Older age at first birth is a risk factor for pancreatic cancer: a meta-analysis

Ai-Jing Luo, Rui-Hua Feng, Xiao-Wan Wang and Fu-Zhi Wang

Changsha and Beijing, China

BACKGROUND: Some studies found that age at first birth is associated with pancreatic cancer; others did not. The present meta-analysis was to evaluate the relationship between age at first birth and pancreatic cancer in women.

DATA SOURCES: We searched PubMed, Embase, and the Cochrane Library for relevant publications on age at first birth and pancreatic cancer up to April, 2014. The eligible studies (six cohorts and five case-controls) were independently selected by two authors. Pooled relative risk (RR) estimates and corresponding 95% confidence interval (95% CI) were calculated using the inverse-variance method.

RESULTS: The pooled RR of pancreatic cancer risk for the highest versus lowest categories of age at first birth was 1.21 (95% CI: 1.01-1.45, *P*=0.314, I^2=13.7%). Consistent relationships were also observed within subgroup analyses stratified by study design, geographic region, and whether the studies included adjustment for cigarette smoking, diabetes, or all of the confounders. In this meta-analysis, no publication bias among studies was observed using Egger's test (*P*=0.383) or Begg's test (*P*=0.436).

CONCLUSION: Our findings suggest that older age at first birth is associated with an increased risk of pancreatic cancer in women and the exact functional mechanism needs further investigation.

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KEY WORDS: pancreatic cancer; age at first birth; risk factor; meta-analysis

Introduction

Pancreatic cancer remains the eighth leading cause of malignancy mortality worldwide.[1] Although pancreatic cancer poses a great disease burden both in morbidity and mortality, its etiology is unclear.[2] Except for cigarette smoking,[3, 4] there are no well-demonstrated risk factors, such as older age, gender, family history, diabetes, and chronic pancreatitis.[5] The lower incidence of pancreatic cancer among women has prompted investigators to hypothesize that reproductive factors and female hormone may play a role.[6]

Among the reproductive factors and female hormone that have been investigated, age at first birth is less likely to be prone to recall bias and misclassification. However, the findings from epidemiologic studies[7-21] on the association between age at first birth and the risk of pancreatic cancer were inconsistent. The inconsistence might be due to limited statistical power. Therefore, we conducted a meta-analysis of all pertained publications to evaluate the relationship between age at first birth and pancreatic cancer risk.

Methods

Literature search

The present meta-analysis was carried out following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines,[22] and the meta-analysis of observational studies in epidemiology (MOOSE) guidelines.[23] We performed a systematic search of the PubMed, Embase, and the Cochrane Library for all medical literature published in English language journals up to April, 2014. Articles were identified using the follow-

Author Affiliations: The Third Xiangya Hospital of Central South University, Changsha 410013, China (Luo AJ); Key Laboratory of Medical Information Research (Central South University), College of Hunan Province, Changsha 410013, China (Luo AJ); School of Public Health, Central South University, Changsha 410078, China (Feng RH); Center for Health Policy and Management, China Academy of Medicine Sciences, Beijing 100020, China (Feng RH and Wang XW); Department of Medicine Management, Bengbu Medical College, Bengbu 233030, China (Wang FZ)

Corresponding Author: Rui-Hua Feng, PhD, Center for Health Policy and Management, China Academy of Medicine Sciences, Yabao Road No. 3, Chaoyang District, Beijing 100020, China (Tel: +86-10-52328852; Email: fengruihua421@hotmail.com)

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ing search terms: ("age at first birth" OR "age at first live birth" OR "age at first delivery" OR "age at first pregnancy" OR "age at first full-term pregnancy" OR "reproductive" OR "reproduction" OR "reproductive factors" OR "reproductive history") AND ("pancreas" OR "pancreatic") AND ("cancer" OR "neoplasm" OR "carcinoma" OR "tumor" OR "adenocarcinoma"). The reference sections of relevant articles were also reviewed by the authors.

Study selection criteria

The eligible studies were independently selected by two authors. Disagreement between the two authors was resolved by discussing with the third author. Inclusion criteria were as follows: 1) description of a cohort or case-control study; 2) assessment of the relationship between age at first birth and pancreatic cancer risk; and 3) presentation of relative risk (RR) [i.e., odds ratio (OR), hazard ratio (HR)] with corresponding 95% confidence interval (CI).

