

REVIEW

Association between Type 2 diabetes mellitus and gastrointestinal cancers: A meta-analysis

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Abstract

In 2020, 19.3 million new cancer cases were reported worldwide, and in 2014, 422 million people had Type 2 diabetes mellitus (T2DM). The association between diabetes mellitus (DM) and cancer is well established, with 5.7% of all incident cancers in 2012 attributable to diabetes. This meta-analysis examined the association between DM and pancreatic cancer (PaC), liver cancer (LC), and colorectal cancer (CRC), along with subgroup analyses on risk modification by the duration of diabetes and gender-based differences. A systematic literature search was conducted on literature databases including PubMed, Google Scholar, Medline, and Scopus for observational studies on DM and these cancers published from January 2005 to March 2023. Accordingly, 36 studies were selected (14 case-control and 22 cohort studies), and summary odds ratio (OR) and risk ratio (RR) were estimated using the Mantel-Haenszel method along with 95% confidence interval (CI). Among cohort studies, CRC showed the highest risk (pooled RR = 2.49, 95% CI: 2.43 – 2.54), followed by PaC (RR = 2.06, 95% CI: 2.0 – 2.13) and LC (RR = 1.70, 95% CI: 1.6 – 1.81). Among case-control studies, LC showed the highest risk (OR = 3.16, 95% CI: 2.89 – 3.46), followed by PaC (OR = 2.8, 95% CI: 2.48 – 3.17) and CRC (OR = 1.43, 95% CI: 1.3 – 1.57). The risk of PaC with DM duration was identified only in cohort studies, with an RR of 2.31 (95% CI: 2.20 – 2.43) for DM <5 years and an RR of 1.67 (95% CI: 1.57 – 1.77) for DM ≥ 5 years. Higher risk was observed in females than males, except in LC, where males showed a higher risk irrespective of study design. In conclusion, diabetes is positively associated with gastrointestinal cancers, with risk varying by DM duration.

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1. Introduction

Worldwide, 19.3 million new cancer cases were reported in the year 2020.¹ Type 2 diabetes mellitus (T2DM) is a chronic illness characterized by hyperglycemia due to metabolic derangements. In 2014, it was estimated that 422 million people globally had diabetes, with a prevalence of 8.5% among adults.² The association between diabetes mellitus (DM) and cancer has been studied for many decades and is well established. In 2012, 5.7% of all incident cancers were attributable to the combined effects of diabetes and high body mass index (BMI), with the largest number of cancer cases attributable to diabetes occurring in East and South-east Asia.³

In India, the National Family Health Survey-5 reveals that 13.5% of the female population and 15.6% of the male population have high blood sugar levels.⁴ As of 2020, there was an estimated 128.6% increase in cancer burden compared to 1991 in India.^{5,6} Most studies linking cancer to diabetes report a strong positive association between DM and colorectal, hepatocellular, gallbladder, and pancreatic cancers (PaC).^{7,8} Globally, 25% of cancers are gastrointestinal, with pancreatic, liver, and colorectal cancers (CRCs) increasing.⁹ Meta-analyses based on cohort studies have reported an association between DM and gastrointestinal cancers.^{10,11} However, limited data are available on variations in gastrointestinal cancer incidence with the duration of DM and gender.

We conducted a meta-analysis based on both case-control and cohort studies published over the past two decades, which provide information on the association between DM and the incidence of gastrointestinal cancers such as pancreatic, liver, and CRC. We also examined the association between these cancers and the duration of diabetes, as well as the role of gender in determining cancer susceptibility in individuals with diabetes.

2. Meta-analysis procedures

2.1. Search strategy

We conducted comprehensive searches across PubMed Central, Google Scholar, Medline, and Scopus databases for articles published between 2005 and 2023, using keywords such as “pancreatic cancer,” “hepatocellular cancer,” “liver cancer,” “colorectal cancer,” “diabetes,” “gastrointestinal cancers,” and “observational studies.” The search strategy in the PubMed Advanced search involved intricate combinations, outlined as follows:

- (i) ((“diabetes”[Title/Abstract] AND “pancreatic cancer”[Title/Abstract] AND “cohort”[Title/Abstract]) OR “diabetes”[Title/Abstract]) AND “pancreatic cancer”[Title/Abstract] AND “case control”[Title/Abstract]
- (ii) ((“diabetes”[Title/Abstract] AND “colorectal cancer”[Title/Abstract] AND “cohort”[Title/Abstract]) OR “diabetes”[Title/Abstract]) AND “colorectal cancer”[Title/Abstract] AND “case control”[Title/Abstract]
- (iii) ((((((“diabetes”[Title/Abstract] AND “hepatocellular carcinoma”[Title/Abstract] AND “cohort”[Title/Abstract]) OR “diabetes”[Title/Abstract]) AND “liver cancer”[Title/Abstract] AND “cohort”[Title/Abstract]) OR “diabetes”[Title/Abstract]) AND “hepatocellular carcinoma”[Title/Abstract] AND “case control”[Title/Abstract]) OR “diabetes”[Title/Abstract]) AND “liver cancer”[Title/Abstract] AND “case control”[Title/Abstract]

Each search was confined to studies published from 2005 to 2023. In addition, the initial 200 Google search results for “observational studies on diabetes and colorectal/pancreatic/liver cancer” were incorporated individually. Reference lists of included articles were manually screened to ensure all relevant studies were identified, minimizing the likelihood of overlooking pertinent studies during the initial online search.

2.2. Exposure and outcome

The literature search and study selection were independently conducted by two investigators, who subsequently reached a final consensus. The studies included in the meta-analysis determined exposure to diabetes through self-administered questionnaires, which were later validated using data from medical registries. Cancer incidence was identified through follow-up via cancer and death registries, with all incident cases being pathologically or radiologically confirmed. Our endpoints of interest were defined as the first cancer diagnosis of interest.

The selected studies reported data on the incidence of various gastrointestinal cancers in subjects with DM compared to those without DM, as well as on the incidence of these cancers in relation to the duration of DM and gender-based differences. Accordingly, 36 studies were selected for inclusion in the meta-analysis: 12 studies on PaC (five case-control and seven cohort studies), 13 studies on CRC (four case-control and nine cohort studies), and 11 studies on liver cancer (LC) (five case-control and six cohort studies).

2.3. Inclusion and exclusion criteria

The studies included in this meta-analysis were required to meet the following criteria: (i) Original studies; (ii) the exposure of interest was diabetes, with the outcome of interest being the incidence of PaC, CRC, or LC; (iii) studies reporting odds ratio (OR) or risk ratio (RR) with 95% confidence interval (CI), or providing sufficient data to manually calculate OR or RR; and (iv) studies involving non-diabetic population as the reference group. Studies that were excluded were: (i) articles published in languages other than English; (ii) studies reporting data on subtypes of DM other than T2DM, including T1DM and gestational DM; and (iii) studies reporting mortality or survival data rather than cancer incidence. The PRISMA flow diagram illustrates the selection process for studies in this meta-analysis, along with the exclusion criteria used (Figure 1).

