Int J Clin Exp Med 2016;9(10):19474-19479
www.ijcem.com /ISSN:1940-5901/IJCEM0031986

Original Article

Prediabetes and the risk of pancreatic cancer: a meta-analysis

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Received May 10, 2016; Accepted July 26, 2016; Epub October 15, 2016; Published October 30, 2016

Abstract: Some studies suggested that prediabetes was associated with the risk of pancreatic cancer. However, the results were controversial. Thus, a meta-analysis was conducted to investigate the association between prediabetes and pancreatic cancer risk. PubMed, EMBASE, and Cochrane database were searched. The association was estimated by hazard ratio (HR) with its 95% confidence interval (CI). 12 studies (n=2983532) were eligible based on the inclusion/exclusion criteria. Prediabetes was significantly associated with the increased risk of pancreatic cancer (HR=1.21, 95% CI 1.13-1.28, *P*<0.00001; I^2=20%). The subgroup analysis on the basis of study design showed that prospective cohort studies (HR=1.19, 95% CI 1.11-1.27, *P*<0.00001; I^2=9%) and nested case-control studies (HR=1.60, 95% CI 1.23-2.07, *P*=0.0004; I^2=0%) had significantly results, respectively. However, retrospective cohort studies showed marginal result (HR=1.36, 95% CI 0.94-1.97, *P*=0.10; I^2=0%). Subgroup analysis was performed according to gender, both male prediabetes patients (HR=1.15, 95% CI 1.07-1.23, *P*<0.0001; I^2=10%) and female prediabetes patients (HR=1.33, 95% CI 1.12-1.57, *P*=0.001; I^2=0%) had increased pancreatic cancer risk. In conclusion, this meta-analysis suggested that prediabetes may be a risk factor of pancreatic cancer.

Keywords: Prediabetes, pancreatic cancer, association

Introduction

Pancreatic cancer is one of the most common cause of death worldwide. More than 46000 pancreatic cancer cases were diagnosed and 39000 people died from this cancer in the United States in 2014 [1]. The prognosis for pancreatic cancer patients is very poor. Thus, it is important to detect risk factors of pancreatic cancer.

The term 'prediabetes' is a condition where the body tissues are exposed to abnormally high levels of insulin for extended periods, that may persist for many years. The World Health Organization (WHO) has defined prediabetes as a state of intermediate hyperglycemia using two specific parameters, impaired fasting glucose (IFG) defined as fasting plasma glucose (FPG) of 6.1-6.9 mmol/L (110 to 125 mg/dL) and impaired glucose tolerance (IGT) defined as 2 h plasma glucose of 7.8-11.0 mmol/L (140-200 mg/dL) after ingestion of 75 g of oral glucose load or a combination of the two based on a 2 h oral glucose tolerance test (OGTT) [2]. Recently, some studies suggested that prediabetes was associated with the risk of pancreatic cancer. However, the results were controversial [3-14]. For example, Grote et al. indicated that prediabetes patients had increased pancreatic cancer risk [12]. However, Inoue et al. did not find the same result in their study [9]. Thus, we performed a meta-analysis to assess the association between prediabetes and the risk of pancreatic cancer.

Methods

Publication search

PubMed, EMBASE, and Cochrane database were searched. The terms: "Pancreatic cancer or pancreatic neoplasms" and ("prediabetic state" or prediabetes) were used. Additional studies were identified by a hand search from the reference of original studies or review articles. There was no language restriction.

