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Polyphenol Intake and the Risk of Pancreatic Cancer: A Systematic Review and Meta-analysis of Observational Studies

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ABSTRACT

Background: Considering the antioxidant effects of polyphenols, it remains unclear whether dietary polyphenols can affect the risk of pancreatic cancer. This study assessed the association between polyphenol intake and the risk of pancreatic cancer. **Methods:** Articles published until April 2023 in PubMed, Scopus, and the Web of Science (ISI) were searched. Observational studies on the association between dietary polyphenol intake and the odds of pancreatic cancer were also included. Odds ratios (ORs) with 95% confidence intervals (CIs) were used as effect sizes. Furthermore, standard methods were used to evaluate the heterogeneity, sensitivity, and publication bias. The Newcastle-Ottawa Scale (NOS) was used for quality assessment. **Results:** Eight studies were included. Although this systematic review and meta-analysis revealed no relationship between the intake of total flavonoids, flavan-3-ols, flavones, flavonols, flavanones, anthocyanidins, and pancreatic cancer odds; in qualitative analysis, a positive relationship was observed between genistein and the aflavin intake and pancreatic cancer risk. **Conclusions:** No relationship was observed between polyphenol intake and pancreatic cancer odds. Polyphenols have poor bioavailability and bioaccessibility, which may have affected their results. Therefore, more high-quality studies with precise designs are required to determine whether a relationship exists.

Introduction

Pancreatic cancer is the 12th most common malignancy and the 7th leading cause of cancer-related mortality worldwide (Bray *et al.*, 2018). In the last two decades, the incidence of pancreatic cancer has doubled each year from 1990 to 2017. There was an increase in the number of deaths for both sexes from 196,000 in 1990 to 441,000 in 2017 (Pourshams *et al.*, 2019). This disease is highly aggressive and has a poor survival rate, which imposes a critical global burden (Maisonneuve and Lowenfels, 2010). Failure to treat pancreatic cancer is due to the lack of appropriate screening and diagnostic methods, the location of the pancreas, the difficulty of biopsy from the pancreatic tissue, the aggressive nature of

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this disease, and the low response to chemotherapy and radiotherapy (Maisonneuve and Lowenfels, 2010). Therefore, prevention is the best choice to reduce the incidence and mortality rates of pancreatic cancer. Modifiable risk factors, including smoking, alcohol consumption, obesity, and diet, are associated with increased disease risk (Klein, 2021, Rawla *et al.*, 2019). It has been shown that dietary factors affect pancreatic cancer by more than 30%, and there is evidence that certain foods can increase the risk of pancreatic cancer, while others may protect against it (Maisonneuve and Lowenfels, 2015, Michaud *et al.*, 2005, Midha *et al.*, 2016). Several observational studies have shown an inverse association between fruits and vegetables and pancreatic cancer (Anderson *et al.*, 2009, Chan *et al.*, 2005, Ghadirian and Nkondjock, 2010, Jansen *et al.*, 2011, Liu *et al.*, 2014, Wu *et al.*, 2016). Fruits and vegetables are rich in antioxidants and anti-inflammatory compounds. Therefore, their intake might reduce oxidative stress, inflammation, and cancer risk (Liu, 2013, Slavin and Lloyd, 2012). Polyphenols are a large family of phytochemicals found in a wide variety of fruits, vegetables, flowers, and leaves (David *et al.*, 2016, Miean and Mohamed, 2001, Rawla *et al.*, 2019, Slimestad *et al.*, 2020, Tian and Liu, 2020). Polyphenols have been investigated for their beneficial effects on several diseases and their symptoms (Bao *et al.*, 2020, Goñi Cambrodón and Hernández Galiot, 2019, Lichota *et al.*, 2019, Sanches-Silva *et al.*, 2020, Serra *et al.*, 2020, Singh *et al.*, 2020).

The results of studies on the effects of polyphenols on pancreatic cancer are contradictory (Arem *et al.*, 2013, Bobe *et al.*, 2008, Molina-Montes *et al.*, 2016, Mouria *et al.*, 2002, Vuong *et al.*, 2014, Yamagiwa *et al.*, 2020). In 2002, Mouria et al. reported that food-derived polyphenols inhibited the growth of pancreatic cancer cells and prevented metastasis by causing mitochondrial dysfunction, which led to the release of cytochrome c, caspase activation, and apoptosis (Mouria *et al.*, 2002). Arem *et al.* studied 2,379 patients diagnosed with pancreatic cancer. This study failed to support the hypothesis of an association between the total intake of polyphenols or any type of flavonoid and the risk of pancreatic cancer (Arem *et al.*, 2013). Furthermore, Molina-Molina-Montes *et al.* reported no association between the intake of flavonoids, flavonoid subclasses, or lignans and pancreatic cancer risk (Molina-Montes *et al.*, 2016).