2.4. Data extraction

Among the 36 observational studies included in this meta-analysis, there were 14 case-control studies with

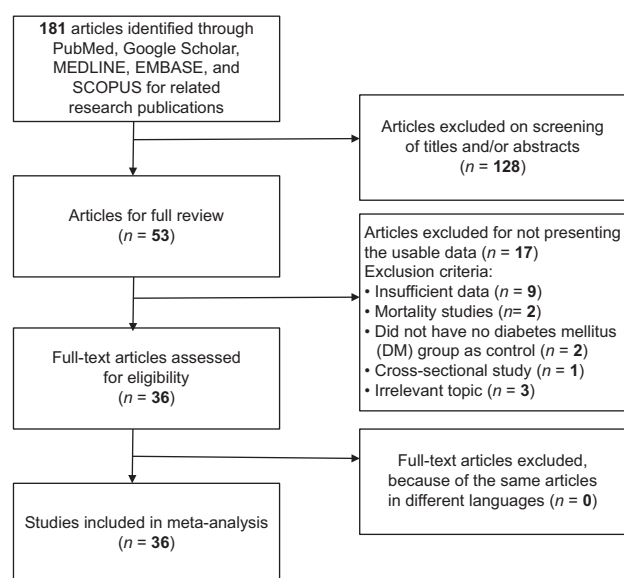


Figure 1. PRISMA flow diagram. The diagram shows the search and selection process

15,482 cases and 72,171 controls, and 22 cohort studies with 69,289 cancers and 1,71,98,014 cohort subjects. All studies underwent independent verification by two investigators. In case-control studies, data on the number of cancer cases and the number of controls with and without a history of DM were extracted. In cohort studies, data on the number of cancers with or without exposure to DM, and cohort subjects with or without exposure to DM, were extracted.

When considering cancer incidence in relation to the duration of diabetes, subjects at risk were stratified into two groups: one group with DM for <5 years and the other group with DM for ≥5 years. Adjusted risks for these two groups were obtained against subjects with no history of DM, and thus pooled risk using adjusted ORs or RRs were calculated separately for those <5 years and those ≥5 years of DM. Data on gender-based differences in determining the effect of DM on cancer incidence were also collected. Adjusted ORs or RRs were extracted from studies that reported gender-specific data, and pooled risks were calculated by comparing individuals with DM to those without DM.

The pooled ORs or RRs along with 95% CI were computed using the Mantel-Haenszel method. In instances where data were unavailable, pooled ORs or RRs were calculated by applying a general variance-based method (based on the CI).¹² Heterogeneity among studies was evaluated using Cochran's Q-test for statistical significance and the I^2 -statistic for percentage of variation).¹³ $P < 0.05$ was considered statistically significant. If the I^2 statistic yielded a small value, indicating negligible variation across studies, the fixed-effect model was chosen; otherwise, the random-

effect model was utilized. Graphical representation of ORs or RRs, along with their 95% CIs for individual studies as well as pooled risks, is displayed in forest plots. These plots depict each study's effect size denoted by a square and their corresponding 95% CIs represented by horizontal lines.

3. Results

3.1. Study characteristics

Among the 36 observational studies, data were collected from countries including the United States of America (USA), China, Italy, Sweden, the United Kingdom (UK), the Netherlands, Korea, Singapore, Spain, and India. DM was determined through self-reporting by participants in 22 studies, hospital record verification in 10 studies, and direct blood sampling in four studies (Tables 1-3). This meta-analysis includes one men-only¹⁴ and three women-only¹⁵⁻¹⁷ cohort studies. Common confounding factors accounted for in these studies included age, gender, BMI or obesity, alcohol consumption, smoking, family history of cancer, ethnicity, physical activity, and education status. In addition, studies focusing on PaC considered a history of pancreatitis, studies on CRC included a history of hormone replacement therapy, non-steroidal anti-inflammatory drug use, and total energy intake from fat in the diet, while LC studies accounted for hepatitis virus infection as a confounding factor.

3.2. PaC

Among the 12 studies reporting PaC (five case-control studies^{15,18-21} and seven cohort studies^{14,15,22}), the association between the duration of DM and PaC was examined. All the case-control studies showed a significant risk among subjects with DM. The total number of cases (subjects with PaC and DM) was 804, and controls (subjects with PaC but without DM) were 558. The pooled OR was 2.80 (95% CI: 2.48 – 3.17). These studies exhibited heterogeneity with a P -value of 0.01 ($I^2 = 69\%$). After excluding one study with a high Q -value,¹⁸ homogeneity was observed ($P = 0.431$). Among the seven cohort studies, six showed a significant risk among subjects with DM.^{14-16,22-24} The total number of cases (subjects with both PaC and DM) was 5,878, and controls (subjects with PaC but without DM) were 13,785. The pooled RR was 2.06 (95% CI: 2.0 – 2.13) (Tables 1 and 2, Figures 2 and 3).

The pooled risk from case-control studies showed an OR of 4.07 (95% CI: 3.35 – 4.94) for DM <5 years and an OR of 2.26 (95% CI: 1.89 – 2.70) for DM ≥5 years. Pooled analysis of cohort studies revealed an RR of 2.31 (95% CI: 2.20 – 2.43) for DM <5 years and an RR of 1.67 (95% CI: 1.57 – 1.77) for DM ≥5 years. Case-control studies showed homogeneity with $I^2 < 25\%$, while cohort studies showed

Table 1. Diabetes mellitus and gastrointestinal cancers: Case-control studies with data on gender subgroups

Gastro-intestinal cancer	Study	Total				OR (95% CI)	Male	Female
		Cancer		Control			Adjusted OR (95% CI)	Adjusted OR (95%CI)
		DM	No DM	DM	No DM			
Pancreatic cancer	Wang <i>et al.</i> ¹⁸	76	455	161	1,538	1.60 (1.19 – 2.14)	1.40 (0.96 – 2.22)	1.70 (1.00 – 2.70)
	Ben <i>et al.</i> ¹⁹	403	1,055	151	1,377	3.48 (2.84 – 4.27)	-	-
	Lipworth <i>et al.</i> ²⁰	103	585	125	2,077	2.93 (2.22 – 3.86)	-	-
	Hassan <i>et al.</i> ²¹	194	614	79	729	2.92 (2.20 – 3.87)	2.00 (1.40 – 3.00)	4.20 (2.20 – 8.10)
	Henry <i>et al.</i> ¹⁵	28	172	42	631	2.45 (1.47 – 4.06)	-	-
Results	Pooled OR					2.80 (2.48 – 3.17)	1.69 (1.30 – 2.19)	2.45 (1.62 – 3.69)
	I ² (<i>P</i> -value)					69.70 (0.010)	0.0 (0.403)	55.47 (0.105)
Colorectal cancer	Woo <i>et al.</i> ²⁵	153	917	237	2,538	1.79 (1.44 – 2.22)	1.47 (1.13 – 1.90)	1.92 (1.24 – 2.98)
	Rosato <i>et al.</i> ²⁶	159	988	188	1,406	1.20 (0.96 – 1.51)	1.13 (0.85 – 1.52)	1.49 (0.94 – 2.36)
	Li <i>et al.</i> ²⁸	302	5,699	1,946	50,158	1.36 (1.21 – 1.55)	1.23 (1.03 – 1.46)	1.26 (1.04 – 1.52)
	Ferreira <i>et al.</i> ²⁷	33	77	16	94	2.51 (1.30 – 4.91)	-	-
Results	Pooled OR					1.43 (1.30 – 1.57)	1.26 (1.11 – 1.44)	1.37 (1.16 – 1.61)
	I ² (<i>P</i> -value)					57.07 (0.072)	0.0 (0.376)	36.44 (0.207)
Liver cancer	Davila <i>et al.</i> ³⁶	892	1,169	1,198	4,985	3.17 (2.85 – 3.53)	-	-
	Donadon <i>et al.</i> ³⁷	145	320	62	428	3.13 (2.25 – 4.35)	3.14 (2.17 – 4.54)	3.12 (1.45 – 6.70)
	Hassan <i>et al.</i> ³⁸	140	280	115	989	4.30 (3.25 – 5.70)	4.28 (3.07 – 5.98)	3.51 (2.04 – 6.02)
	Miele <i>et al.</i> ³⁹	69	154	52	332	2.90 (1.90 – 4.30)	-	-
	Li <i>et al.</i> ⁴⁰	56	244	56	461	1.90 (1.26 – 2.82)	1.81 (1.03 – 3.18)	2.00 (1.13 – 3.54)
Results	Pooled OR					3.16 (2.89 – 3.46)	3.29 (2.63 – 4.13)	2.75 (1.94 – 3.90)
	I ² (<i>P</i> -value)					39.14 (0.160)	55.94 (0.119)	0.0 (0.546)

Abbreviations: T2DM: Type 2 diabetes mellitus; CI: Confidence interval; OR: Odds ratio.

heterogeneity, with the <5 years group showing I^2 of 96% ($P < 0.001$) and ≥ 5 years group an I^2 of 67% ($P = 0.005$) (Table 3).