Inclusion and exclusion criteria

For the selection of eligible studies in this meta-analysis should meet all of the following criteria:

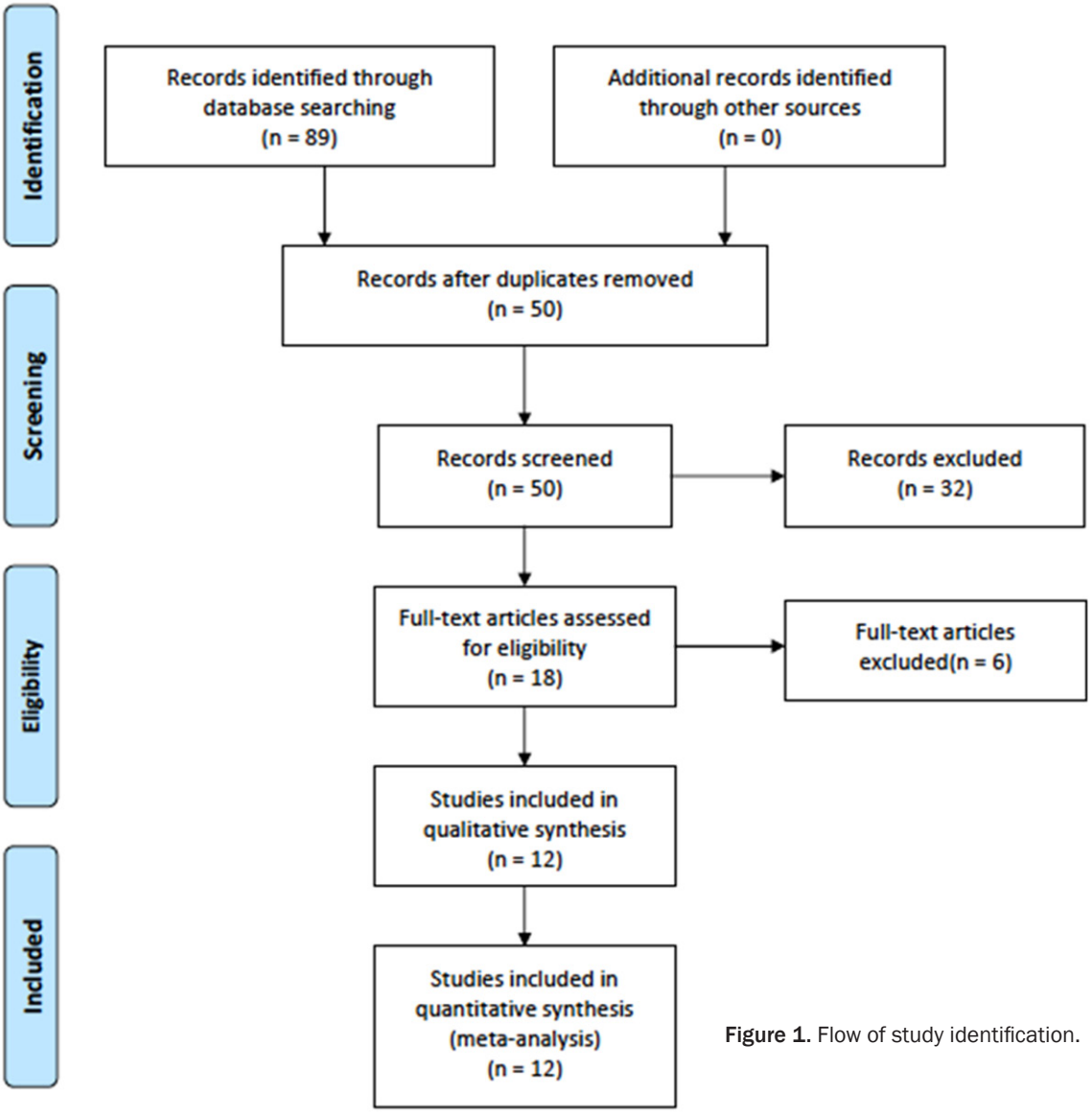

Figure 1. Flow of study identification.

(a) estimation the association between prediabetes and the risk of pancreatic cancer; (b) the study should be designed as a cohort or case-control study; (c) sufficient original data for calculating hazard ratio (HR) with its 95% confidence interval (CI). Additionally, studies were excluded if they did not include sufficient data.

