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Review Article

No association between pesticide exposure and pancreatic cancer risk: a meta-analysis

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Abstract: Objective: Association between pesticide exposure and pancreatic cancer risk has been conflicting and poorly explored. This present study conducted a meta-analysis to quantitatively assess the association between pesticide exposure and incidence of pancreatic cancer. Methods: Systematic searches of PubMed and Embase databases, up to October 2017, were conducted to identify relevant studies. Studies that reported relative estimates with 95% confidence intervals for association between pesticide exposure and pancreatic cancer risk were included. Fixed or random effects models were used to calculate summary risk estimates. Results: Eleven studies were included in the meta-analysis. Comparing the highest with the lowest pesticide exposure, there was no association between pancreatic cancer incidence and pesticide exposure when all studies were analyzed (odds ratio [OR] = 1.02; 95% CI, 0.69-1.35). Significant heterogeneity was observed across these studies (P = 0.007, I^2 = 62.1%). Publication bias was revealed according to asymmetry of the Begg's funnel plot. Subgroup analysis showed that pesticide exposure was associated with a significant increased risk of pancreatic cancer in case-control studies (OR = 1.47; 95% CI, 1.13-1.93), but a decreased risk in prospective cohort studies (OR = 0.56; 95% CI, 0.30-0.82). Conclusion: The present meta-analysis suggests no association between pesticide exposure and risk of pancreatic cancer. Further well-designed studies are warranted to confirm this association.

Keywords: Epidemiology, meta-analysis, pancreatic cancer, pesticide exposure

Introduction

Pancreatic cancer is one of the most lethal malignancies in developed and developing countries [1]. Incidence of this disease has increased rapidly over recent years. Most patients have an extremely poor prognosis, as pancreatic cancer progresses rapidly and most therapies have limited benefit [2]. The etiology of pancreatic cancer remains unclear. Cigarette smoking is the most established risk factor for pancreatic cancer, yet only about 25% of newly diagnosed cases can be attributed to smoking [3]. Several occupational exposures have been linked to excess risk of pancreatic cancer, however, most associations have not been well established [4].

Agricultural occupations have been associated with increased risk of pancreatic cancer in some studies [5-7]. Specific agricultural agents that may be responsible for these excesses have been linked to pesticides. Pesticides have been reported to be toxic to organs. Previous meta-analyses have shown that exposure to pesticides is associated with increased risk of childhood leukemia, as well as kidney and bladder cancer [8-10]. Epidemiological investigations of exposure to pesticides and risk of pancreatic cancer have been carried out. Results of these findings, however, have been inconsistent. Some studies have demonstrated exposure as a significant risk factor for pancreatic cancer [11, 12], whereas others have not revealed significant effects [13, 14]. These inconsistent conclusions may be due to relatively small sample sizes or heterogeneity among different populations. Therefore, the purpose of the present study was to reassess the relationship between exposure to pesticides and risk of pancreatic cancer by conducting a meta-analysis on all relevant published epidemiological studies.