To the authors' knowledge, no systematic review or meta-analysis has been conducted to assess the association between polyphenol intake and the risk of pancreatic cancer. Therefore, this study aimed to investigate the association between polyphenol intake and pancreatic cancer odds by conducting a systematic review and meta-analysis of observational studies.

Materials and Methods

Study protocol

This review was reported based on the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) (Stroup *et al.*, 2000) and Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Moher *et al.*, 2010). The protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews, registration number: CRD42023487302).

Search strategy

Articles published until April 2023 in PubMed, Scopus, and the Web of Science (ISI) were searched. The inclusion and inclution criteria were shown in **Table 1**. There were no restrictions on the language or publication dates. Furthermore, to find any other related articles, a manual, comprehensive search in Google Scholar and searches of the references of related published articles were performed. The search was updated to August 2024 to include any relevant published studies.

Eligibility criteria

Two independent researchers (Forootani B. and Yekrang Safakar H) screened the relevant studies according to the eligibility criteria, and contradictions were resolved by a third investigator (Salehi-Abargouei A). Studies were included in this review if they 1) were a prospective cohort

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(cohort, case-cohort, or nested case-control), case-control, or cross-sectional; 2) investigated the association between polyphenol intake as exposure and pancreatic cancer odds as an outcome; 3) were performed in adults; and 4) had enough information about the desired outcomes (odds ratio (OR), relative risk (RR), hazard ratio (HR), and 95% confidence interval (CI)) for polyphenols of interest. Moreover, animal studies, randomized control trials, and studies without the necessary data for extraction were excluded.

Table 1. PICOS criteria for inclusion and exclusion of studies.

Criteria	Inclusion	Exclusion
Population	Adults (18 or more), regardless of health status	Animal studies, randomized control trials, and studies that did not have the necessary data for extraction were excluded
Intervention (Exposure)	Higher intake of polyphenols	
Comparator	Lower intake of polyphenols	
Outcome	Pancreatic cancer	
Study design	Observational studies	

Data extraction

The necessary data for eligible studies, including the author's last name, publication year, study name, location, sample size, design, type of polyphenol, age, sex, association measures, and confounding variables, were extracted independently by two investigators (Goodarzi S and Mirjalili F). The OR, RR, HR, and 95% CI were extracted for different quantile of polyphenol intake. The highest and lowest quantile of polyphenol intake were considered.

Quality assessment and grading of recommendations

Two investigators (Goodarzi S and Mirjalili F) assessed the quality of the included articles separately using the modified Newcastle-Ottawa scale (NOS) for cohort and case-control studies. This tool has several domains for evaluating the risk of bias, including selection, comparability, and outcome for cohort studies, and selection, comparability, and exposure for case-control studies. Each domain was assigned a maximum of four, two, and three points. According to the NOS) scores of 0–3 indicate poor quality, scores of 4–6 indicate fair quality, and scores of 7–9 indicate high quality (Stang, 2010).

The GRADE assessment for developing recommendations was performed using GRADE Pro software (https://gdt.gradepro.org/app/) (Guyatt *et al.*, 2008). The GRADE assessment and recommendation were measured by Goodarzi S debated and revised by a second investigator (Salehi-Abargouei A), and discussed and agreed upon by all authors.

Statistical methods

The authors assessed the association between high polyphenol intake and the risk of pancreatic cancer. All data were converted to log ORs with standard errors (SEs) using the OR, RR, HR, and 95% CI as effect sizes for the meta-analyses. A random-effects model was used to pool effect sizes. The heterogeneity between studies was determined using the Q Cochrane test and I^2 statistic (Higgins and Thompson, 2002). An I value $\geq$ 50% was considered to indicate heterogeneity and was reduced using a random-effects model. To estimate the impact of each study on the overall effect size, a sensitivity analysis was performed using the leave-one-out method as follows: one study was eliminated each time, and the analysis was performed again. To distinguish publication bias from other sample-size-related effects, funnel plots, Begg's rank correlation, and Egger's weighted regression tests were used (Deeks *et al.*, 2005). If evidence of publication bias was observed, Duval & Tweedie's "trim and fill" analysis was performed to adjust for the effects of publication bias (Duval and Tweedie, 2000). This meta-analysis was performed using STATA software, version 17.0. The significance of the

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probability value (p-value) was also set at < 0.05.