Data extraction

Two investigators reviewed and extracted data from all the eligible publications. Disagreement was resolved by consensus. The following data were extracted: name, year of publication, study design, age, gender, sample size, duration of follow-up, and covariates.

Statistical analysis

Statistical analysis was conducted by using STATA statistical package (version 11, STATA, College Station, TX). The association of prediabetes and the risk of pancreatic cancer was estimated by HR with 95% CI. The heterogeneity was tested by the Q-statistics with *P*-values <0.1. Dependent on the results of heterogeneity test among individual studies, the fixed effect model (Mantel-Haenszel) or random effect model (DerSimonian and Laird) was selected to summarize the combined HR and their 95% CI. The significance of the pooled HR was determined by the Z test. Subgroup analyses were carried out by study design and gen-

Table 1. Characteristics of the included studies

First author	Year	Study design	Mean age	Female (%)	Follow-up years	Sample size	Adjusted for
Gapstur	2000	Prospective cohort	39.9	42.6	25	35658	Age, race, cigarette smoking status, body mass index
Batty	2004	Retrospective cohort	51.5	0	25	18006	Age, employment grade, smoking status, physical activity, systolic blood pressure, blood pressure-lowering medication, marital status, disease at study entry, unexplained weight loss, body mass index, triceps skin fold thickness, height adjusted forced expiratory volume in one second, plasma cholesterol
Jee 1	2005	Prospective cohort	45.3	0	10	829770	Age, smoking, alcohol use
Jee 2	2005	Prospective cohort	49.6	100	10	468615	Age, smoking, alcohol use
Stolzenberg-Solomon	2005	Prospective case- cohort	57	0	13.8	29133	Age, smoking, body mass index
Ansary-Moghaddam	2005	Retrospective cohort	46.3	35.3	6.8	519643	Age, sex, smoking, body mass index
Yun	2006	Prospective cohort	50	0	10	446407	Age, diabetes status, body mass index, exercise, alcohol use
Inoue 1	2009	Retrospective cohort	56.5	0	10.2	9548	Age, study area, smoking status, weekly alcohol intake, total serum cholesterol
Inoue 2	2009	Retrospective cohort	55.5	100	10.2	18176	Age, study area, smoking status, weekly alcohol intake, total serum cholesterol
Johansen	2010	Prospective cohort	44	50	12	577315	Age, smoking, body mass index
Zhou	2010	Cohort	53.4	68.7	36.8	26460	Age, cohort, sex, body mass index, systolic blood pressure, cholesterol, smoking status
Grote	2011	Nested case-control	58	51.7	5.3	932	Age, sex, smoking, body mass index, matched for date, food, drink, centre
Hirakawa	2012	Prospective cohort	40.3	57	19	2438	Age, sex, body mass index, cholesterol, smoking, alcohol intake, family history of cancer, physical activity, dietary factors
Wolpin	2013	Nested case-control	63	71.5	12.2	1431	Age, sex, body mass index, cohort, smoking, fasting time, race

Table 2. Results of the meta-analysis

	Test of association		Heterogeneity	
	HR (95% CI)	*P* value	I^2 (%)	*P* value
All studies	1.21 (1.13-1.28)	<0.00001	20	0.23
Design				
Prospective cohort	1.19 (1.11-1.27)	<0.00001	9	0.36
Retrospective cohort	1.36 (0.94-1.97)	0.10	0	0.47
Nested case-control	1.60 (1.23-2.07)	0.0004	0	0.50
Gender				
Male	1.15 (1.07-1.23)	<0.0001	10	0.35
Female	1.33 (1.12-1.57)	0.001	0	0.49
Adjust age, smoking, BMI	1.33 (1.17-1.52)	<0.0001	22	0.24
Adjust alcohol	1.18 (1.10-1.28)	<0.00001	6	0.38

BMI, body mass index.

