	Processed meat	Quintile	1.04 (0.85–1.27)	Race, education, diabetes, smoking status, first-degree family history of PC, BMI, alcohol, age, calories, and carbohydrate intake, saturated fat, and N-(carboxymethyl)lysine advanced glycation end products	9
Ghorbani[23]	2016	Iran	co	54/50,045	Men & women	2004–2015	FFQ-116	Processed meat	Tertile	1.16 (0.60–2.22)	History of diabetes, BMI, smoking, education, alcohol, opium, age, total energy intake, gender, MET, wealth score, and area	7
Taunk[24]	2016	USA	co	1417/322,846	Men & women	1995–2005	FFQ-124	Processed meat	Quintile	1.02 (0.95–1.24)	Age, energy, smoking, BMI, education, race, self-reported diabetes, and energy-adjusted saturated fat	9

BMI, body mass index; cc, case-control; co, cohort; FFQ, food frequency questionnaire; MET, metabolic equivalent task; NR, not reported; NS, not specified.

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