



PANCREATIC CANCER RISK FACTORS: A SUMMARY REVIEW OF META-ANALYTICAL AND PROSPECTIVE COHORT STUDIES PART 1. COFFEE AND TEA CONSUMPTION

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ФАКТОРЫ РИСКА РАКА ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ: ОБЗОР МЕТА-АНАЛИЗОВ И ПРОСПЕКТИВНЫХ КОГОРТНЫХ ИССЛЕДОВАНИЙ ЧАСТЬ 1. ПОТРЕБЛЕНИЕ КОФЕ И ЧАЯ

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Summary

Pancreatic cancer (PC) is one of the top 5 causes of mortality from cancer. The role of dietary factors in the etiology of PC is unclear. We reviewed some meta-analytical or pooled reports dealing with the association between coffee (C) and tea (T) consumption and PC risk. C components can have anticarcinogenic effect: meta-analysis by Dong (2011) confirmed, that pooled relative risk (RR) of PC in high C lovers comparing with non/lowest C drinkers was 0.68 (95% CI 0.51–0.84). But in the "US NIH-AARP Diet and Health Study" (2015) after adjustment for smoking, PC risk were not significant: never C drinkers compared with C drinkers ≥ 6 cups per day (cpd) HR 1.24 (0.93–1.65). In the European Prospective Investigation (2013) neither C, nor T were also associated with PC risk, but the previous Italian multicenter study (1995) was demonstrated, that ingestion of > 3 cpd lead to significantly increased PC risk (odds ratio (OR) 2.53; 1.53–4.18). A meta-analysis by Zeng (2014) indicate, that green T consumption > 2 cpd (OR 0.95, 0.85–1.06) was not associated with PC risk. However, the subgroup analysis of different countries in meta-analysis by Chen (2014) showed a statistical decrease in PC risk by high T consumption in a Chinese population (Risk ratio=0.76, 0.59–0.98). Nevertheless meta-analysis, pooled and case-control

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studies are prone to some limitations (recall, selection bias) — different dietary patterns, adjustment for different confounders, etc. Further research is needed to clarify the biological mechanisms in the possible inverse relationship between C, T intake and PC risk.

Key words: pancreatic cancer, meta-analysis, prospective cohort studies, risk, coffee, tea

Резюме

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Рак поджелудочной железы (РПЖ) является одной из пяти причин смертности от рака. Роль диетических факторов в этиологии РПЖ неясна. Мы рассмотрели некоторые мета-анализы, касающиеся взаимосвязи между потреблением кофе (К) и потреблением чая (Ч) и риском РПЖ. Компоненты К могут оказывать антиканцерогенное действие: мета-анализ Dong (2011) подтвердил, что объединенный относительный риск (RR) РПЖ у любителей К, сравнимый с непьющими К, составлял 0,68 (95% ДИ 0,51–0,84). Но в исследовании «US NIH-AARP Diet and Health Study» (2015) после корректировки на курение риск РПЖ был незначимым: HR=1,24 (0,93–1,65) при сравнении непьющих К и потребителей К≥6 чашек в день (чвд). В Европейском проспективном исследовании (2013) ни К, ни Ч также не были связаны с риском РПЖ, но в предыдущем итальянском многоцентровом исследовании (1995) было показано, что потребление > 3 чвд приводит к значительному росту риска РПЖ (отношение шансов (OR) 2,53, 1,53–4,18). Мета-анализ Zeng (2014) показал, что потребление зеленого Ч> 2 чвд (OR_{0,95} 0,85–1,06) не связано с риском РПЖ. Несмотря на это, в мета-анализе Chen (2014) анализ подгрупп по разным странам показал, что в китайской популяции при высоком потреблении Ч достоверно снижался риск РПЖ (Risk ratio = 0,76, 0,59–0,98). Необходимо учитывать, что мета-анализы, исследования «случай-контроль» подвержены некоторым ограничениям: системные ошибки при опросе, создании выборки, например, разные диетические порции, корректировка по различным факторам и т.д. Требуются дальнейшие исследования для уточнения биологических механизмов возможной обратной зависимости между потреблением К, Ч и риском РПЖ.