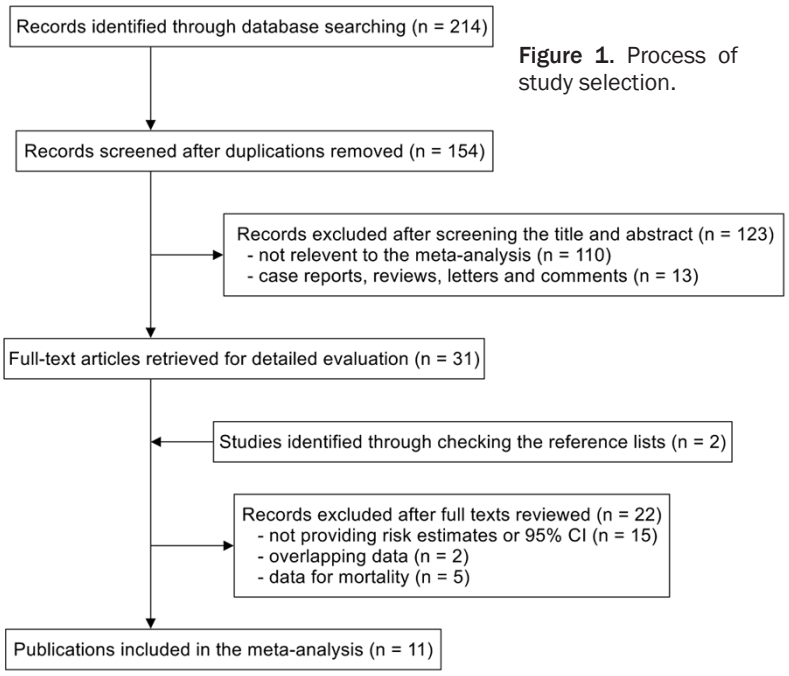

Figure 1. Process of study selection.

Methods

Search strategy

The study selection process was performed following PRISMA [15]. This study searched PubMed and Embase databases for relevant studies published, up through October 2017. This search was carried out using the free text words: "pesticide OR herbicide OR fungicide OR insecticide" and "pancreas OR pancreatic" and "neoplasm OR cancer". The search was limited to English language articles. Reference lists of related studies, reviews, or meta-analyses were also checked. All searches were performed, independently, by two investigators. Differences were resolved by discussion.

Selection criteria

All studies investigating association between pesticide exposure and incidence of pancreatic cancer were considered relevant to this meta-analysis. Inclusion criteria were as follows: 1) Exposure of interest was any type of pesticides; 2) For outcomes, incidence of pancreatic cancer was reported; and 3) Risk estimates, such as relative risk (RR) or odds ratio (OR) with 95% confidence intervals (CIs), were given. Case reports, letters, review articles, and comments were excluded during the process of study selection. Studies reporting pancreatic cancer in agricultural and related occupations, but lacking information on pesticides exposure, were also excluded. Concerning studies that reported results using the same or overlapping data, only the study with the largest number of patients was included.

Data extraction

Data from each study were independently extracted from all potential publications, including name of first author, publication year, design of study, country, number of cases and participants, verification of pancreatic cancer, type of pesticide assessed, adjusted factors, risk estimates for the highest compared with lowest category of pesticide exposure with corresponding 95% CIs, and exposure assessment. Since pancreatic cancer is a relatively rare disease, RR was assumed to be approximately the same as OR, with the OR used as the study outcome. If a study provided several ORs, the ORs reflecting the greatest degree of control for potential confounders were selected.

Study quality assessment

All included studies were non-randomized studies. Quality of these studies was assessed according to the Newcastle-Ottawa scale [16], recommended by the Cochrane Collaboration. Stars were allocated to each study with a range of 0-9 and total points of < 7 and ≥ 7 were assigned for low and high quality studies, respectively.

Statistical analyses

Summary ORs and 95% CIs were calculated by combining study specific estimates with a fixed or random effects model, depending on between-study heterogeneity [17, 18]. Heterogeneity between studies was identified using the standard Cochran's Q test [18] and I^2 statistic [19]. An I^2 statistic of 50% or more or a value of $P < 0.10$ for the Q-test indicates a consider-

Table 1. Characteristics of included epidemiological studies on exposure of pesticides and pancreatic cancer