Females showed greater risk in two case-control^{18,21} and five cohort studies.^{14,16,22-24} After pooling adjusted risks, case-control studies showed an OR of 1.69 (95% CI: 1.30 – 2.19) for males and an OR of 2.45 (95% CI: 1.62 – 3.69) for females. Cohort studies revealed a pooled RR of 1.76 (95% CI: 1.70 – 1.82) for males and a pooled RR of 1.90 (95% CI: 1.80 – 2.01) for females (Figures 4-7). Case-control studies showed homogeneity, while cohort studies had heterogeneity with $I^2 > 90\%$ (Tables 1 and 2).

3.3. CRC

Among the four case-control studies²⁵⁻²⁸ examining the association between DM and CRC, three showed a significant risk.^{25,27,28} In contrast, all nine cohort studies reported a significant risk.^{16,17,29-35} In the case-control studies, the total number of cases (subjects with both CRC and DM) was 647, and controls (subjects with CRC but without DM) were 7,681. After pooling the results, the case-control studies showed a pooled OR of 1.43 (95%

CI: 1.30 – 1.57), while the cohort studies showed a pooled RR of 2.49 (95% CI: 2.43 – 2.54). Homogeneity was observed among the case-control studies ($I^2 = 57\%$, $P = 0.07$), whereas the cohort studies exhibited considerable heterogeneity ($I^2 = 99\%$) (Tables 1 and 2, Figures 2 and 3).

A total of seven studies (two case-control^{25,26} and five cohort^{16,17,32,34,35}) reported on the duration of DM. The pooled risk from case-control studies showed an OR of 1.56 (95% CI: 1.22 – 2.0) for DM <5 years and an OR of 1.32 (95% CI: 1.04 – 1.67) for DM ≥ 5 years (Figures 4-7). Cohort studies revealed a pooled RR of 1.39 (95% CI: 1.29 – 1.50) for DM <5 years and an RR of 1.44 (95% CI: 1.37 – 1.51) for DM ≥ 5 years (Table 3).

Females showed a slightly higher risk in three case-control studies^{25,26,28} and seven cohort studies.^{16,17,29,33-35} The pooled OR was 1.26 (95% CI: 1.11 – 1.44) for males and 1.37 (95% CI: 1.16 – 1.61) for females. The pooled RR was 1.30 (95% CI: 1.28 – 1.32) for males and 1.44 (95% CI: 1.40 – 1.47) for females. There was homogeneity among the case-control studies, while the cohort studies showed an I^2 of 82% ($P < 0.001$) for males and 49% ($P = 0.06$) for females (Tables 1 and 2).

Table 2. Diabetes mellitus and gastrointestinal cancers: Cohort studies with data on gender subgroups

Gastro-intestinal cancer	Study	Total				RR (95% CI)	Male	Female
		Cancer		Control			Adjusted RR (95% CI)	Adjusted RR (95% CI)
		DM	No DM	DM	No DM			
Pancreatic cancer	Wotton <i>et al.</i> ²³	49	267	7,211	175,353	4.43 (3.30 – 6.02)	1.05 (0.93 – 1.17)	1.15 (1.01 – 1.30)
	Atchison <i>et al.</i> ¹⁴	1,656	5,983	543,544	3,586,224	1.82 (1.73 – 1.92)	1.50 (1.42 – 1.59)	Male only
	Henry <i>et al.</i> ¹⁵	25	267	2,180	35,525	1.52 (1.00 – 2.30)	Female only	1.86 (1.23 – 2.83)
	Luo <i>et al.</i> ¹⁶	39	378	7,735	135,258	3.40 (2.65 – 4.36)	Female only	1.79 (1.29 – 2.49)
	Lee <i>et al.</i> ²⁴	2,916	5,673	963,576	3,973,721	2.12 (2.02 – 2.21)	2.20 (2.09 – 2.34)	2.22 (2.07 – 2.38)
	Setiawan <i>et al.</i> ⁵¹	128	280	15,705	32,882	0.96 (0.78 – 1.18)	-	-
	Huang <i>et al.</i> ²²	1,065	937	442,566	1,055,059	2.70 (2.48 – 2.95)	1.85 (1.60 – 2.14)	1.85 (1.61 – 2.14)
Results	Pooled RR					2.06 (2.00 – 2.13)	1.76 (1.70 – 1.82)	1.90 (1.80 – 2.01)
	I ² (P-value)					93.91 (<0.001)	98.29 (<0.001)	94.79 (<0.001)
Colorectal cancer	He <i>et al.</i> ²⁹	694	2,855	30,637	164,956	1.30 (1.20 – 1.41)	1.12 (1.00 – 1.26)	1.34 (1.19 – 1.52)
	Flood <i>et al.</i> ¹⁷	42	447	2,396	42,631	1.66 (1.21 – 2.30)	Female only	1.60 (1.18 – 2.18)
	Jarvandi <i>et al.</i> ³⁰	872	6,726	40,573	435,849	1.40 (1.30 – 1.50)	1.23 (1.13 – 1.34)	1.36 (1.19 – 1.56)
	Sikdar <i>et al.</i> ³³	414	1,249	24,890	95,675	1.27 (1.13 – 1.42)	1.30 (1.28 – 1.32)	1.44 (1.40 – 1.48)
	Luo <i>et al.</i> ¹⁶	155	1,631	7,735	135,258	1.65 (1.40 – 1.94)	Female only	1.57 (1.32 – 1.87)
	Peeters <i>et al.</i> ³¹	2,759	2,359	297,280	297,680	1.17 (1.11 – 1.23)	-	-
	Dankner <i>et al.</i> ³⁴	10,920	7,950	501,750	155,5671	4.19 (4.07 – 4.31)	1.45 (1.37 – 1.55)	1.48 (1.39 – 1.57)
	Pan <i>et al.</i> ³⁵	190	1,721	28,378	463,051	1.80 (1.54 – 2.10)	1.23 (0.99 – 1.52)	1.05 (0.84 – 1.30)
	Pang <i>et al.</i> ³²	292	2,732	29,714	477,398	1.71 (1.51 – 1.93)	-	-
Results	Pooled RR					2.49 (2.43 – 2.54)	1.30 (1.28 – 1.32)	1.44 (1.40 – 1.47)
	I ² (P-value)					99.85 (<0.001)	82.31 (<0.001)	49.70 (0.063)
Liver cancer	Schlesinger <i>et al.</i> ⁴¹	23	153	8 574	354 648	6.20 (4.00 – 9.62)	-	-
	Koh <i>et al.</i> ⁴²	87	412	5 382	55 440	2.16 (1.71 – 2.72)	2.11 (1.58 – 2.81)	2.14 (1.41 – 3.25)
	Nakamura <i>et al.</i> ⁴³	18	158	1 158	26 074	2.54 (1.55 – 4.15)	-	-
	Luo <i>et al.</i> ¹⁶	17	66	7,735	137,611	4.57 (2.70 – 7.80)	-	-
	Pan <i>et al.</i> ³⁵	194	1,746	28,378	463,051	1.81 (1.56 – 2.10)	1.51 (1.25 – 1.84)	1.48 (1.15 – 1.90)
	Yi <i>et al.</i> ⁴⁴	1,196	1,548	164,290	337,612	1.60 (1.50 – 1.71)	-	-
Results	Pooled RR					1.70 (1.60 – 1.81)	1.67 (1.42 – 1.95)	1.63 (1.32 – 2.03)
	I ² (P-value)					67.83 (0.01)	72.24 (0.057)	54.50 (0.138)

Abbreviations: DM: Diabetes mellitus, RR: Risk ratio, CI: Confidence interval.