Ключевые слова: рак поджелудочной железы, мета-анализы, проспективные когортные исследования, риск, кофе, чай

Pancreatic cancer (PC) is one of the most severe and treatment-refractory tumors and this disease occupies 4 place cause of worldwide cancer-related mortality with approximately 338,000 new cases diagnosed each year, accounting for 2.4% of all cancer cases [1]. PC is a quickly fatal disease: only 26% of patients survive 1-year post diagnosis and 6% survive 5 years [cite by 2]. Abdominal pains, jaundice, weight loss – main PC symptoms, are non-specific, and more than 50% of patients were diagnosed at a final stage of disease. Because of absence of high sensitive and specific tests to detect the initial cancer stages, restricted therapeutic options and fast progression, surgery was often not helpful; chemotherapy mainly used for palliative care [3]. Comprehension the etiology of PC important for identify high-risk categories of patients and to get better our possibility to detect any early biomarkers of disease. Although several risk factors associated with PC were studied, the causal factors for PC are far from clarification. PC risk factors comprise for <40% of all tumors [cite by 2]; so, endeavors to decoding of the environmental reasons of this cancer are advantageous to progress in the battle against PC.

Coffee is one of the most commonly used products, with a yearly average consumption of 1.1 kg per capita in the world, which comes round 4.5 kg in western countries [cite by 4]. in these latter days, coffee intake associated with risk reduction of some widespread diseases, including diabetes mellitus type 2, Parkinson's disease and liver cirrhosis [cite by 4]. Coffee consumption can have anticarcinogenic effect in some organs and systems. The components of coffee that deserve attention are caffeine (a purine alkaloid), kahweol (another diterpene), cafestol (a diterpene), and chlorogenic acid (a dietary phenol). Caffeine itself is a protective-affecting cell cycle, proliferation, and apoptosis [5].

671,080 individuals (1496 cancer events) included in meta-analysis by Dong J. (2011) [4]. Authors searched articles published in any language in the electronic databases MEDLINE (1966 to 2010), EMBASE (1985 to 2010), and Science Citation Index Expanded (1945 to 2010) using term “coffee” combined with “pancreatic cancer” or “pancreatic neoplasm” or “pancreatic carcinoma”. Was shown, that in contrast with individuals who did not or rarely drank coffee per day, the pooled relative risk (RR) of PC was 0.82 (95% Confidence Interval (CI): 0.69–0.95) for regular coffee drinkers, 0.86 (0.76–0.96) for low to moderate coffee drinkers, and 0.68 (0.51–0.84) for high coffee lovers. The summary RR was 0.73 (95% CI: 0.63–0.84) for men and 0.82 (0.52–1.11) for women [4]. These data were also similar in researches from Europe, North America, and the Asia-Pacific region: the RR = 0.86 (95% CI: 0.50–1.22) taking into account the 4 studies performed in Europe, 0.81 (95% CI: 0.67–0.95) examining 6 studies from North America, and 0.76 (95% CI: 0.52–0.99) for the 4 Asian studies, but without significant differences by sex. In them authors confirm the conclusions about an inverse connection between coffee drinking and PC risk [4].

Opposite results on the relationship between coffee consumption and PC risk has been informed in both clinical and epidemiological studies. During the research “US NIH-AARP Diet and Health Study” (USA), over 4155 256 person-years of follow-up, 1541 incident first primary PC occurred [6]. After adjustment for tobacco smoking history, risk estimates for coffee drinking were not significant; compared with never coffee drinkers, the hazard ratios – HR (95% CI) were 1.05 (0.85–1.30), 1.06 (0.86–1.31), 1.03 (0.85–1.25), 1.00 (0.79–1.25), and 1.24 (0.93–1.65) for <1, 1, 2–3, 4–5, and ≥6 cups per day, respectively. In a prospective study the noted zero

association was consistent in all the investigated strata (sex, smoking status, coffee caffeination, and prevalent diabetes mellitus type 2) and did not detect any relationships between PC risk and coffee intake [6].