Authors and publication year	Study design	Country	Study period	Cases/ subjects	Verification of pancreatic cancer	Type of pesticide	Study quality	Variables of adjustment	Exposure assessment
Wiklund et al. 1989	Cohort	Sweden	1965-1982	12/20245	Cancer register	Pesticides	5	Age and sex	Self-administered questionnaire
Kauppinen et al. 1995	Case-control	Finland	1984-1987	595/2217	Cancer register	Pesticides	8	Age, gender, tobacco smoking, diabetes mellitus, and alcohol consumption.	Self-administered questionnaire
Fryzek et al. 1997	Case-control	USA	1994-1995	66/197	Histologically confirmed	Insecticides, herbicides, rodenticides, DDT, ethylan	8	Age, gender, ethnicity, county group of residence, stomach ulcer, first degree relative with breast cancer.	Interview
Alguacil et al. 2000	Case-control	Spain	1992-1995	185/423	Histologically confirmed	Pesticides	8	Age, sex, hospital, and consumption of alcohol and of tobacco.	Interview
Ji et al. 2001	Case-control	USA	1986-1989	484/2529	Histologically confirmed	Pesticides, insecticides, fungicides, herbicides	8	Age, study area, gender, cigarette smoking, income and alcohol consumption.	Interview
Lo et al. 2007	Case-control	Egypt	2001-2004	194/388	Histologically confirmed	Pesticides	6	Age, sex, residence, and active smoking.	Interview
Andreotti et al. 2009	Cohort	USA	1993-2004	93/82596	Cancer register	Pesticides, herbicides, insecticides, fungicides	8	Age, cigarette smoking, diabetes, and applicator type.	Self-administered questionnaire
Santibanez et al. 2015	Case-control	Spain	1995-1999	161/616	Histologically confirmed	Pesticides	7	Age, sex, province, educational level, alcohol drinking and tobacco smoking.	Interview
Antwi et al. 2015	Case-control	USA	2000-2014	2092/4445	Histologically confirmed	Pesticides	7	Age, sex, smoking, diabetes, body mass index, and education.	Interview
Fritschi et al. 2015	Case-control	Australia	2007-2011	504/1147	Histologically confirmed	Pesticides, herbicides, insecticides, fungicides	7	Age, sex, smoking.	Interview
Louis et al. 2017	Cohort	USA	1993-2013	55/28909	Cancer register	Insecticides	7	Age, education, state of residence, pack-years smoked, and alcohol consumption.	Self-administered questionnaire

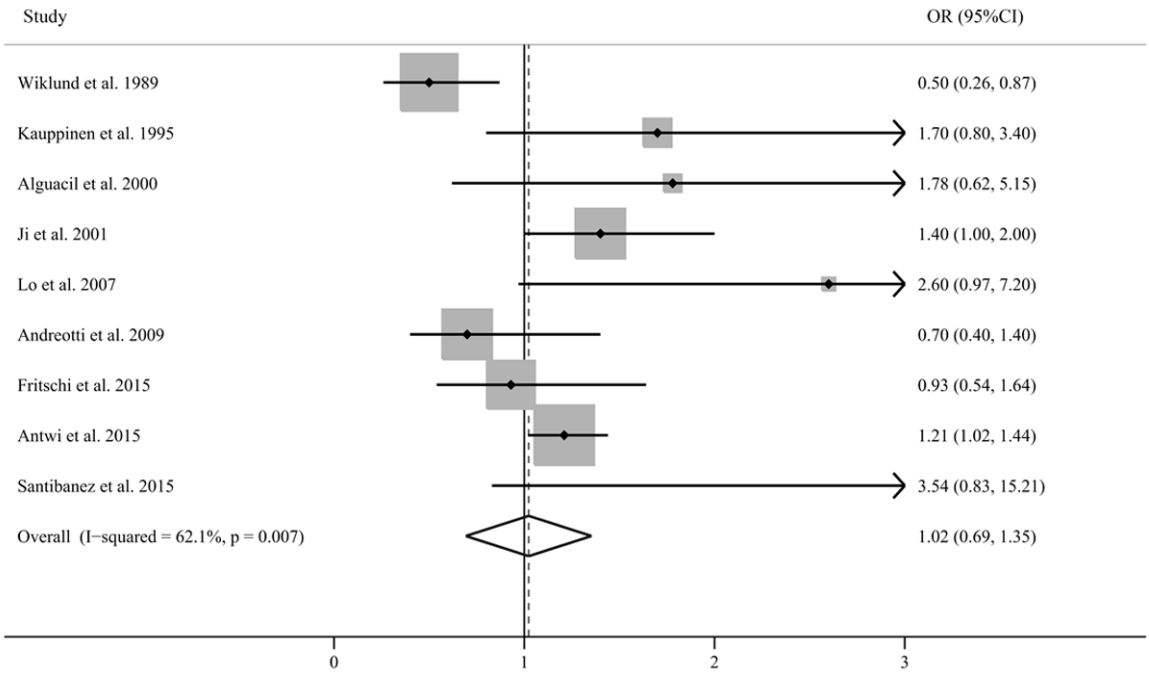

Figure 2. Forest plot showing risk estimates from included studies on association between pesticide exposure and risk of pancreatic cancer.

