INTRODUCTION

Pancreatic cancer is the eighth most common cause of death from cancer worldwide. About 46,420 new pancreatic cancer cases were diagnosed and 39,590 people died from this cancer in the United States in 2014. Although the diagnosis and treatment of pancreatic cancer has been evident improvement, the five-year survival rate for the disease is still no more than 5%. Thus, it is very important to detect modifiable risk factors that may develop into the primary prevention for this cancer. Coffee is one of the most popular beverages over the world. Since the early 1980s, epidemiologic studies on the relationship between coffee consumption and pancreatic cancer risk have been conducted in different countries, and two meta-analysis studies have been performed on this topic too. However, the results of the two meta-analysis studies were contrary to each other. Furthermore, several new prospective cohort studies on this topic had been published recently, and the results of these new cohort studies are inconsistent too. Therefore, it is necessary to perform an...
update meta-analysis to quantitatively summarize the association between coffee consumption and pancreatic cancer risk. Moreover in order to reduce the bias, we recruited prospective cohort studies only.

METHODS

Search strategy: We searched CBM (China Biology Medicine disc) and MEDLINE for studies of coffee consumption and pancreatic cancer risk up to June 2015. Key words searched were as follows: (pancreatic OR pancreas) AND (cancer OR tumor OR carcinoma) AND (coffee OR caffeine OR drinking OR beverages OR diet OR lifestyle). Moreover, we have scan reference lists of retrieved articles to search for additional studies. The language of the studies was limited to English or Chinese.

Study selection: The inclusion criteria for the present meta-analysis were: (1) prospective cohort study design; (2) presented the consumption of coffee; and (3) provided the relative risk (RRs) (or odds rations or hazard ration) with their confidence intervals (CIs) (or data to calculate them). The exclusion criteria were: (1) case-control design; (2) data about coffee consumption was insufficient; (3) duplicate reports; (4) if multiple articles were from the same study population, only the one with largest sample or most information was included.

Data extraction: Two authors (Ran and Wang) independently extracted all data and tabulated them, discrepancies were resolved by discussion. The following data from each eligible study was extracted: first author’s last name, year of publication, country, period of follow-up, number of participants, RRs of pancreatic cancer with corresponding 95% CIs for each level of coffee consumption, and variables adjusted for the statistical analysis.

Statistical analysis: For all the included cohort studies, we computed overall RRs with 95% CIs for the highest versus lowest level of coffee consumption. Then subgroup analysis to evaluate the influence of geographic areas was performed too.

Statistical heterogeneity was investigated by Q test and I² statistic. For the Q test, \( P < 0.10 \) was considered present heterogeneity. If the heterogeneity was statistically significant, a random effects model was conducted. Otherwise, a fixed effects model was used.

For the dose-response analysis of coffee consumption, the method proposed by Greenland et al was used to evaluate linear trends (study-specific slopes) from the correlated natural logs of the RRs through categories of coffee consumption.\(^{26}\) We only recruited those studies that showed the number of cases and person-years and RRs with variance estimates for at least three quantitative exposure categories. For each study, we assigned the midpoint of each exposure category as the dose corresponding, and the open-ended upper category was assumed to have the same amplitude as the previous category.

Finally, publication bias was evaluated by the Begg’s and Egger’s tests. Statistical analyses were performed with Stata (version 12.0; StataCorp, College Station, TX, USA).

RESULTS

Study characteristics: A total of 20 cohort studies were identified in this meta-analysis, including 1341876 participants and 2872 cases of pancreatic cancer.\(^{1-21,24,25}\) The process of selecting studies is shown in Fig.1. Of the all eligible studies, nine studies were conducted in America (the United States),\(^{1-10,12,14}\) four studies in Asia (Japan),\(^{16,18,19,21}\) and seven studies in Europe (two each in Norway, Sweden, Finland, and one study was conducted in ten European countries by the European

Fig.1: Flow diagram of selection of relevant publications.
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### Table I: Characteristics of Studies of Coffee Consumption and Pancreatic cancer risk.