3.4. LC

Among the five case-control studies³⁶⁻⁴² and six cohort studies^{16,35,41-44} examining the association between DM and LC, a significant risk was observed in all studies. The pooled OR for case-control studies was 3.16 (95% CI: 2.89 – 3.46), and the pooled RR for cohort studies was 1.70 (95% CI: 1.60 – 1.81). Case-control studies showed homogeneity ($I^2 = 39\%$, $P = 0.2$), while cohort studies exhibited heterogeneity ($I^2 = 67\%$, $P = 0.01$). The heterogeneity in cohort studies reduced to 56% after excluding one study⁴¹ with a very high RR (6.20) (Tables 1 and 2, Figures 2 and 3).

The pooled risk from case-control studies showed an OR of 2.08 (95% CI: 1.47 – 2.93) for DM <5 years and an

OR of 5.14 (95% CI: 3.81 – 6.93) for DM ≥5 years. Pooled analysis of cohort studies revealed an RR of 1.91 (95% CI: 1.58 – 2.31) for DM <5 years and an RR of 1.63 (95% CI: 1.30 – 2.03) for DM ≥5 years (Figures 4-7). These results were extracted from three case-control studies³⁸⁻⁴⁰ and four cohort studies^{16,35,41,42} (Table 3).

In LC, males with DM showed a higher risk than females with DM. From three case-control studies,^{37,38,40} the summary OR was 3.29 (95% CI: 2.63 – 4.13) for males and OR 2.75 (95% CI: 1.94 – 3.90) for females. From two cohort studies,^{35,42} the summary RR was 1.67 (95% CI: 1.42 – 1.95) for males and 1.63 (95% CI: 1.32 – 2.03) for females. Cohort studies showed moderate heterogeneity

Table 3. Diabetes mellitus and gastrointestinal cancers: Association with the duration of diabetes

Study design	Pancreatic cancer			Colorectal cancer			Liver cancer		
	Study	DM		Study	DM		Study	DM	
		<5 years	≥5 years		<5 years	≥5 years		<5 years	≥5 years
Case-control studies	Wang <i>et al.</i> ¹⁸	2.40 (1.40 – 4.00)	2.00 (1.20 – 3.40)	Woo <i>et al.</i> ²⁵	1.76 (1.30 – 2.38)	1.69 (1.07 – 2.66)	Hassan <i>et al.</i> ³⁸	3.21 (1.92 – 5.36)	6.13 (4.26 – 8.82)
	Ben <i>et al.</i> ¹⁹	4.43 (3.44 – 5.72)	2.11 (1.51 – 2.94)	Rosato <i>et al.</i> ²⁶	1.21 (0.78 – 1.88)	1.2 (0.91 – 1.57)	Miele <i>et al.</i> ³⁹	2.77 (1.01 – 7.58)	8.62 (2.40 – 31.00)
	Lipworth <i>et al.</i> ²⁰	5.17 (2.71 – 9.87)	2.35 (1.7 – 3.26)				Li <i>et al.</i> ⁴⁰	1.26 (0.73 – 2.16)	3.02 (1.69 – 5.4)
	Hassan <i>et al.</i> ²¹	4.00 (2.5 – 6.6)	2.40 (1.70 – 3.40)						
	Henry <i>et al.</i> ¹⁵	4.00 (0.94 – 16.9)	2.79 (0.97 – 8.04)						
Results	Pooled OR	4.07 (3.35 – 4.94)	2.26 (1.89 – 2.70)	Pooled OR	1.56 (1.22 – 2.00)	1.32 (1.04 – 1.67)	Pooled OR	2.08 (1.47 – 2.93)	5.14 (3.81 – 6.93)
	<i>I</i> ²	14.03	0.0	<i>I</i> ²	47.24	36.63	<i>I</i> ²	54.18	16.28
	<i>P</i> -value	0.324	0.95	<i>P</i> -value	0.168	0.209	<i>P</i> -value	0.11	0.30
Cohort studies	Wotton <i>et al.</i> ²³	4.25 (3.00 – 5.91)	1.38 (0.43 – 3.42)	Flood <i>et al.</i> ¹⁷	0.97 (0.33 – 2.89)	1.49 (0.91 – 2.45)	Schlesinger <i>et al.</i> ⁴¹	2.25 (1.19 – 4.28)	2.09 (1.12 – 3.90)
	Atchison <i>et al.</i> ¹⁴	1.83 (1.66 – 2.02)	1.38 (1.23 – 1.54)	Luo <i>et al.</i> ¹⁶	1.44 (1.16 – 1.78)	1.44 (1.10 – 1.89)	Koh <i>et al.</i> ⁴²	2.41 (1.73 – 3.35)	2.14 (1.38 – 3.33)
	Henry <i>et al.</i> ¹⁵	1.70 (0.78 – 3.67)	2.62 (1.48 – 4.65)	Dankner <i>et al.</i> ³⁴	1.48 (1.35 – 1.63)	1.52 (1.44 – 1.60)	Luo <i>et al.</i> ¹⁶	2.49 (1.19 – 5.21)	3.77 (1.74 – 8.17)
	Luo <i>et al.</i> ¹⁶	1.32 (0.83 – 2.10)	2.17 (1.35 – 3.50)	Pan <i>et al.</i> ³⁵	0.87 (0.64 – 1.19)	0.94 (0.70 – 1.25)	Pan <i>et al.</i> ³⁵	1.56 (1.20 – 2.04)	1.18 (0.87 – 1.61)
	Lee <i>et al.</i> ²⁴	2.14 (2.00 – 2.29)	1.76 (1.62 – 1.91)	Pang <i>et al.</i> ³²	1.28 (1.07 – 1.53)	1.16 (1.02 – 1.32)			
Results	Setiawan <i>et al.</i> ⁵¹	3.71 (2.83 – 4.88)	1.61 (1.18 – 2.21)				Pooled RR	1.91 (1.58 – 2.31)	1.63 (1.30 – 2.03)
	Huang <i>et al.</i> ²²	6.91 (5.76 – 8.3)	1.96 (1.62 – 2.38)				<i>I</i> ²	39.10	72.54
	Pooled RR	2.31 (2.20 – 2.43)	1.67 (1.57 – 1.77)	Pooled RR	1.39 (1.29 – 1.50)	1.44 (1.37 – 1.51)	<i>P</i> -value	0.18	0.012
	<i>I</i> ²	96.93	67.61	<i>I</i> ²	66.88	82.42			
	<i>P</i> -value	<0.001	0.005	<i>P</i> -value	0.02	<0.001			

Abbreviations: DM: Diabetes mellitus; OR: Odds ratio; RR: risk ratio; CI: Confidence interval.