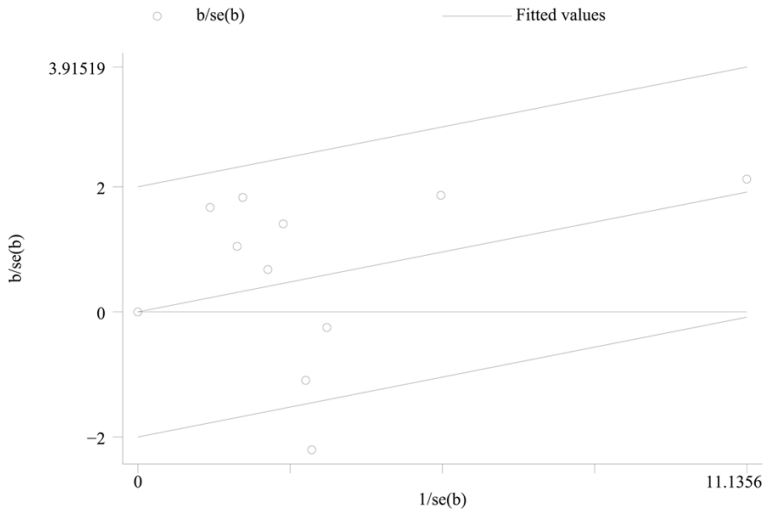

Figure 3. Galbraith plot showing that one study might have contributed to heterogeneity.

able level of heterogeneity [20]. Sensitivity analysis was performed to determine the influence of each study on the pooled OR by repeating the meta-analysis and omitting each study, one at a time. A Galbraith plot was also used to detect studies that contributed to heterogeneity [21]. Subgroup analyses stratified by study design, geographical region, study quality, method of exposure assessment, verification of pancreatic cancer, and number of confounding factors was performed. Meta-regression analysis was used to explore potential sources of heterogeneity. Potential publication bias was assessed using both Begg's [22] and Egger's [23] tests. Trim-and-fill method was used to evaluate publication bias if asymmetry was found on Begg's funnel plot [24]. Statistical significance was determined using the two-tailed test, where $P < 0.05$ is considered significant. STATA version 11 (Stata corporation, College station, Texas, U.S.A.) was employed to conduct all statistical analyses.

Results

Figure 1 demonstrates the detailed process of article identification and selection. A total of 11 studies were identified with data eligible for