| Study            | Country      | Study period/Subjects | Consumption categories | Relative risk (95% ci) | Adjustments                      |
|------------------|--------------|-----------------------|------------------------|------------------------|----------------------------------|
| Nomura 1981 [4]  | America      | 1968-1981 28/8032     | nondrinkers            | 1.00 (reference)       | age, smoking                     |
|                  |              |                       | 1-2 cup/d              | 2.74 (0.61-12.36)      |                                  |
|                  |              |                       | 3-4 cup/d              | 1.80 (0.36-8.89)       |                                  |
| Whittemore 1983 [5] | America     | 1966-1983 84/412     | nondrinkers            | 1.00 (reference)       | age, college, class year         |
| Snowdon 1984 [6] | America      | 1960-1980 71/23912    | <1 cup/d               | 1.00 (reference)       | age, sex                         |
| Jacobsen 1986 [7] | Norway       | 1967-1978 63/16555    | ≤2 cup/d               | 1.00 (reference)       | age, smoking, residence          |
|                  |              |                       | 3-4 cup/d              | 1.22 (0.23-2.20)       |                                  |
|                  |              |                       | 5-6 cup/d              | 0.53 (0.24-1.99)       |                                  |
| Hiatt 1988 [8]   | America      | 1978-1984 48/122894   | nondrinkers            | 1.00 (reference)       | age, smoking, alcohol, ethic, blood glucose |
|                  |              |                       | 1-3 cup/d              | 0.9 (0.4-2.1)          |                                  |
|                  |              |                       | >4 cup/d               | 0.7 (0.2-1.9)          |                                  |
| Mills 1988 [9]   | America      | 1976-1983 40/34000    | Never                  | 1.00 (reference)       | age, sex                         |
|                  |              |                       | < Daily                | 0.65 (0.22-1.89)       |                                  |
|                  |              |                       | ≥ Daily                | 0.71 (0.34-1.48)       |                                  |
| Zheng 1993 [10]  | America      | 1966-1986 56/17633    | ≤2 cup/d               | 1.00 (reference)       | age, smoking, alcohol            |
|                  |              |                       | 3-4 cup/d              | 0.6 (0.3-1.2)          |                                  |
|                  |              |                       | 5-6 cup/d              | 0.7 (0.4-1.6)          |                                  |
| Stensvold 1994 [11] | Norway      | 1977-1988 41/42973   | ≤2 cup/d               | 1.00 (reference)       | age, smoking, country of residence |
|                  |              |                       | 3-4 cup/d              | 2.58 (0.58-23.44)      |                                  |
|                  |              |                       | 5-6 cup/d              | 2.80 (0.65-25.27)      |                                  |
|                  |              |                       | ≥7 cup/d               | 2.32 (0.51-21.58)      |                                  |
| Shibata 1994 [12] | America      | 1981-1990 63/13979    | <1 cup/d               | 1.00 (reference)       | age, sex, smoking                |
|                  |              |                       | 1cup/d                 | 1.82 (0.75-4.43)       |                                  |
|                  |              |                       | 2-3 cup/d              | 1.67 (0.74-3.77)       |                                  |
|                  |              |                       | ≥4 cup/d               | 0.88 (0.28-2.80)       |                                  |
| Harnack 1997 [13] | America      | 1986-1994 66/33976    | ≤7cup/week             | 1.00 (reference)       | age, smoking                      |
|                  |              |                       | 8-17.5cup/week         | 1.91 (0.92-4.00)       |                                  |
|                  |              |                       | ≥17.5cup/week          | 2.15 (1.08-4.30)       |                                  |
| Michaud 2001 [14] | America      | 1980-1998 288/136593  | nondrinkers            | 1.00 (reference)       | age, smoking, body mass           |
|                  |              |                       | <1 cup/d               | 0.94 (0.65-1.36)       | index, diabetes mellitus, history of cholecystectomy |
|                  |              |                       | 1 cup/d                | 0.60 (0.38-0.94)       |                                  |
| Isaksson 2002 [15] | Sweden       | 1961-1997 131/21884   | 0-2 cup/d              | 1.00 (reference)       | age, sex, smoking                |
|                  |              |                       | 3-6 cup/d              | 0.91 (0.60-1.38)       |                                  |
| Lin 2002 [16]    | Japan        | 1988-1997 225/99527   | nondrinkers            | 1.00 (reference)       | age, smoking                      |
|                  |              |                       | 1-2 cup/m              | 0.78 (0.46-1.26)       |                                  |
|                  |              |                       | 1-4 cup/w              | 0.55 (0.34-0.86)       |                                  |
| Stolzenberg-Solomon 2002 [17] | Filand | 1985-1997 163/27111  | reference category     | 1.00 (reference)       | age, smoking                      |
|                  |              |                       | low                    | 1.48 (0.89-2.46)       |                                  |
|                  |              |                       | moderately low         | 1.12 (0.61-2.03)       |                                  |
|                  |              |                       | moderately high        | 1.72 (1.01-2.86)       |                                  |
|                  |              |                       | high                   | 0.95 (0.54-1.68)       |                                  |
The sample size varied from 412 to 477 cases, and the number of pancreatic cancer cases ranged from 21 to 865 (Table-I).

**Highest versus lowest drinking category:** As various measurement units for coffee consumption were used in the included studies, we just considered to compare the highest coffee consumption category with lowest coffee consumption category, and take the latter as the reference category.