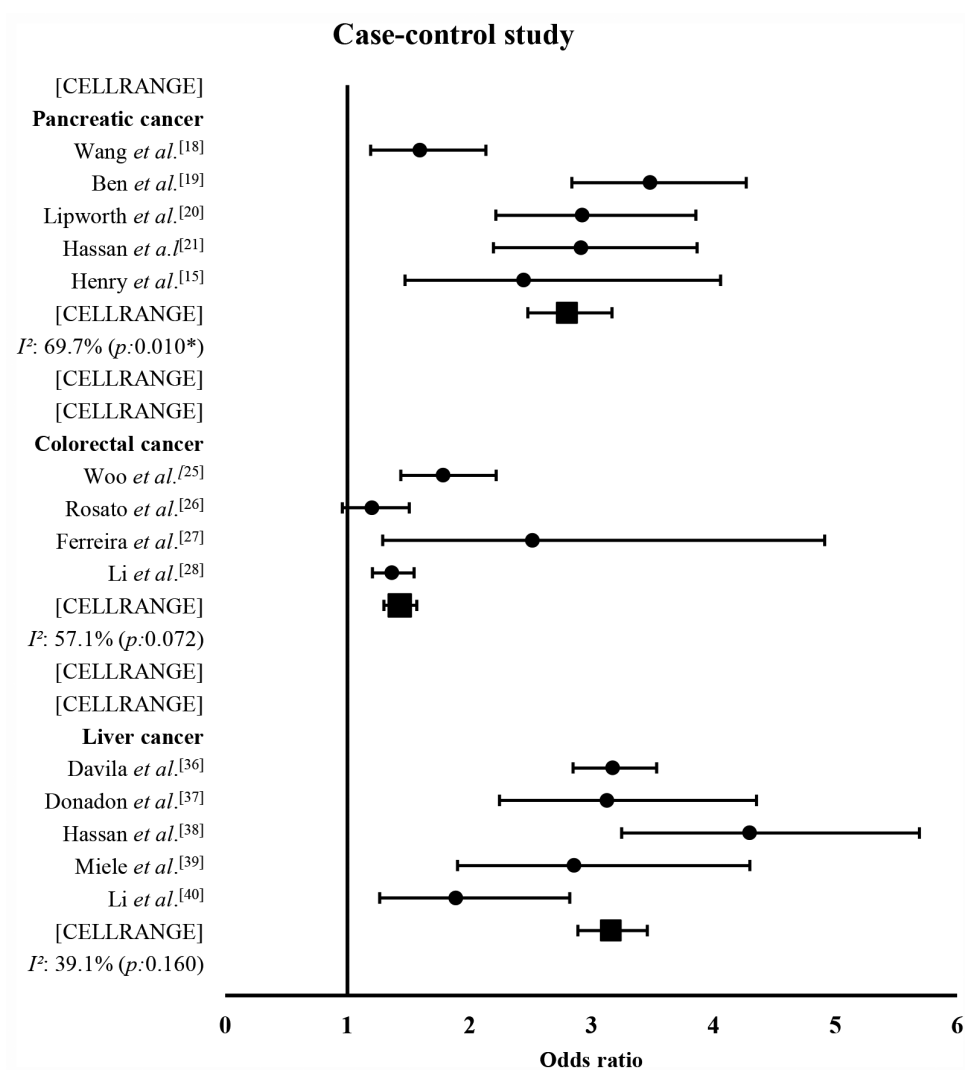


Figure 2. Forest plot showing association between diabetes mellitus (DM) and gastrointestinal cancers for case-control studies
Abbreviation: OR: Odds ratio.

among males ($I^2 = 72\%$, $P = 0.06$), while case-control studies showed homogeneity (Tables 1 and 2).

4. Discussion

The present study discovers a significantly increased risk of cancers in three gastrointestinal organs — pancreas, colorectum, and liver — associated with DM. Specifically, a shorter duration of DM is associated with an increased risk of PaC, while other cancers did not show consistent patterns. Gender-based analysis revealed a higher risk of PaC and CRC in females, whereas males showed a higher risk of LC. Previous meta-analyses on cohort studies have reported an association between DM and cancer at multiple sites.^{3,7,10} However, this meta-analysis is the first to investigate the association between the duration of DM and gastrointestinal cancers.

The pancreas, colorectum, and liver are key organs involved in the pathogenesis of DM. The elevated risk of cancer in DM is believed to arise from several factors, including hyperinsulinemia, hyperglycemia, and chronic inflammation. Cancer and DM also share common risk factors such as obesity, older age, smoking, alcohol, and the use of certain anti-diabetic medications such as DPP-4 inhibitors and GLP-1 receptor agonists.^{45,46} Mendelian randomization studies, which consider genetically predicted DM/insulin levels, have also reported a direct association between DM and cancer at major sites. However, genetically predicted fasting glucose levels or HbA1c levels failed to show such an association.³

The higher incidence of gastrointestinal cancers might be due to the dual impact of DM along with an increase in sedentary lifestyles and the adoption of highly processed,