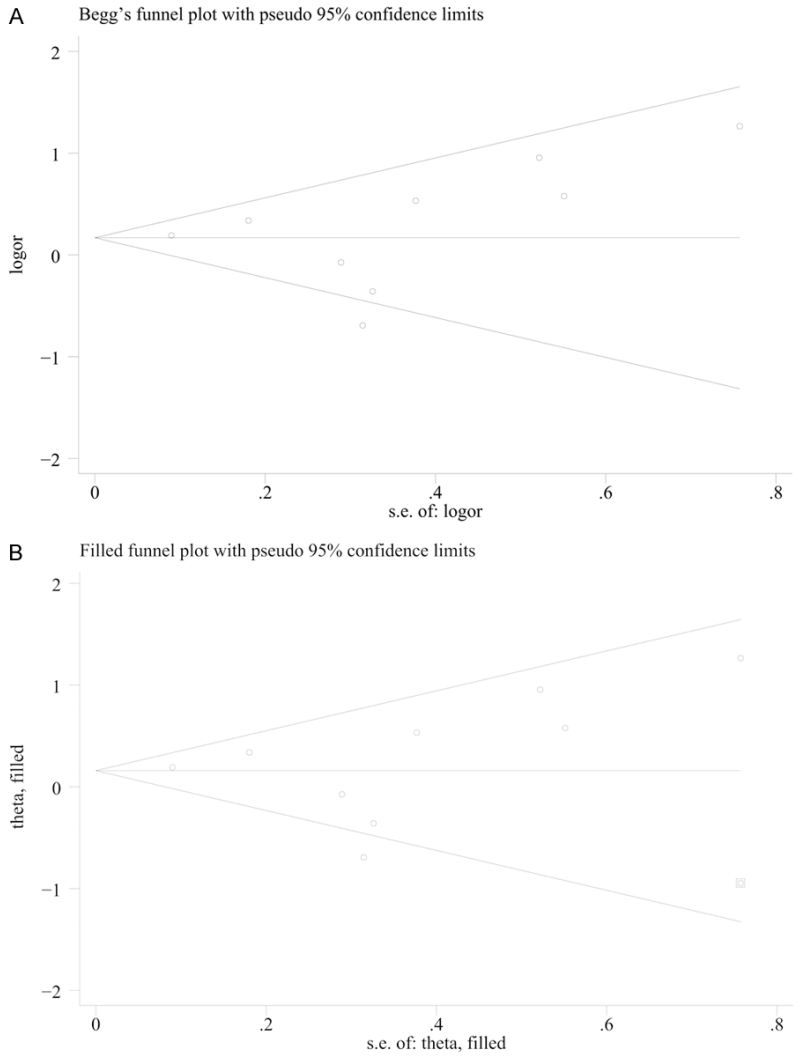

Figure 4. A. Funnel plot of pesticide exposure and risk of pancreatic cancer. B. The trim-and-fill test identified 1 possible missing study.

inclusion in this meta-analysis [5, 7, 13, 14, 25-32]. There were 3 cohort [13, 25, 33] and 8 case-control studies [5, 7, 14, 27, 28, 30-32]. Five studies were from the United States [7, 13, 27, 32, 33], four from Europe [5, 25, 28, 31], one from Egypt [30], and one from Australia [14]. Diagnosis of pancreatic cancer was made based on cancer register [5, 13, 25, 33] or histological diagnosis [7, 14, 27, 28, 30-32]. Pesticide exposure information was collected from interviews [7, 14, 27, 28, 30-32] or questionnaires [5, 13, 25, 33]. Quality scores of each study, assessed by the Newcastle-Ottawa Quality Assessment Scale (NOS), ranged from 5 to 8 (with a mean of 7.2). Nine articles were considered as high quality [5, 7, 13, 14, 27, 28, 31-33] and 2 articles as low quality [25, 30]. Nine studies provided ORs adjusted for more than 3 confounding factors [5, 7, 13, 27, 28, 30-33] and 2 studies adjusted less than or equal to three confounding factors [14, 25]. Nine studies considered total pesticides as the main exposure [5, 7, 13, 14, 25, 28, 30-32], whereas 5 studies investigated certain types of pesticides (herbicide, insecticide, or fungicide) [7, 13, 14, 27, 33]. Detailed characteristics of eligible studies are shown in **Table 1**.

Pooled ORs of the highest versus lowest level of pesticide exposure are shown in **Figure 2**. When these studies were analyzed together, no association was observed between pesticide exposure and risk of pancreatic cancer (OR = 1.02; 95% CI, 0.69-1.35), with significant heterogeneity among studies (p = 0.007, I^2 = 62.1%). A Galbraith plot revealed that the study by Wiklund et al. [25] was the major source of heterogeneity (**Figure 3**). After excluding this study, there was no study heterogeneity (P = 0.407, I^2 = 3.0%) and the combined OR (95% CI) was 1.16 (0.98-1.34). According to sensitivity analysis, excluding one study at a time, the summary OR for pancreatic cancer ranged from 1.01 (0.67-1.34), when the study by Lo et al. was excluded, to 1.16 (0.98-1.34), when the study by Wiklund et al. was excluded.