Results

A total of 14230 reports were identified, 3790 duplicate records were removed, 9521 records were marked as ineligible after title and abstract screening, and 651 studies were excluded because they were irrelevant to this meta-analysis or did not meet the eligibility criteria. After reviewing the full texts of the articles, 260 studies were removed for the following reasons: 259 reports of other cancers and one study did not have enough data. Finally, 8 articles that met the eligibility criteria were included in the evaluation and analysis. A complete explanation of the study selection process is shown in **Figure 1**.

Characteristics of the included studies

Eligible studies are presented in **Table 2**. The total number of participants involved in the analysis was 1350913, with 5212 cases of pancreatic cancer. The age range of the population was 25-80. These studies were published between 2002 and 2020 and were performed in Italy (Rossi *et al.*, 2012), the United States (4 studies) (Arem *et al.*, 2013, Arts *et al.*, 2002, Cutler *et al.*, 2008, Nöthlings *et al.*, 2007), Finland (Bobe *et al.*, 2008), European countries (Molina-Montes *et al.*, 2016) and Japan (Yamagiwa *et al.*, 2020). One study was conducted exclusively on male participants (Bobe *et al.*, 2008), two on female participants (Arts *et al.*, 2002, Cutler *et al.*, 2008) and the rest of the studies included both sexes. One study had a case-control design, whereas seven studies had cohort designs. The follow-up duration ranged from 8 (Nöthlings *et al.*, 2007) to 18 (Cutler *et al.*, 2008) years. All investigations used a validated food frequency questionnaire to assess dietary polyphenol intake, and the highest and lowest intakes of polyphenols were considered.

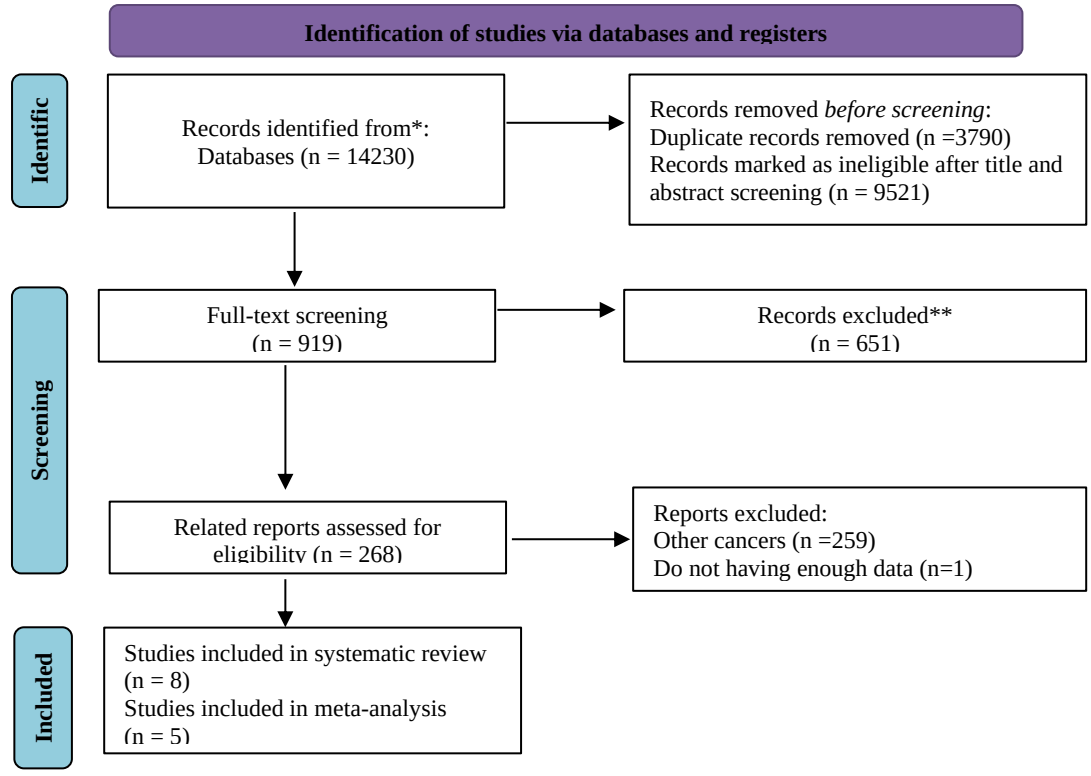

Figure 1. Flow diagram of the study selection procedure for systematic review and meta-analysis

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Table 2. Epidemiologic studies on polyphenols intake in association with pancreatic cancer risk.