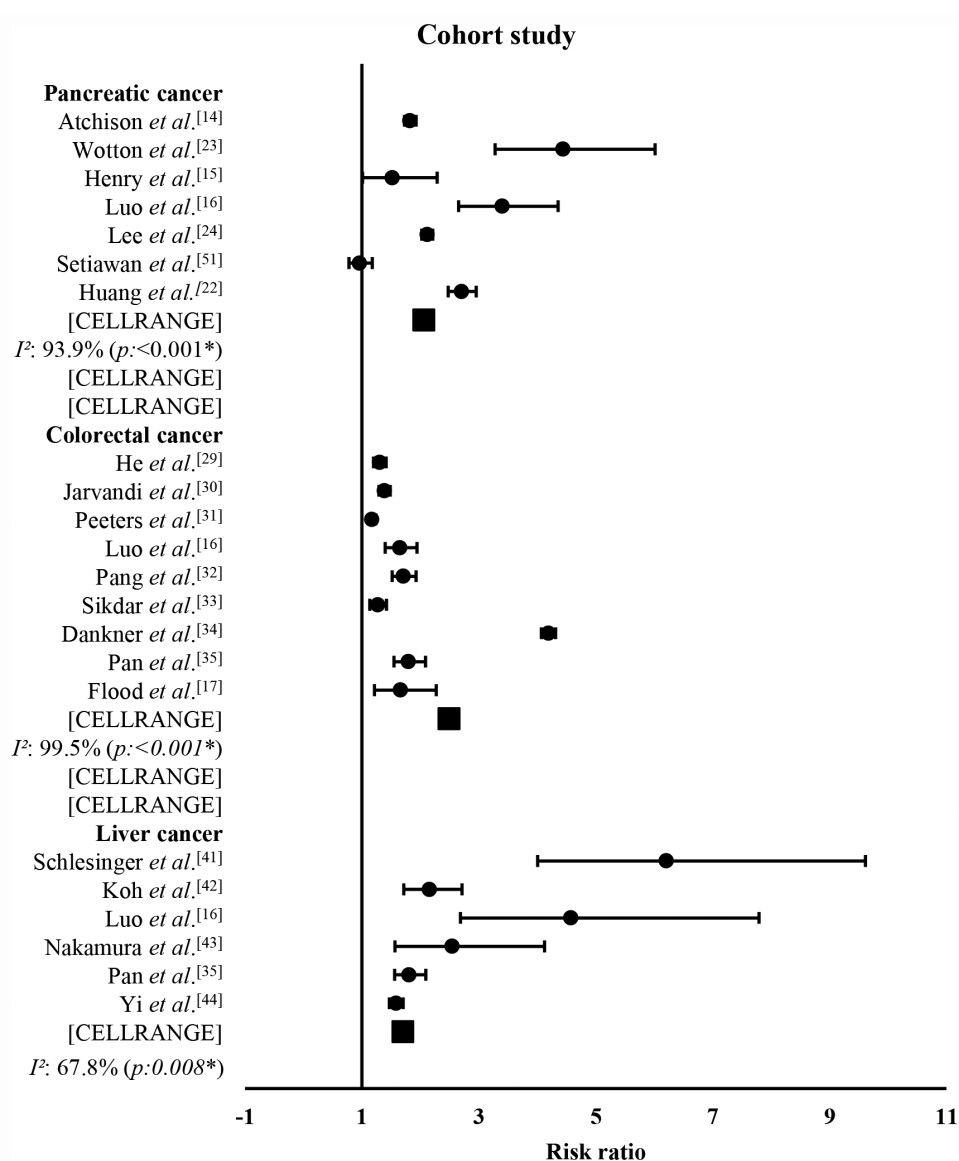


Figure 3. Forest plot showing association between diabetes mellitus (DM) and gastrointestinal cancers for cohort studies
Abbreviation: RR: Risk ratio.

high-fat Western diets, which promote insulin resistance and hyperinsulinemia. Increased levels of insulin-like growth factor-1 in DM also promote tumor cell proliferation and survival.⁴⁷

Among cohort studies, CRC was found to have the strongest association with DM, with diabetics having about 2.5 times higher risk than non-diabetics. Numerous previous studies on multiple cancer sites have similarly reported a greater risk for CRC.⁴⁸ For instance, a meta-analysis on cohorts from the CHANCES consortium in the UK and USA found no association between DM and all cancers combined, but CRC showed a 17% higher risk.¹¹ Guraya⁴⁹ found a 21% higher risk of CRC overall and a higher risk

in women compared to men with DM. The present meta-analysis includes a greater number of studies and a larger sample size. The colorectum is more exposed to high insulin levels through the portal system and to high levels of the tumor-promoting growth factor IGF-1, associated with diabetes, thereby becoming more susceptible to cancers.⁵⁰

Cohort studies exhibited heterogeneity in PaC and CRC in the pooling of results. After excluding three studies,^{14,22,51} the I^2 value for PaC decreased to 77% ($P = 0.004$). However, after excluding four studies,^{29,31,32,34} the I^2 value for CRC showed little change in heterogeneity ($P < 0.001$). This discrepancy might arise from differences in the magnitude of sampling in each cohort study.

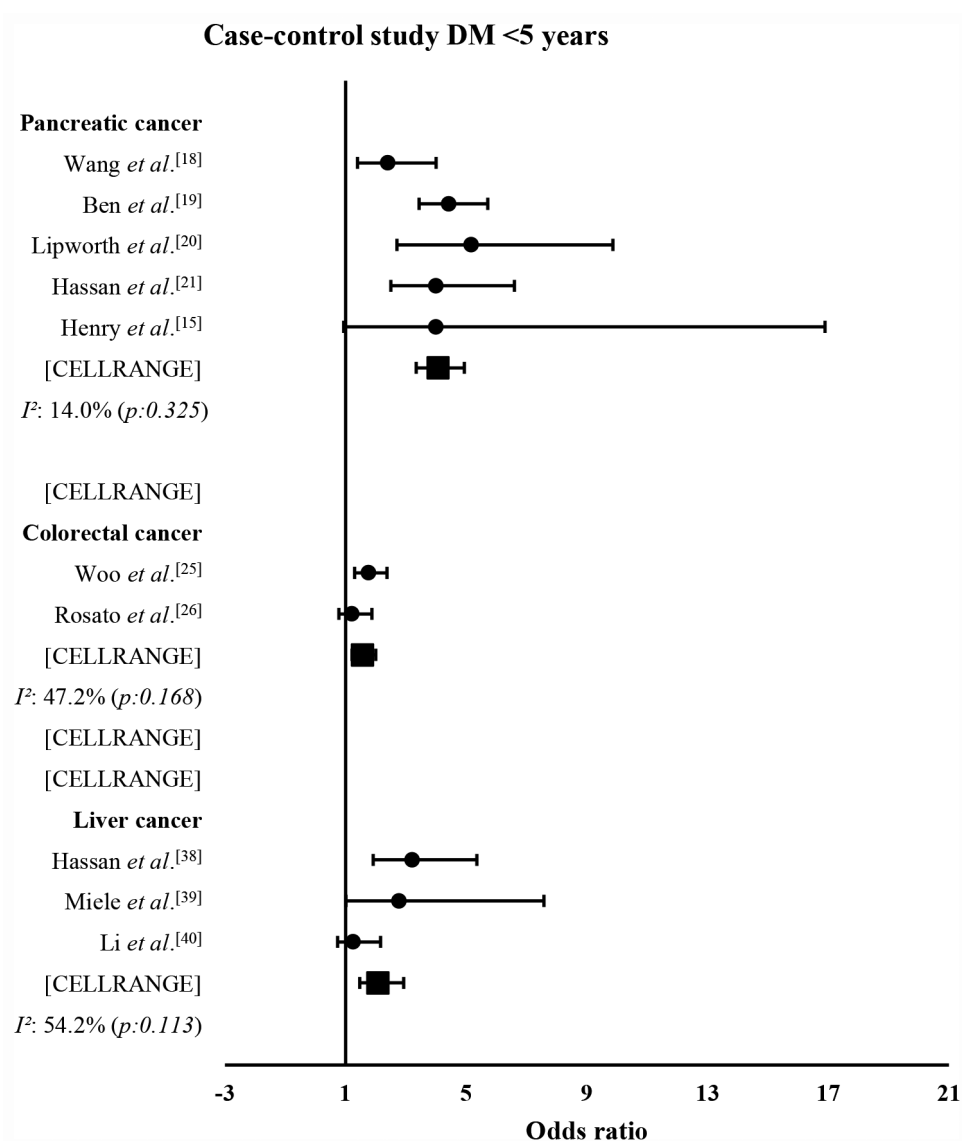


Figure 4. Forest plot showing association between diabetes mellitus (DM) duration <5 years and gastrointestinal cancer for case-control studies
Abbreviation: OR: Odds ratio.

Among case-control studies, LC showed a three-fold increased risk with DM, and homogeneity was observed. This result is higher than that observed in previous studies and is probably due to the pooled values extracted from case-control studies. A meta-analysis in 2012 observed that this risk was independent of alcohol consumption or viral hepatitis status.⁵² DM is a major cause of non-alcoholic fatty liver disease, and the chronic inflammatory state in DM promotes its progression to LC.⁵³

The present analysis showed an elevated incidence of PaC within the first 5 years after a DM diagnosis. DM diagnosed <5 years showed a four-fold increased risk, while DM diagnosed ≥5 years had only a two-fold increased risk

in the pooled analysis of case-control studies. In cohort studies, DM diagnosed <5 years showed a two-fold elevated risk, while DM diagnosed ≥5 years showed a 1.6-fold elevated risk. Among the included studies, the probability of reverse causality — DM being caused by cancer — was reduced by considering cancer cases reported more than 1 year after a DM diagnosis. The temporal association between DM and PaC has been a much-debated topic. New-onset DM caused by pancreatic conditions, called pancreatogenic diabetes, is a potential marker for early detection of PaC, and the cost-benefit ratio of concurrent screening of PaC with a new DM diagnosis is a potential area for further research.