Visual inspection of Begg's funnel plot revealed asymmetry (**Figure 4A**). This raised the possibility of publication bias, although Egger's test was not statistically significant (P = 0.487). Therefore, sensitivity analysis using the trim and fill method was performed. This conservatively imputed hypothetical negative unpublished studies to mirror the positive studies

Table 2. Subgroup analysis of pesticides exposure and risk of pancreatic cancer by study design, sex, geographical region, study quality, number of adjusted factors, and type of pesticides

Outcome of interest	No. of studies	OR (95% CI)	$P_{heterogenity}$	I^2 (%)
Study design				
Cohort	2	0.56 (0.30, 0.82)	0.643	0
Case-control	7	1.47 (1.13, 1.93)	0.717	0
Geographical region				
Europe	4	1.02 (0.14, 1.90)	0.184	38.0
United States	5	1.13 (0.80, 1.46)	0.203	34.9
Egypt	1	2.60 (0.93, 7.23)	-	-
Australia	1	0.93 (0.53, 1.64)	-	-
Study quality				
High	7	1.16 (0.99, 1.33)	0.38	6.2
Low	2	0.52 (0.22, 0.82)	0.188	42.2
Number of adjusted factors				
> 3	7	1.19 (1.01, 1.37)	0.180	44.3
≤ 3	2	0.60 (0.33, 0.87)	0.375	7.0
Method of assessment				
Questionnaire	2	0.91 (0.27, 3.00)	0.013	83.9
Interview	7	1.15 (0.98, 1.33)	0.364	8.4
Verification of pancreatic cancer				
Histologically confirmed	7	1.18 (1.00, 1.36)	0.322	14.4
Cancer registry	4	0.65 (0.38, 0.91)	0.109	54.8
Type of pesticides				
Insecticides	4	0.66 (0.44, 0.89)	0.578	0
Herbicides	3	1.00 (0.58, 1.29)	0.642	0
Fungicides	3	0.69 (0.27, 1.11)	0.896	0

that caused funnel plot asymmetry. The imputed 1 study produced a symmetrical funnel plot (**Figure 4B**). Pooled analysis, incorporating hypothetical studies, also showed no significant association between pesticide exposure and pancreatic cancer (OR 1.12; 95% CI, 0.85-1.50, p < 0.001).

Next, stratified analyses were performed based on by various study characteristics (**Table 2**). First, a statistically significant protective effect of pesticide exposure on pancreatic cancer was observed in cohort studies (OR = 0.56; 95% CI, 0.30-0.82), while a significant positive association was observed in case-control studies (OR = 1.47; 95% CI, 1.13-1.93). There was no evidence of heterogeneity among both cohort and case-control studies (I^2 = 0). Next, pooled ORs grouped by geographical regions were calculated. Pooled OR was 1.02 (95% CI, 0.14-1.90) in European studies and 1.13 (95% CI 0.80-1.46) in American studies. According to separated analyses by study quality, a significant negative association between pesticide exposure and pancreatic cancer was observed in the low score group (OR = 0.52, 95% CI, 0.22-0.82), but a borderline positive association was found in the high score group (OR = 1.16, 95% CI 0.99-1.33). Considering the number of adjusted factors, effect estimates for studies that adjusted for more than and less than or equal to three confounders were ORs of 1.16 (95% CI 0.99-1.33) and 0.52 (95% CI 0.22-0.82), respectively. This study also investigated exposure assessment. ORs were 1.15 (95% CI 0.98-1.33) for studies using interviews to collect information and 0.91 (95% CI 0.27-3.00) for studies using self-administered questionnaires. When further separated by verification of pancreatic cancer, the ORs were 1.18 (95% CI 1.00-1.36) for studies in which pancreatic cancer was histologically confirmed and 0.65 (95% CI 0.38-0.91) for studies that obtained information from the cancer registry. Pooled ORs varied significantly in subgroups of study quality, number of adjusted factors, and verification of pancreatic cancer (P < 0.05). Therefore, potential sources (study design, geographic area, study quality, number of adjusted factors, method of assessment, and verification of pancreatic cancer) of heterogeneity were explored using meta-regression. As a result, only study design (P = 0.014) was identified as a possible source of heterogeneity in the overall meta-analysis. When stratified by type of pesticide, insecticide exposure was significantly associated with decreased pancreatic cancer risk (OR = 0.66, 95% CI 0.44-0.89), while no such effects were observed in herbicide and fungicide exposure.

Discussion

The question of whether pesticide exposure is independently associated with incidence of pancreatic cancer remains controversial. This current meta-analysis analyzed 11 epidemiologic studies to evaluate the association between pesticide exposure and risk of pancreatic cancer. To the best of our knowledge, this was the first meta-analysis evaluating the relationship. Results indicated that evidence was lacking concerning a relationship between pesticide exposure and increased or reduced pancreatic cancer risk.