First author, (Year), Country	Design/Follow-Up (year)	Cases/Controls or Cohort size	Sex	Age, dietary assessment	Polyphenols	Contrast	Adjusted OR	Adjustments	Quality Score
Rossi *et al.* (2012), Italy.	Case–control/-	326/652	F, M	80.34, FFQ	Flavanols, Flavanones, Flavonols, Flavones Anthocyanidins, Proanthocyanidins	Q5 vs Q1	0.63(0.38-1.03) 0.68(0.41-1.14) 0.69(0.42-1.13) 0.88(0.53-1.46) 0.83(0.43-1.60)	Age, Gender, Center of study, Year of the interview, Education, History of diabetes, Tobacco smoking, Alcohol drinking, and Nonalcohol energy intake.	6
Arem *et al*. (2013), USA.	Prospective-Cohort/10.6	2379/537104	F, M	71.50, FFQ	Total flavonoids, Flavan-3-ols, Flavones, Flavonols Flavanones, Anthocyanidins, Isoflavones	Q5 vs Q1	1.09(0.96-1.24) 1.03(0.91-1.17) 1.09(0.95-1.25) 1.09(0.95-1.24) 1.06(0.92-1.21) 1.10(0.96-1.27) 0.96(0.84-1.09)	Age, Gender, Smoking, Diabetes, BMI, Alcohol, Calories, Saturated fat and Red meat intake	8
Bobe *et al*. (2008), Finland.	Prospective-Cohort/16.1	306/27111	M	69.50, FFQ	Total flavonoids, Flavan-3-ols, Flavones, Flavonols Kaempferol, Myricetin Quercetin, Catechin Epicatechin, Apigenin, Luteolin	Q5 vs Q1	0.90(0.64-1.28) 0.92(0.64-1.31) 0.99(0.70-1.42) 0.91(0.64-1.30) 0.93(0.65-1.33) 1.04(0.73-1.49) 1.07(0.75-1.53) 0.95(0.66-1.36) 0.90(0.63-1.28) 1.06(0.74-1.51) 1.09(0.77-1.56)	Age, Years of smoking, Total number of cigarettes per day, Self-reported history of diabetes mellitus, and Energy-adjusted saturated fat intake.	7
Molina-Montes *et al.* (2016), EU countries.	Prospective-Cohort/11.3	865/477309	F, M	70.25, FFQ	Total flavonoids, Flavan-3-ols, Flavones, Flavonols Flavanones, Anthocyanidins, Flavanols Proanthocyanidins, Anthocyanidins, Isoflavones Lignans, Theaflavins	Q5 vs Q1 Q4 vs	1.10(0.85-1.42) 1.23(0.93-1.62) 0.95(0.73-1.25) 1.31(1.00-1.72) 0.84(0.66-1.07) 1.02(0.78-1.33) 1.13(0.87-1.46) 1.02(0.80-1.31) 1.02(0.78-1.33) 0.91(0.64-1.28) 0.99(0.74-1.34)	Age, Gender, Centre, Total energy intake from fat and nonfat sources, BMI, Smoking status and intensity, Alcohol intake, Diabetes status at recruitment	5

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						Q1	1.35(1.03-1.75)	
Nothlings *et al.* (2007), USA.	Prospective-Cohort/8	529/183518	F, M	75.45, FFQ	Flavonols, Quercetin Kaempferol, Myricetin Flavonols, Quercetin Kaempferol, Myricetin Flavonols, Quercetin Kaempferol, Myricetin	Q5 vs Q1 Q4 vs Q1 Q4 vs Q1	0.77(0.58-1.03) 0.80(0.60-1.06) 0.78(0.58-1.05) 0.85(0.65-1.12) 0.78(0.55-1.13) 0.79(0.55-1.14) 0.72(0.49-1.04) 0.72(0.50-1.03) 0.87(0.60-1.25) 0.85(0.58-1.23) 0.87(0.60-1.27) 0.97(0.69-1.37)	Age, History of diabetes mellitus, Family history of pancreatic cancer, BMI, Smoking status, Processed and red meat intake, Energy intake	6
Arts *et al*. (2002), USA.	Prospective-Cohort/13	130/33339	F	69.55, FFQ	Catechins	Q4 vs Q1	0.74(0.46-1.20)	Age, Total energy intake, BMI, Waist-to-hip ratio, Physical activity, Smoking, Alcoho, fruit and vegetable.	5
Yamagiwa *et al*. (2020), Japan.	Prospective-Cohort/16.9	577/90185 263/48286 314/41899	F, M	69.40, FFQ	Genistein, Genistein, Genistein	Q4 vs Q1	1.33(1.03-1.73) 1.46(1.00-2.12) 1.22(0.85-1.74)	Age, Gender, Smoking, Physical activity, History of diabetes mellitus, Family history of pancreatic cancer, BMI, intak of Ethanol, Fish, Meat, Vegetable, Fruit, Coffee, and Energy.	8
Cutler *et al*. (2008), USA.	Prospective-Cohort/18	230/34708	F	69.55, FFQ	Total flavonoid, Isoflavones Anthocyanidins, Flavones Flavanones, Flavonols Flavan-3-ols, Proanthocyanidins, Total, Proanthocyanidins	NR	NR	Age, Gender, Daily energy intake, Education level, Race, BMI, Multivitamin use, Activity level, Smoking history, and Pack years.	6