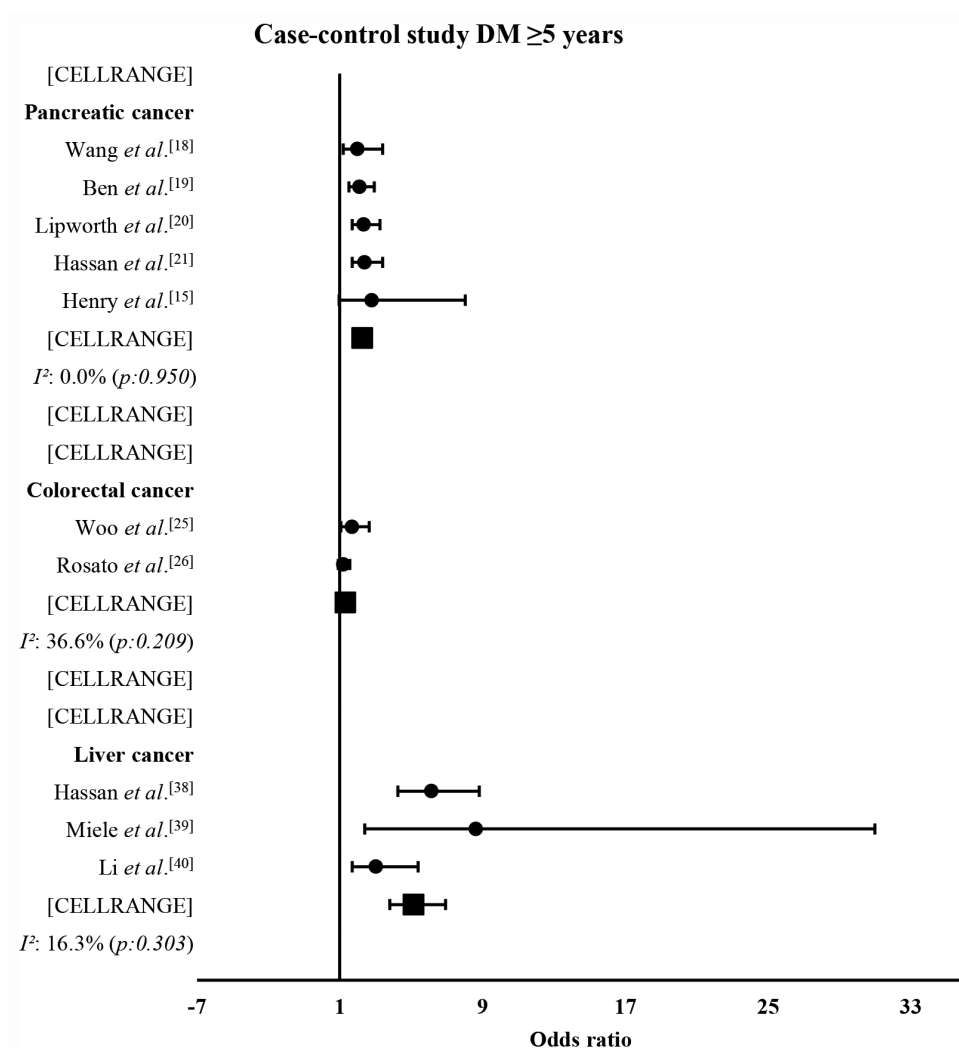


Figure 5. Forest plot showing association between diabetes mellitus (DM) duration ≥ 5 years and gastrointestinal cancer for case-control studies
Abbreviation: OR: Odds ratio.

A study that controlled for common risk factors in both DM and cancer reported that the highest risk for cancer occurred in the initial few years of DM, characterized by hyperinsulinemia. As the duration of DM increased and insulin levels decreased, the risk of cancer also decreased.⁵⁴

The heightened risk for PaC in the early years of DM could be attributed to the proximity of pancreatic cells to the source of hyperinsulinemia. Insulin, known for its growth-promoting effects on tumor cells through IGF-1 activation, stimulates cancer growth in an autocrine manner. However, some studies have suggested an increased risk of PaC in subjects followed up for more than 10 years, indicating that the elevated risk in the initial few years might actually represent undetected PaC presenting as hyperglycemia.^{19,55} Unlike PaC, CRC, and LC did not exhibit a consistent pattern across both study designs. CRC demonstrated a

higher risk in the <5 years group in case-control studies, whereas the association was reversed in cohort studies. A cohort study indicated the highest RR for CRC in the subgroup with a DM duration of <2 years (RR: 1.47, 95% CI: 1.10 – 2.28), with the risk steadily decreasing in those with a duration of ≥ 5 years and becoming insignificant in those >10 years (RR: 0.95, 95% CI: 0.78 – 1.28).³²

LC showed varying associations with DM duration. Case-control studies revealed a 1.5 times higher risk in the DM duration of ≥ 5 years group, while cohort studies showed a 17% higher risk in the group with a duration of <5 years. A meta-analysis of cohort studies noted that a short history of DM was associated with a higher RR for LC, although there was only a slight difference in summary RR (SRR) (SRR = 3.76; 95% CI: 2.90 – 4.87 vs. SRR = 3.17; 95% CI: 2.40 – 4.17).⁵² DM is often accompanied by chronic