Statistically significant heterogeneity was discovered among overall studies ($P = 0.007$, $I^2 = 62.1\%$), possibly distorting pooled risk estimates. When studies that obviously contributed to the heterogeneity, according to the Galbraith plot, were excluded and meta-analysis was repeated, there was no significant heterogeneity. In addition, sensitivity analysis showed that the present results were less likely affected by a single study, suggesting that findings were stable and robust.

In subgroup analysis, it was found that pesticide exposure was associated with a significant increased risk of pancreatic cancer in case-control studies, but a decreased risk in cohort groups. Meta-regression analysis also suggested that the study design was the major source of heterogeneity. It is generally believed that case-control studies provide weaker evidence regarding association than cohort studies, as they are more likely to be subjected to selection and recall bias. In addition, due to poor survival of pancreatic cancer, most studies have relied on surrogate interviews, in which accurate exposure information is difficult to collect for case-control studies. However, only 2 cohort studies concerned this relationship, having insufficient statistical power. More large and well-design cohort studies are necessary to better illuminate the relationship between pesticide exposure and risk of pancreatic cancer. Interestingly, the present results imply that insecticides, not herbicides or fungicides, may contribute protective effects on incidence of pancreatic cancer. This is worthy of further investigation in future studies due to the limited number of studies included.

Biological mechanisms by which pesticides may be involved in the etiology of pancreatic cancer remain unknown. Laboratory evidence has supported the hypothesis that some pesticides may be pancreatic carcinogens. Direct exposure of the pancreatic ductal epithelium to pesticides is possible because some organochlorine compounds may accumulate and reach high concentrations in the pancreas, as it is a lipid-rich organ [27]. Some pesticides are themselves genotoxic agents, sufficient to cause gene mutations or DNA rearrangements. Some may modulate the expression of oncogenes, including ras genes, while other pesticides linked to human carcinogenesis may also alter immune function [34, 35]. A Spanish case-control study found that serum organochlorine levels were significantly higher in pancreatic cancer cases with K-ras mutation than in cases without a mutation, indicating that it could play a part in the pathogenesis of exocrine pancreatic cancer through modulation of K-ras activation [36]. Inconsistency between experimental and epidemiology studies may be partly explained by the low bioavailability of these active compounds in human plasma and the drug accumulation could not achieve high levels in the pancreas. For example, nitrosamine compounds in pesticides have been implicated as a significant cause of cancer, including pancreatic cancer [37, 38]. Regulations were implemented by the United States Environmental Protection Agency to reduce nitrosamine contamination in pesticides in the 1980s. Subsequent lower levels of nitrosamine exposure may have no carcinogenic effects in regularly exposed individuals.

As a meta-analysis of observational studies, a potential limitation of this study was the inadequate control of all known confounding factors in included studies. This may have distorted the association between pesticide exposure and risk of pancreatic cancer, although most studies included in this analysis performed adjustments for a wide range of confounders. Another limitation was the existence of publication bias, as suggested by Begg's funnel plot. Although loose search criteria were used, small negative studies are less likely to be published. This study did not seek to include unpublished data or papers in other languages. However, the trim-and-fill method identified one possible missing study that would not have altered results. In addition, a proportion of diagnoses were made in the absence of histological verification, due to the morbidity associated with

pancreatic biopsies and lack of effective treatment for this disease. Diagnostic misclassification has been shown to bias risk estimates for pancreatic cancer [39]. Finally, pesticides refer to a complex group of molecules, thus all types of pesticides may not have the same properties regarding modulation of cancer risk. However, pesticide exposure was not the focus of included studies. Only 5 studies were available for specific types of pesticides [7, 13, 14, 27, 33], preventing calculation of precise summary risk estimates with high statistical power.

In conclusion, the present meta-analysis of observational studies suggests no association of pesticide exposure with pancreatic cancer risk. Considering the limitations of included studies, further well-designed prospective studies are necessary to confirm this association.

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Disclosure of conflict of interest

None.

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