***M**: Male; **F**: Female; **FFQ**: Food frequency questionnaire; **Q**: Quantile; **BMI**: Body mass index; **NR:** Not reported; **USA**: United States of America*

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Quality assessment

Studies were identified as poor, fair, or high quality according to the modified NOS thresholds, of 0-3, 4-6, and 7-9, respectively (Stang, 2010). The authors classified three studies as high (Arem *et al.*, 2013, Bobe *et al.*, 2008, Yamagiwa *et al.*, 2020) and five as fair (Arts *et al.*, 2002, Cutler *et al.*, 2008, Molina-Montes *et al.*, 2016, Nöthlings *et al.*, 2007, Rossi *et al.*, 2012).

Meta-analysis

Dietary polyphenol intake and pancreatic cancer odds: Three articles with cohort designs were included in the analysis of total flavonoid intake and flavan-3-ols to the odds of pancreatic cancer (Arem *et al.*, 2013, Bobe *et al.*, 2008, Molina-Montes *et al.*, 2016). The mean follow-up time for the pooled studies was 12.6 years (range 10.6-16.1 years). No associations between total flavonoid (Q5 vs. Q1: OR=1.07, 95% CI: 0.96, 1.19, I^2=0.00%, P-value for heterogeneity=0.58) or flavan-3-ol (Q5 vs. Q1: OR=1.05, 95% CI: 0.94, 1.17, I^2=0.00%, P-value for heterogeneity=0.39) intake and cancer risk were detected, with no evidence of heterogeneity (**Figures 2 and 3**).

Four studies (three cohorts and one case-control) were included in the analysis of the association between flavones and the odds of pancreatic cancer (Arem *et al.*, 2013, Bobe *et al.*, 2008, Molina-Montes *et al.*, 2016, Rossi *et al.*, 2012). The mean follow-up time was 12.6 years (range 10.6-16.1 years). Furthermore, there was no significant difference in the odds of pancreatic cancer according to the highest intake of flavones compared to the lowest intake (Q5 vs. Q1: OR=1.04, 95% CI: 0.93, 1.17; **Figure 3**), with no evidence of heterogeneity (I^2=0.00%, *P*=0.71).

Five studies (four cohorts and one case-control) assessed the association between flavonol intake and pancreatic cancer risk (Arem *et al.*, 2013, Bobe *et al.*, 2008, Molina-Montes *et al.*, 2016, Nöthlings *et al.*, 2007, Rossi *et al.*, 2012). The mean follow-up time was 11.5 years (range 8-16.1 years). The pooled OR for pancreatic cancer, comparing the highest versus lowest flavonol intake quintiles, was also Q5 vs. Q1 (OR=1.02, 95% CI: 0.86, 1.21; **Figure 3**), and the heterogeneity was low (I^2=44.66%, *P*=0.12).

Three articles (two cohort and one case-control) were included in the analysis of flavanone and anthocyanidin intake concerning the pancreatic cancer odds (Arem *et al.*, 2013, Molina-Montes *et al.*, 2016, Rossi *et al.*, 2012). The mean follow-up time for these studies was 11 years (range 10.6-11.3 years). The overall ORs for flavanone and anthocyanidin intake to the risk of pancreatic cancer were as follows: Q5 vs. Q1: OR=0.91, 95% CI: 0.73, 1.15, with high heterogeneity (I^2=58.21%, *P*=0.09); and Q5 vs. Q1: OR=1.07, 95% CI: 0.95, 1.21, **Figure 3**, with low heterogeneity (I^2=0.00%, *P*=0.65).