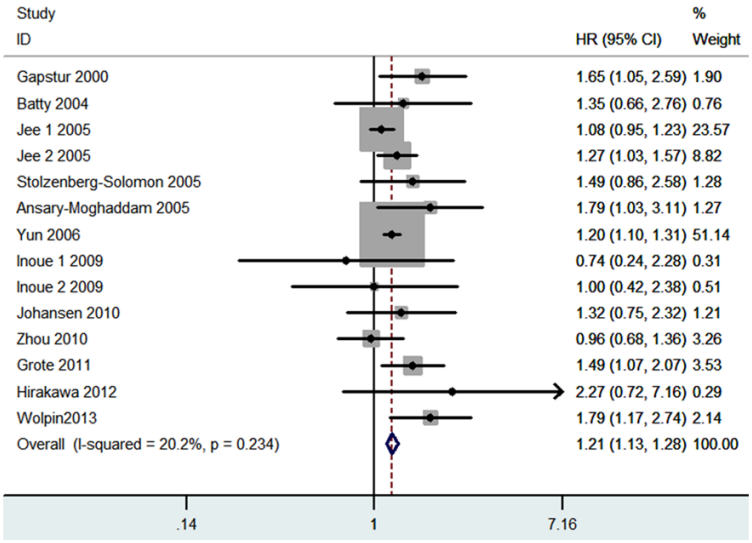

Figure 2. Meta-analysis for the association between prediabetes and the risk of pancreatic cancer.

der. The sensitivity analysis was used to detect the robust of the result. Publication bias was investigated with Egger's linear regression test. All the *P*-values were two sided. *P*-value less than 0.05 was considered statistically significant.

Results

Study characteristics

The process of selection of studies in the meta-analysis is summarized in a flow diagram (**Figure 1**). Database search revealed 89 potentially relevant publications. Eventually, 12 studies were eligible based on the inclusion/exclusion criteria. Two studies reported two cohort studies, respectively. Thus, 14 studies with 2983532 subjects were included in this meta-analysis. The main characteristics of included studies are shown in **Table 1**.

Meta-analysis results

Results of this meta-analysis are showed in **Table 2**. As shown in **Figure 2**, prediabetes was significantly associated with the increased risk of pancreatic cancer (HR=1.21, 95% CI 1.13-1.28, *P*<0.00001; I^2=20%). The subgroup analysis on the basis of study design showed that prospective cohort studies (HR=1.19, 95% CI 1.11-1.27, *P*<0.00001; I^2=9%) and nested case-control studies (HR=1.60, 95% CI 1.23-2.07, *P*=0.0004; I^2=0%) had significantly results, respectively. However, retrospective cohort studies showed marginal result (HR=1.36, 95% CI 0.94-1.97, *P*=0.10; I^2=0%). Subgroup analysis was performed according to gender, both male prediabetes patients (HR=1.15, 95% CI 1.07-1.23, *P*<0.0001; I^2=10%) and female prediabetes patients (HR=1.33, 95% CI 1.12-1.57, *P*=0.001; I^2=0%) had increased pancreatic cancer risk.

One cohort was excluded at each time to investigate the influence of the individual data set on the overall results. The association remained insignificant when any single study was excluded, confirming the stability of the results (**Figure 3**). In an analysis limited to the studies with adjustment for age, smoking, body mass index, the result was still statistically significant (HR=1.33, 95% CI 1.17-1.52, *P*<0.0001; I^2=22%). In an analysis limited to the studies with adjustment for alcohol use, the result was also statistically significant (HR=1.18, 95% CI 1.10-1.28, *P*<0.0001; I^2=6%).