In the European Prospective Investigation into Nutrition and Cancer cohort Study were included 477,312 participants without cancers who completed a dietary questionnaire and were followed up to determine PC incidence between 1992 and 2000 [7]. When divided into fourths, neither total intake of coffee (adjusted HR, 1.03; 95% CI, 0.83–1.27; high versus low intake), decaffeinated coffee (HR, 1.12; 95% CI, 0.76–1.63; high versus low intake), nor tea were associated with PC risk (HR, 1.22, 95% CI, 0.95–1.56; high versus low intake) [7].

In the prospective cohort analyses were included 60,041 Finnish men and women (age 26–74 years) without cancer history at baseline, they were prospectively followed up for onset of gastric and/or PC [8]. The multivariate-adjusted HR of PC incidence for high drinkers (≥ 10 cups of coffee per day) compared with nondrinkers were 0.75 (95% CI, 0.40–1.41) (P for trend = 0.19) and 0.82 (95% CI, 0.38–1.76) (P for trend = 0.95) for the men and women, respectively. Therefore, coffee consumption did not associate with PC risk [8].

In the Italy meta-analysis by Turati F. et al. (2012), included on 37 case-control and 17 cohort studies (10,594 cases), confirmed that coffee intake was not related to PC risk [9]. But the previous Italian multicenter study, performed by the Italian Pancreatic Cancer Study Group in 1995, was demonstrated, that ingestion of >3 coffee cups per day lead to significantly increased PC risk (odds ratio (OR) 2.53; 95% CI, 1.53–4.18) [10]. What is more in each sex group a significant dose-response association ($p < 0.001$) was detected, and this relationship between PC risk and coffee intake still held after controlling for main confounding factors (smoking or alcohol use). This research assumed a causal relationship between coffee consumption and PC risk [10]. Roasted coffee contains a complex mixture of >1000 chemicals. Maybe, since the 1995s, the composition of coffee has changed somewhat? In most meta-analysis did not provide information on coffee type, serving size, or brewing method.

A meta-analysis by Nie K. et al. (2016) of coffee use and PC risk in China, which include 20 prospective cohort studies, proves, that coffee consumption may weakly increase PC risk: RR1.06 (95% CI = 0.94–1.20) [11]. In the other China meta-analysis the overall RR for highest versus lowest coffee consumption was 0.75 (95% CI 0.63–0.86). Accordingly, a reduced PC risk was associated with high coffee consumption [12]. The interesting results of Japan meta-analysis (1996) formed a U-shaped curve of the dose-response relationship between coffee use and PC risk: it turned out that that small amount of coffee might prevent PC, whereas large amounts might cause PC [13].

In 2016 was carried out a meta-analysis of 105 prospective observational studies from major electronic databases (PubMed, The Cochrane Library, and EMBASE) on coffee and cancer incidence [14]. Authors reports, that coffee consumption was associated with significantly reduced risk of oral, pharynx (RR0.69), liver (RR0.46), colon (RR0.87), prostate (RR0.89), endometrial cancer (RR0.73) and melanoma (RR0.89) and increased lung cancer risk (RR2.18). No association was found between coffee intake and esophageal (RR0.86), stomach