The overall RR for highest coffee consumption versus lowest coffee consumption was 0.75 (95%CI, 0.63-0.86). Statistic significant heterogeneity was found among these studies ($I^2 = 37.8\%$, $P$ for heterogeneity =0.045) (Fig.2). Neither Egger’s test ($P$ for bias =0.436) nor Begg’ test ($P$ for bias =0.078) indicated a significant publication bias (Fig.3).

**Subgroup analysis on geographic areas:** Nine studies had been conducted in the America, analysis of the nine studies showed that there was no association between coffee consumption and pancreatic cancer risk (RR, 0.88; 95%CI, 0.64-1.12; $P$ for heterogeneity =0.738). And similar result was found in the seven studies in Europe (RR, 0.88; 95%CI, 0.70-1.16; $P$ for heterogeneity =0.111). In contrast, when the four studies in Asia were pooled, coffee consumption was associated with a reduced pancreatic cancer risk (RR, 0.88; 95%CI, 0.70-1.06; $P$ for heterogeneity =0.187) (Fig.2).

**Dose-response meta-analysis:** Nine studies were included in the dose-response analysis for the relationship between coffee consumption and pancreatic cancer risk. The pooled RR for an increment of one cup/day of coffee consumption was 0.99 (95%CI, 0.96-1.03), without statistically significant. The Goodness-of-fit indicated no significant heterogeneity among these studies ($Q = 35.29; p = 0.23$).

**DISCUSSION**

Up to now, more and more evidences, which is provided by epidemiological studies have demonstrated the inverse association between coffee consumption and some cancer risk, such as breast cancer, prostate cancer, liver cancer, and colorectal cancer. However the relationship between coffee consumption and pancreatic cancer risk had a series of inconsistent result. In 2011, a meta-analysis based on fourteen cohort studies showed a significant association between coffee consumption and reduced pancreatic cancer risk (RR, 0.68; 95%CI, 0.51-0.84). After that, Turati et al performed another meta-analysis with 37 case-control studies and 17 cohort studies, the result suggested non-significant association between coffee consumption and the risk of pancreatic cancer (RR, 1.13; 95%CI, 0.99-1.29). Specially, our update meta-analysis, which is based on 20 cohort studies.
studies, supported the protective effect of high coffee consumption for pancreatic cancer risk (RR, 0.75; 95%CI, 0.63-0.86).

In our meta-analysis, when the 20 studies were pooled, high coffee consumption was associated with a reduced pancreatic cancer risk, but the results of subgroup, which stratify by geographic area, were diverse. Studies in America and Europe showed a non-significant association between coffee consumption for pancreatic cancer risk. In contrast, studies in Asia revealed a significant inverse association between coffee consumption and pancreatic cancer risk. The diverse results among subgroup analysis may be owing to different race and environment.

Fig.2: Forest plot (random-effects model) of coffee consumption (highest versus lowest category) & pancreatic cancer risk.

Fig.3: Begg’s funnel plot for publication bias.
Coffee interferes the cancerous process with different stages. The molecular mechanisms for anticancer effects of coffee compounds are as follows: (1) The antioxidant of coffee may reduce reactive oxygen species (ROS), that can induce DNA damage provoked. (2) Coffee can enhance endogenous defense systems by inducing a complex of nuclear clear factor erythroid-2-like 2 factor (Nrf2), and the cafestol of the coffee can increase the endogenous antioxidant too. (3) Coffee’s chemopreventive effect can induce DNA repair capacity. In vitro experiment suggested that cafestol and kahweol decreased 50% genotoxicity of human-derived hepatoma cells. (4) Coffee consumption can decreased inflammation marker, such as the level of IL-18, c-reactive protein and E-selectin. Several compounds of coffee can also inhibit the activation of nuclear factor kappa B (NF-kB), that is the key transcription factor of inflammatory process. (5) Experiment showed that coffee component cafestol, kahweol, and caffeine can induce apoptosis. These molecular mechanisms could well explain our findings in our meta-analysis that high coffee consumption with a decreased pancreatic cancer risk.

Several limitations of our meta-analysis should be discussed. First, we could not obtain enough information to calculate the adjusted RR in some studies, so we just combined unadjusted RRs. This could have influence on the quality of the meta-analysis. Second, as all cohort studies, the potential bias could not be completely avoided. Third, different classification coffee consumption among studies may contribute to the heterogeneity when pooled analysis. Finally, the different measurement units, brewing method, and coffee type may be the cause of heterogeneity too.

In summary, the present meta-analysis suggested that high coffee consumption is associated with a reduced pancreatic cancer risk. However, the result should be accepted with caution, due to the potential confounder and bias could not be completely excluded. Further well designed studies are needed to confirm the finding.

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Authors’ Contribution:

RHQ and WJZ proposed the study. RHQ and SCQ performed research and wrote the first draft. RHQ and WJZ collected and analyzed the data. RHQ is the guarantor.

All authors contributed to the design and interpretation of the study and to further drafts.