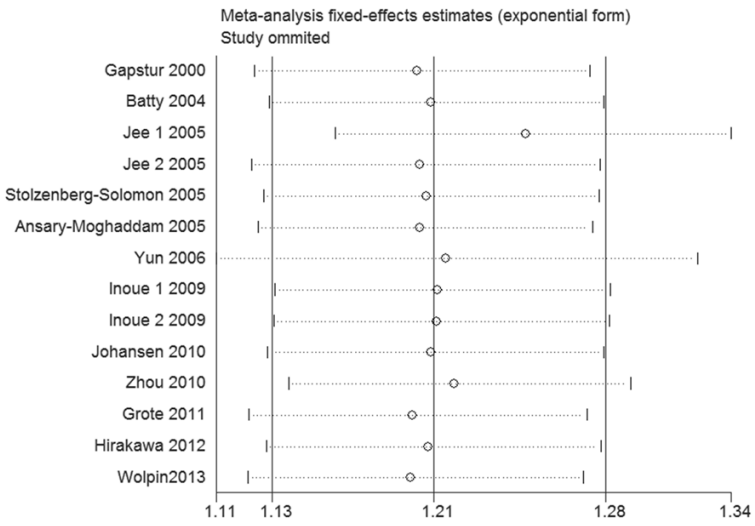

Figure 3. Sensitivity analysis for the association between prediabetes and the risk of pancreatic cancer.

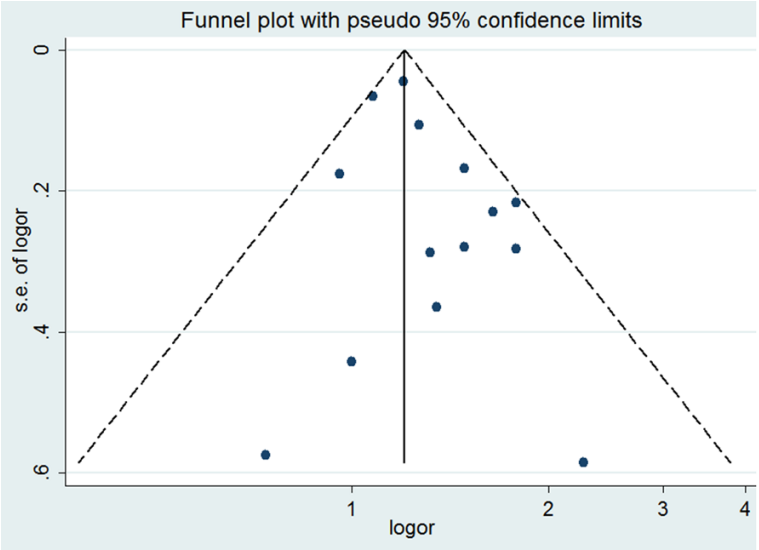

Figure 4. Funnel plot for the association between prediabetes and the risk of pancreatic cancer.

Both funnel plots and Egger's test were conducted to assess publication bias. The funnel plot was symmetrical (**Figure 4**), and no publication bias was found by Egger's test (P=0.120).

Discussion

This meta-analysis with more than 2900000 subjects explored the association of prediabetes and the risk of pancreatic cancer. We found that high prediabetes was significantly associated with the increased risk of pancreatic cancer. In addition, both male prediabetes patients and female prediabetes patients showed increased pancreatic cancer risk.

Abe et al. suggested that oxidative stress and accumulated advanced glycation end-products induced by hyperglycaemia at the cellular level may play important roles in cancer development and progression [15]. Rajpathak et al. indicated that hyperinsulinaemia and increased level of bioavailable insulin-like growth factor I related to insulin resistance [16]. Insulin resistance may promote cancer cell proliferation and may also relate to worse cancer outcome [17].

The major strength of this study is its large sample size and sufficient statistical power. Other strengths include the fact that funnel plots and Egger's tests indicated that there was no significant publication bias. Furthermore, sensitivity analysis suggested that our results were stable.

Against this, several obvious limitations should be identified. First, as a meta-analysis of observational studies, it was prone to bias (e.g., recall and selection bias) inherent in the original studies. However, the adjusted HRs were used in this meta-analysis and the results were not changed in sensitivity analyses, suggesting that our results were robust. Second, lacking of the original data of the eligible studies limited the evaluation of the subgroup analyses by age and other factors.

In conclusion, this meta-analysis suggested that prediabetes may be a risk factor of pancreatic cancer.

Disclosure of conflict of interest

None.

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