(RR1.15), PC (RR1.02), renal (RR0.79), breast (RR0.99), ovarian cancer (RR1.04) and lymphoma (RR1.23, in all cases $p > 0.05$). Several theories have been proposed that try to explain this coffee effect. Coffee contains caffeine, which can prevent oxidative DNA damage, modify the apoptotic response and reverse the cell cycle checkpoint function, cafestol and kahweol were recognized as anticarcinogenic [cite by 14]. An anti-tumor effect was supported by Feng et al. (2005), in addition, they showed that chlorogenic acids can clear away reactive oxygen species [15]. In 2015, it was proved that caffeine suppresses the progression of hepatocellular carcinoma through the Akt signaling pathway [16]. Furthermore, Higdon J. V. et al. (2006) demonstrated that coffee use decreased the exposure of epithelial cells to carcinogens in the colon by increasing colonic motility [17]. In addition, coffee has been reported to reduce the synthesis and secretion of bile acids, potential promoters of colon carcinogenesis [cite by 14]. Coffee has been associated with the frequency and spectrum of K-ras mutation in tumors of pancreas [18]. Related this topic, we found interesting article about coffee intake and gene mutation in PC [19]. In case-case study PANKRAS II Study Group analyzed the association between coffee intake and cases with and without K-ras gene mutations in exocrine PC in Spain. Among regular coffee drinkers K-ras mutations were more common than among non-regular coffee drinkers (82.0% versus 55.6%, $p = 0.018$). The OR, adjusted by age, sex, smoking and alcohol drinking was 5.41 (95% CI 1.64–17.78). Authors conclude that among non-regular coffee drinkers the K-ras gene may be activated less often than among regular drinkers in exocrine PC [19].

In general, investigations assessing coffee intake and PC risk have yielded mixed results, whereas findings for tea intake have mostly been zero [20]. As for the consumption of tea was proved, that a mixture of **green tea** catechins significantly inhibited viability, migration, expression of matrix metalloproteinases MMP-9 and MMP-2, aldehyde dehydrogenase 1 activity, colony and spheroid formation and induced apoptosis cancer stem cell [21]. Although the laboratory and animal studies demonstrate that green tea inhibits development and progression of PC, but data from epidemiologic studies about tea and cancer were inconsistent. Zhang Y. F. et al. (2015) studied 87 datasets (57 articles), which contained a total of 49,812 incident cases and suggested, that high tea consumption had no significant effect on the risk of gastric, rectal, colon, lung, pancreatic, liver, breast, prostate, ovarian, bladder cancers or gliomas, yet high tea consumption was associated with a reduced risk of oral cancer (risk ratio 0.72; 95% CI 0.54–0.95; $P = 0.021$) [22]. A meta-analysis including 2,317 incident cases and 288,209 subjects indicate, that overall, neither high versus low green tea consumption (OR0.99, 95% CI 0.78–1.25), nor an enlargement in green tea intake >2 cups per day (OR0.95, 95% CI 0.85–1.06) was associated with PC risk [23]. In the other meta-analysis of PC risk and tea intake, includes 8 case-control studies and 6 cohort studies, the summary OR for high versus low tea intake was 0.95 (95% CI 0.84–1.08), so there was also not found any relation between tea consumption and PC risk [24], also, as in the meta-analysis by Bhoo-Pathy N. et al. [7], Turati F. et al. [9].

In the another larger Chinese meta-analysis a total of 14 studies were included (8078 PC patients, with a

total of 859783 patients) [25] pointed out that tea intake does not have a significant connection with PC risk (Risk ratio (RiR)=0.99, 95% CI: 0.89–1.11, P=0.9). However, the subgroup analysis of different countries showed a statistical decrease in PC risk by high consumption of tea in a Chinese population (RiR=0.76, 95% CI: 0.59–0.98, P=0.036). Similar results were found in the elderly (>60 years old) (RiR=0.76, 95% CI: 0.60–0.96, P=0.023) [25]. Despite the positive results in some prospective researches [26, 27], yet in large studies cumulative epidemiologic evidence suggests that green tea consumption is not associated with PC.

All epidemiologic study designs are subject to limitations and biases, including recall bias, social desirability

bias, and selection bias, which affect the interpretation of reported results. For example, differential misclassification of beverages consumption and recall of dietary patterns between cases and controls could contribute to biased risk estimates [28]. Standard coffee cups are smaller in Europe or in Japan than in the USA, and the difference in the strength of the coffee brewed may compensate for the different serving size between countries [29]. It is probable that the results based on the adjustment for different confounders were different from those based on standardized adjustments [4]. However, it is necessary to continue researching of modifiable PC risk factors for its primary prevention, which involves the identification and eradication of carcinogenic factors.

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