Qualitative analysis

In a study by Cutler *et al.*, there was no association between pancreatic cancer incidence and total flavonoids, flavanones, anthocyanidins, flavones, flavonols, and flavan-3-ols in postmenopausal females (Cutler *et al.*, 2008). Arem *et al.*, Molina-Montes *et al.*, and Cutler *et al.* reported that isoflavones are not related to the incidence of pancreatic cancer (Arem *et al.*, 2013, Cutler *et al.*, 2008, Molina-Montes *et al.*, 2016). In one study, an inverse association was observed between the odds of pancreatic cancer and the use of proanthocyanidins for proanthocyanidins more than 3-mers (Rossi *et al.*, 2012). Moreover, two studies did not demonstrate this relationship (Cutler *et al.*, 2008, Molina-Montes *et al.*, 2016). There was no relationship between kaempferol, myricetin, or quercetin and pancreatic cancer according to Gerd Bobe *et al.* and Ute Nothlings *et al* (Bobe *et al.*, 2008, Nöthlings *et al.*, 2007). Additionally, two studies did not observe this relationship with catechins (Arts *et al.*, 2002, Bobe *et al.*, 2008), and no association between flavanols and pancreatic cancer was observed in these two studies (Molina-Montes *et al.*, 2016, Rossi *et al.*, 2012). The remaining polyphenols, including epicatechin, apigenin, luteolin, and lignans, did not show any association (Bobe *et al.*, 2008, Molina-Montes *et al.*, 2016).

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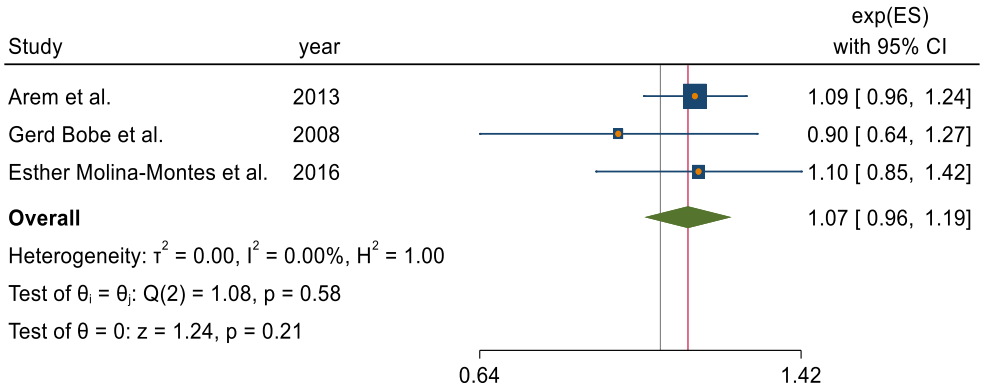

Figure 2. Meta-analysis of dietary intake of total flavonoids and risk of pancreatic cancer.