When there were multiple studies from the same population, we selected the study with the maximum number of cases and most available information. Systematic reviews, conference abstracts, and case reports were excluded.

Data extraction

Two authors independently extracted the following data from each eligible study using a purpose-designed form: last name of the first author, year of publication, country, study period/follow-up years, study design, cases/cohort size (i.e., controls), age, categories of age at first birth, study-specific adjusted estimates with their 95% CIs, and confounding factors for matching or adjustments. In this meta-analysis, we utilized the risk estimates that were adjusted for the largest number of confounders.

Data synthesis and analysis

RR was used to measure the association between age at first birth and pancreatic cancer risk. OR and HR were deemed equivalent to RR because the incidence rate of pancreatic cancer is low.[24] For age at first birth, we conducted a meta-analysis of the comparison of the highest versus lowest category of age in each study. For studies in which the lowest category of age was not used as a reference, we used the effective count method recommended by Hamling et al[25] to recalculate the RR.

Pooled RRs estimates and corresponding 95% CIs were calculated using the inverse-variance method. When substantial heterogeneity was observed ($I^2 \geq 50\%$), the pooled RR was reported based on the random-effect model (DerSimonian and Laird method).[26] Otherwise, the pooled RR was reported based on the fixed-effect model (the inverse-variance method). The extent of heterogeneity across studies was quantified by calculating both the I^2 and Cochrane Q statistics. For the Q statistic, a P value <0.1 was considered as significant heterogeneity; for the I^2 statistic, heterogeneity was interpreted as absent (I^2: 0-25%), low (I^2: 25.1%-50%), moderate (I^2: 50.1%-75%), or high (I^2: 75.1%-100%).[27, 28] Subgroup analyses were performed according to study design (case-control vs cohort studies), geographic regions (North America vs Europe vs Asia), and adjustments for smoking, body mass index (BMI), diabetes, or adjustment for smoking, BMI and diabetes. Finally, we carried out sensitivity analyses excluding one study at a time to explore whether the results were strongly influenced by a specific study. Publication bias was detected via Egger's linear regression,[29] Begg's rank correlation method[30] and funnel plot. A P value <0.05 for Egger's or Begg's tests was considered as significant publication bias. All statistical analyses were performed using STATA version 12.0 (StataCorp, College Station, TX, USA).

Results

Literature search and study characteristics

The process of study selection is shown in Fig. 1. Eleven studies were eligible for this meta-analysis.[7-17] Characteristics of the 11 included studies are shown in Table 1. The included articles, which represent 2535 cases, were published between 1992 and 2013. Among these studies, six were cohort[11-14, 16, 17] and five were case-controls.[7-10, 15] Of the six cohort studies, cohort sizes ranged from 37 459 to 328 610, and the number of cases varied from 154 to 323. Of the five case-control studies, the number of cases

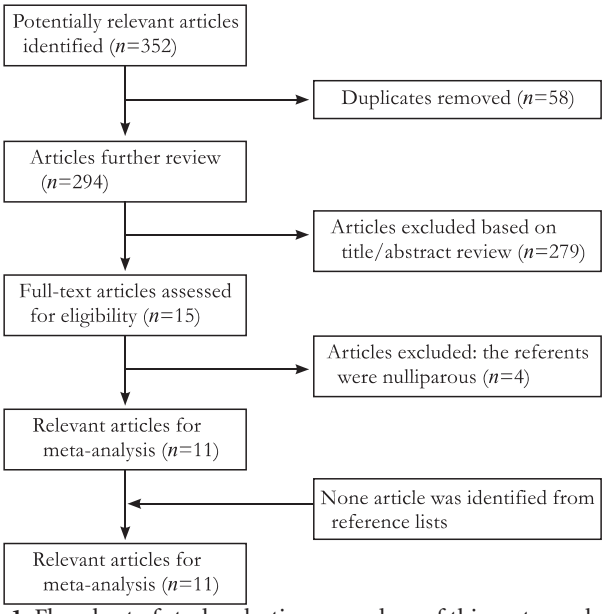

Fig. 1. Flowchart of study selection procedure of this meta-analysis.