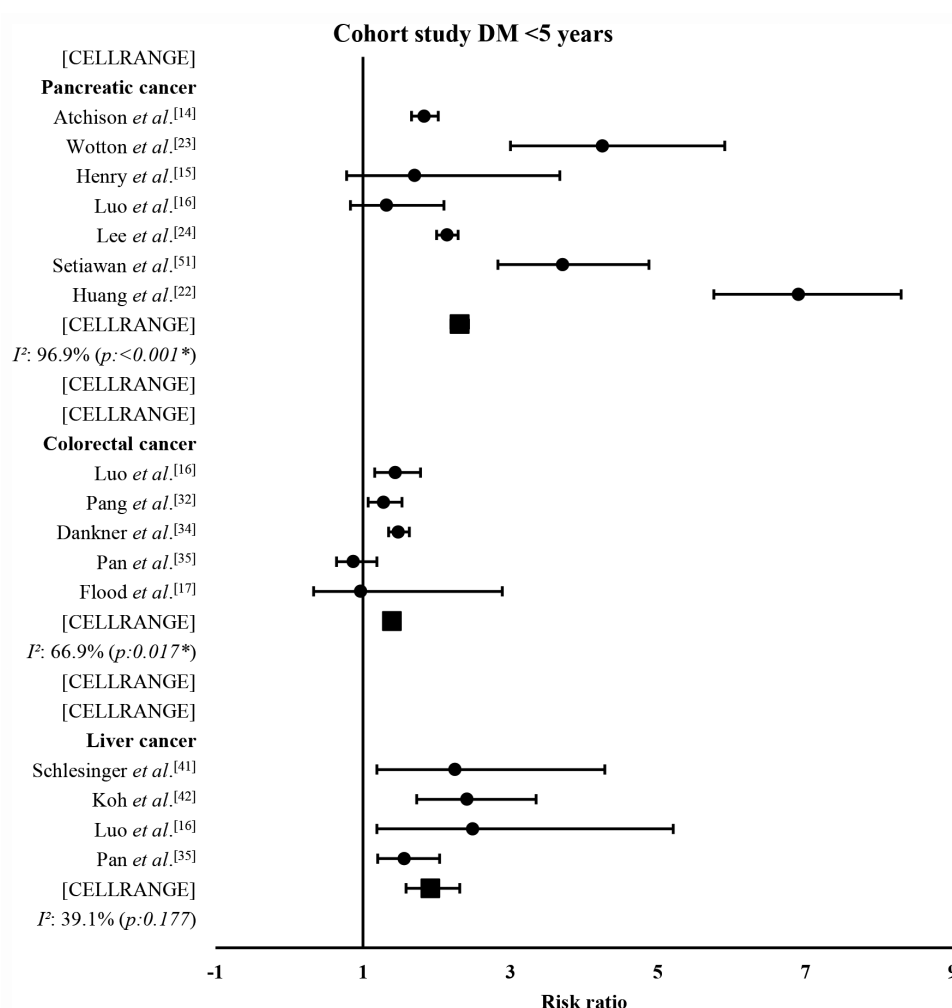


Figure 6. Forest plot showing association between diabetes mellitus (DM) duration <5 years, and gastrointestinal cancer for cohort studies
Abbreviation: RR: Risk ratio.

hepatitis, fatty liver, and cirrhosis, with LC often being the culmination of these conditions. It is indicated that DM is associated with hepatocarcinogenesis through the development of non-alcoholic steatohepatitis, as evidenced by *in-vitro* studies, animal models, and epidemiologic studies. Several studies also observed an increased risk with DM duration. A cohort study reported that the risk for LC increased over the years since DM diagnosis.⁵⁶ Therefore, it is plausible that the slightly higher risk in the earlier group might indeed be hyperglycemia caused by LC.

In the present study, females exhibited a higher risk for PaC and CRC cancers, whereas males showed a higher risk for LC. This result aligns with the results of a large-scale meta-analysis conducted in 2018 on 121 cohort studies, which reported that females with diabetes had a 6% greater risk of all cancers compared to males with diabetes.⁵⁷ Poor glycaemic control and long exposure to insulin resistance

and hyperinsulinemia in women were cited as possible reasons for the higher risk observed in females. In addition, a meta-analysis of studies on CRC reported a 4% higher risk in females than males.⁵⁰ The elevated risk for LC in men is likely attributed to risk modification by factors such as BMI and smoking status. Studies have identified male sex, viral hepatitis, and alcohol consumption as factors increasing LC risk in diabetics.⁵² This study corroborates previous findings on the role of diabetes and various attributes of diabetic patients in gastrointestinal cancers.

The shorter duration of DM in newly diagnosed cancer cases could indicate reverse causality, particularly in gastrointestinal cancers, given the close link between the pancreas, liver, and colon, and glucose metabolism and insulin secretion.⁵⁸ The heightened susceptibility in females with DM to gastrointestinal cancers, in addition to their inherent risk of gynecological cancers such as breast

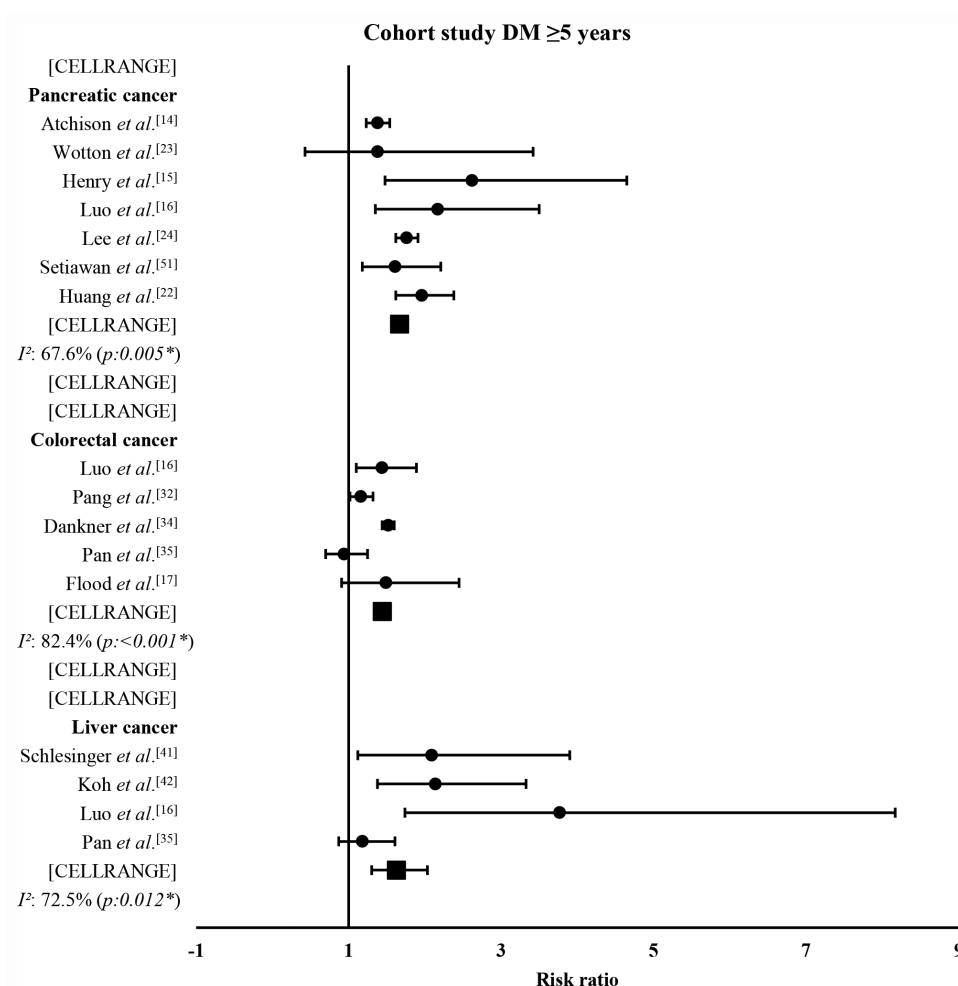


Figure 7. Forest plot showing association between diabetes mellitus (DM) duration ≥5 years and gastrointestinal cancer for cohort studies
Abbreviation: RR: Risk ratio.

and endometrial cancers, is concerning. Previous studies have highlighted lesser adherence to medication among females as one of the factors contributing to this gender-based disparity.⁵⁷

The present meta-analysis offers several strengths: (i) consideration of both case-control and cohort studies, (ii) inclusion of studies from diverse regions covering multiple ethnicities, and (iii) calculation of SRRs and ORs from crude data, ensuring uniformity across studies. However, this analysis also has certain limitations: (i) variations in the fixed duration of diabetes across studies, which could introduce disparities in pooled values; (ii) inclusion of single-sex studies, potentially biasing sex-specific analyses; and (iii) exclusion of the association between DM and other gastrointestinal cancers such as esophageal and gastric cancers due to fewer published articles satisfying inclusion criteria and lesser established associations between diabetes and other cancers.

5. Conclusion

There is a positive association between DM and gastrointestinal cancers. A shorter duration of diabetes was associated with a higher risk for PaC, irrespective of study design. Screening newly diagnosed DM patients for markers of PaC could offer significant advantages in early detection and intervention. LC and CRC, which tend to develop with increasing duration of DM, timely screening and regular follow-up are essential for early detection and intervention. In addition, males with DM are at greater risk of LC, highlighting the importance of efforts to reduce contributing risk factors, particularly alcoholism.

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Conflict of interest

There is no competing interest that could be perceived as prejudicing the impartiality of the research reported.

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