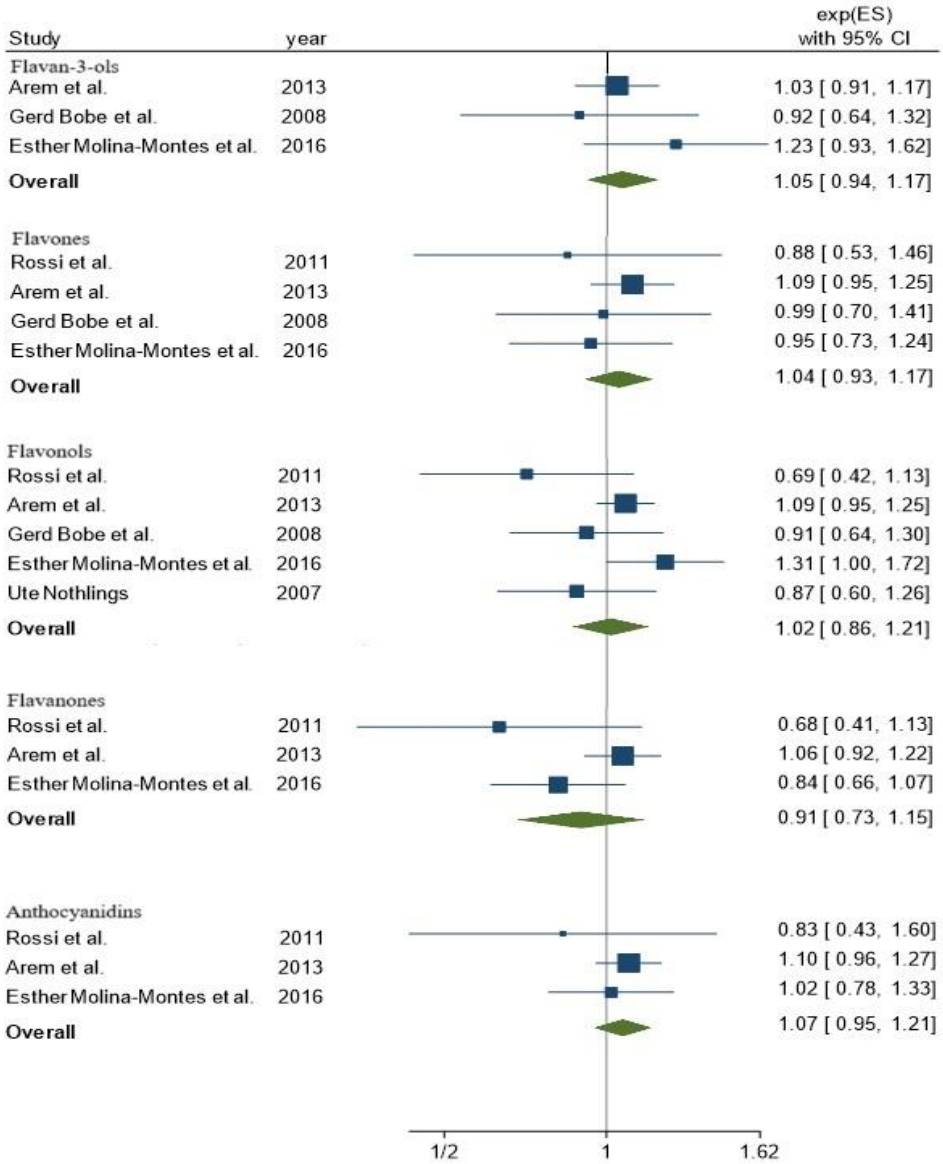

Figure 3 Meta-analysis of dietary intake of flavonoids subclasses and risk of pancreatic cancer.

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Sensitivity analysis

According to the sensitivity analysis, by removing one study each time, the results did not change significantly for polyphenols, which showed that the results for total flavonoids, flavan-3-ols, flavones, flavonols, flavanones, and anthocyanidins were consistent and reliable.

Publication bias

An overview of the Begg funnel plot did not show any asymmetry in the meta-analysis of the total flavonoid, flavan-3-ol, flavone, or anthocyanidin intake to the odds of pancreatic cancer. No evidence of substantial publication bias was identified for total flavonoids (*P*=0.45 Begg's test; *P*=0.29 for Egger's test), flavan-3-ols (*P*=0.96, Begg's test; *P*=1.00, Egger's test), flavones (*P*=0.27, Begg's test; *P*=0.73, Egger's test), or anthocyanins (*P*=0.35, Begg's test; *P*=0.29, Egger's test). Although Begg's test for flavonol intake and cancer risk was significant (*P*=0.08), Egger's test did not confirm bias (*P*=0.13). Egger's test for the association between flavones and cancer revealed a significant publication bias (*P*=0.03), but Begg's test was not significant (*P*=0.29). Using the "trim and fill" method, two potentially missing studies were imputed for flavonol and flavanone intake, and no significant change in overall associations was observed.

In summary, the overall association between flavonoids and pancreatic cancer risk using the random effects model is shown in **Table 3**.

Table 3. Meta-analysis showing the overall association between flavonoids and pancreatic cancer risk, using random effects model.

Exposure	Number of Studies	Meta-analysis	Heterogeneity		Publication bias		
		Effect size (95% CI)	P-value				
			Effect	within heterogeneity	Begg's test	Egger's test	I^2 (%)
Total flavonoid	3	1.07(0.96,1.19)	0.21	0.58	0.29	0.45	0.00
Flavan-3-ols	3	1.05(0.94,1.17)	0.40	0.39	1.00	0.96	0.00
Flavones	4	1.04(0.93,1.17)	0.47	0.71	0.73	0.27	0.00
Flavonols	5	1.02(0.86,1.21)	0.83	0.12	0.08	0.13	44.66
Flavanones	3	0.91(0.73,1.15)	0.43	0.09	0.29	0.03	58.21
Anthocyanidins	3	1.07(0.95,1.21)	0.26	0.65	0.29	0.35	0.00

P-value effect < 0.05 is significant, P-value Egger's test and Begg's test < 0.1 is significant.

Discussion

This study investigated the association between polyphenol intake and pancreatic cancer odds in eight observational studies with 1384252 participants and 5342 pancreatic cancer. This systematic review and meta-analysis revealed no relationship between polyphenol intake and pancreatic cancer odds; however, in two studies, a positive relationship was observed between genistein and theaflavin intake and pancreatic cancer risk.

The authors are unaware of any systematic reviews or meta-analyses published in this field. In line with the results, Arem *et al*., Molina-Montes *et al.*, and Cutler *et al.* reported no association between total flavonoid intake or any flavonoid subtypes and pancreatic cancer risk (Arem *et al.*, 2013, Cutler *et al.*, 2008, Molina-Montes *et al.*, 2016). Although Rossi et al. demonstrated in a case-control study that dietary proanthocyanidins may confer some protection against pancreatic cancer risk, another subclass of flavonoids did not confirm this effect (Rossi *et al.*, 2012). The association between catechin intake and pancreatic cancer incidence reported by Arts et al. was not statistically significant (Arts *et al.*, 2002). A pooled analysis of 15 prospective cohorts, including 52,680 participants and 3,205 prostate cancer patients, revealed no association between the consumption of fruits and vegetables as the main

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source of polyphenols and prostate cancer risk (Petimar *et al.*, 2017).

Consistent with this study, Bobe *et al*. reported a significant relationship between total flavonoids, flavonols, flavan-3-ols, kaempferol, quercetin, catechin, and epicatechin and low pancreatic cancer risk and suggested that a flavonoid-rich diet may reduce the incidence of pancreatic cancer in smokers who do not consume supplemental A-tocopherol and/or B-carotene (Bobe *et al.*, 2008). Similarly, Nothlings *et al.* demonstrated a protective effect of total flavonol intake on pancreatic cancer risk, particularly in current smokers (Nöthlings *et al.*, 2007). Animal studies have shown that food-derived polyphenols, including quercetin and transresveratrol, inhibit pancreatic cancer development and prevent metastasis (Mouria *et al.*, 2002). In both in vitro and in vivo models of pancreatic cancer stem cells, quercetin targets pancreatic cancer stem cells and inhibits their growth by reducing their proliferation, angiogenesis, cancer stem cell marker expression, and inducing apoptosis (Zhou *et al.*, 2010). They reported that hispidulin, a small flavonoid molecule, suppresses angiogenesis and the development of human pancreatic cancer (He *et al.*, 2011).

Studies have shown that polyphenol consumption increases the risk of pancreatic cancer. Yamagiwa reported that the highest intake of genistein was significantly positively associated with the incidence of pancreatic cancer (Yamagiwa *et al.*, 2020).

Polyphenols have long been known as natural antioxidants and secondary plant metabolites, including over 4000 types that are grouped into nine categories: flavonoids, isoflavonoids, aurones, chalconoids, flavonolignans, lignans, stilbenoids, curcuminoids, and tannins. Flavonoids are divided into six subclasses: flavones, isoflavones, flavonols, flavanones, flavanols, and anthocyanins (Cory *et al.*, 2018, Tešić *et al.*, 2018). The anticancer mechanisms of these compounds include inhibition of proliferation, induction of apoptosis, and suppression of the cell cycle. Moreover, polyphenols can modulate signaling pathways and impact epigenetic modifications, such as DNA methylation and the expression patterns of microRNAs (miRNAs) (Nasir *et al.*, 2022). Importantly, the bioavailability of polyphenols is low, and although polyphenol components exist in many foods, their health benefits hinge on the amount of ingested polyphenols, especially their bioavailability and bioaccessibility. The poor bioavailability of polyphenol components in fruit and vegetable matrices is due to their low bioaccessibility in the small intestine due to the physical and chemical interactions of polyphenols with the indigestible polysaccharides of cell walls (Bié *et al.*, 2023).

This study had several limitations. First, dietary assessment techniques and nutrient databases are influenced by measurement errors, which can lead to inaccurate risk assessment. Second, due to the small number of studies, subgroup analysis and meta-analysis of other polyphenol types, including quercetin, were not possible. Third, the adjustments for confounding variables were not the same across all studies. Fourth, the interaction between the highest intake of polyphenols in one study and the lowest intake in another may have affected the results. Notably, the quality of the meta-evidence in the current study was very low. Therefore, future investigations should be conducted to confirm these findings.

Conclusion

In conclusion, the authors did not observe a relationship between polyphenol intake and pancreatic cancer odds. However, polyphenols have poor bioavailability and bioaccessibility, which raises the question of whether the anticancer effect of polyphenols in vitro and in vivo is overstated or whether dietary intake of polyphenols does not have this effect and needs to be consumed as an extract. Notably, the type of polyphenol administered may also be important. Considering these findings, the results of this study should be interpreted with caution, and further high-quality research with a precise design needs to be performed to determine whether there is a relationship.

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Authors' contributions

Salehi-Abargoui A, Forootani B, and Yekrang Safakar H. contributed to the conception and design of this study. Material preparation, data collection, and analysis were performed by Goodarzi S, Mirjali F, Forootani B, and Yekrang Safakar H. The first draft of the manuscript was written by Goodarzi S and Mirjalili F, and all the authors commented on the previous versions of the manuscript. The final draft of the manuscript has been revised by Salehi-Abargouei A, who had primary responsibility for the final content. All the authors have read and approved the final manuscript.

Confilic of interests

The authors declared no conflict of interests .

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