SYSTEMATIC REVIEW AND META-ANALYSIS

DOI: http://dx.doi.org/10.15403/jgld-5527

Long-Term Risk of Colorectal Cancer in Patients With Prediabetes: A Comprehensive Systematic Review and Meta-Analysis

Praneeth Reddy Keesari[1], Akhil Jain[2], Yashwitha Sai Pulakurthi[3], Rewanth R. Katamreddy[3], Ali Tariq Alvi[4], Rupak Desai[5]

1) Department of Internal Medicine, Staten Island University Hospital, Staten Island, New York; 2) Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX; 3) Department of Internal Medicine, New York Medical College - Saint Michael's Medical Center, Newark, NJ; 4) Department of Internal Medicine, HCA Florida, Westside Hospital, Plantation, Florida; 5) Independent Researcher, Atlanta, GA, USA

Address for correspondence:
Akhil Jain, MD
Department of Leukemia, The University of Texas MD Anderson Cancer Center
1515 Holcombe Blvd Houston, TX 77030 United States
akhiljaindr@gmail.com; ajain9@mdanderson.org

Received: 15.02.2024
Accepted: 08.05.2024

ABSTRACT

Background & Aims: Prediabetes is often underdiagnosed and underreported due to its asymptomatic state in over 80% of individuals. Considering its role in promoting cancer incidence and limited evidence linking prediabetes and colorectal cancer (CRC), we conducted a systematic review and meta-analysis to evaluate the incidence of colorectal cancer in people with prediabetes.

Methods: A comprehensive search through PubMed/Medline, Embase, Scopus, and Google Scholar was performed until June 1, 2022, to screen for studies reporting CRC incidence/risk in prediabetics. Binary random-effects models were used to perform meta-analysis and subgroup analyses. Sensitivity analysis was done using leave-one-out method. The quality of the studies was assessed by the Newcastle Ottawa Scale for observational studies.

Results: Seven prospective and one retrospective study comprising 15 cohorts and a pooled number of 854,876 cases and 219,0511 controls were included in the analysis (2 Japan, 2 Korea, 1 Sweden, 1 UK, 1 China, and 1 USA). After combining all the studies, the forest plots for adjusted analysis shows a statistically significant increase in odds of having CRC with prediabetes (OR=1.16; 1.08–1.25, p< 0.01; I2=56.06%) and unadjusted analysis also shows a statistically significant increase in odds of having CRC with prediabetes (OR=1.62; 1.35–1.95, p< 0.01; I2=85.72%). Sensitivity analysis using the Leave-one-out method did confirm equivalent results. Subgroup analysis based on type of study, the odds of developing CRC was higher in prospective studies (OR=1.175; 1.065-1.298) (p=0.001) than retrospective studies (OR=1.162; 1.033- 1.306) (p=0.012). The odds of developing CRC were not significantly higher in ages >60 (OR=1.446; 0.887-2.356) (p=0.139) compared to less than 60 years. The strongest association b/w prediabetes and CRC was found on a median 5-10 years (aOR=1.257; 1.029-1.534) (p=0.025) follow-up compared to < 5 years and 10 years and higher.

Conclusions: This study showed that the odds of developing CRC is 16% higher in patients with prediabetes than those with normal blood glucose. Lifestyle modifications such as weight loss, proper diet, and exercise are essential to control prediabetes. This study further warrants a specific prediabetes screening for patients already at high risk of colorectal cancer with other risk factors.

Key words: prediabetes – hyperglycemia – colon cancer – colorectal cancer – meta-analysis – long-term.

Abbreviations: CI: confidence interval; DM: diabetes mellitus; HR: hazard ratio; CRC colorectal cancer; OR: odds ratio; RR: relative risk.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide, and second only to lung cancer in cancer-related deaths with over 1.9 million new cases and almost 1 million deaths worldwide [1, 2]. More than 50% of cases and deaths are attributable to modifiable risk factors such as a sedentary lifestyle, smoking, or having an unhealthy diet [3]. Regular screening and accessible treatment have evidently reduced or even prevented a large proportion of its incidence and resultant mortality [4]. Men (4.4%) are at a higher risk of developing CRC than women (4.1%) [5].

Surveillance, Epidemiology, and End Results (SEER) data revealed that there is a 3.3% annual decline in incidence rate of CRC among those older than age 65, between 2012 and 2016. Though the incidence of young-onset CRC, i.e. ages <50, decreased from 1975 to 1990, a subsequent annual rise of 2.2% was seen with the most significant increase among

patients between the ages of 20 to 34 [6]. This rise in annual CRC incidence in the young population is of prime concern. This was seconded by a systematic review which included 94 studies, demonstrating the increasing incidence of young-onset colorectal cancer [7, 8].

Furthermore, a retrospective analysis evaluated CRC in 180 patients under the age of 50, 22 (13%) developed recurrence and/or progression of disease to date. Three patients developed metachronous primary colon cancers within 3 to 4 years of their initial resection [9]. Additionally, the prognosis of sporadic CRC was relatively inferior in young patients because of poorer histologic differentiation and delay in diagnosis. Therefore, in such a population, early detection could confer survival benefits. It was also established that postoperative surveillance is essential in young patients due to their higher recurrence rate and metachronous cancer risk [10]. Demonstrated evidence exists regarding risk factors and their implications on cancers, with diabetes being one such risk factor. Cancers of the liver, pancreas and endometrium and their rising incidence were previously proven and demonstrated with the risk of diabetes melitus (DM) [11, 12]. And of note, a meta-analysis of 14 studies, estimated that diabetics were more at stake than non-diabetics for colon cancer [relative risk (RR) =1.38, 95% confidence interval (CI): 1.26-1.51], and for rectal cancer, (RR=1.20, 95%CI: 1.09-1.31). They suggested that DM is an independent risk factor for colon and rectal cancer [13]. Though not entirely clear, in diabetics mechanisms involving the insulin like growth factor (IGF) axis with subsequent cellular damage from inflammatory cytokines provide a foundation for understanding the process of cancer cell proliferation and metastasis [11].

With the rising attention to prediabetes, a precursor state of DM, the idea of cancer and prediabetes-related incidence is being explored, as they might possibly share the exact mechanism in causing cellular damage. In 2014 a meta-analysis concluded that prediabetes showed an increased risk of cancer overall (RR=1.15; 95%CI: 1.06-1.23) with the risk of site-specific cancers with prediabetes being highest for liver, pancreas, endometrial, and stomach/colorectal cancer ($p<0.05$) [14]. As we encourage future studies, we must delve deeper into the association of prediabetes as a risk factor for CRC. Given the limited research on this topic, we explored this connection between prediabetes and CRC through a comprehensive systematic review of literature and meta-analysis.

METHODS

Search Strategy

A comprehensive database search using PubMed/Medline, Embase, Scopus, and Google Scholar was performed until June 1, 2022. Keywords and all the related synonyms were searched for 'colorectal cancer' and 'pre-diabetes / Impaired glucose tolerance'. Case reports, case series and further systematic reviews were excluded from the search (Fig. 1).

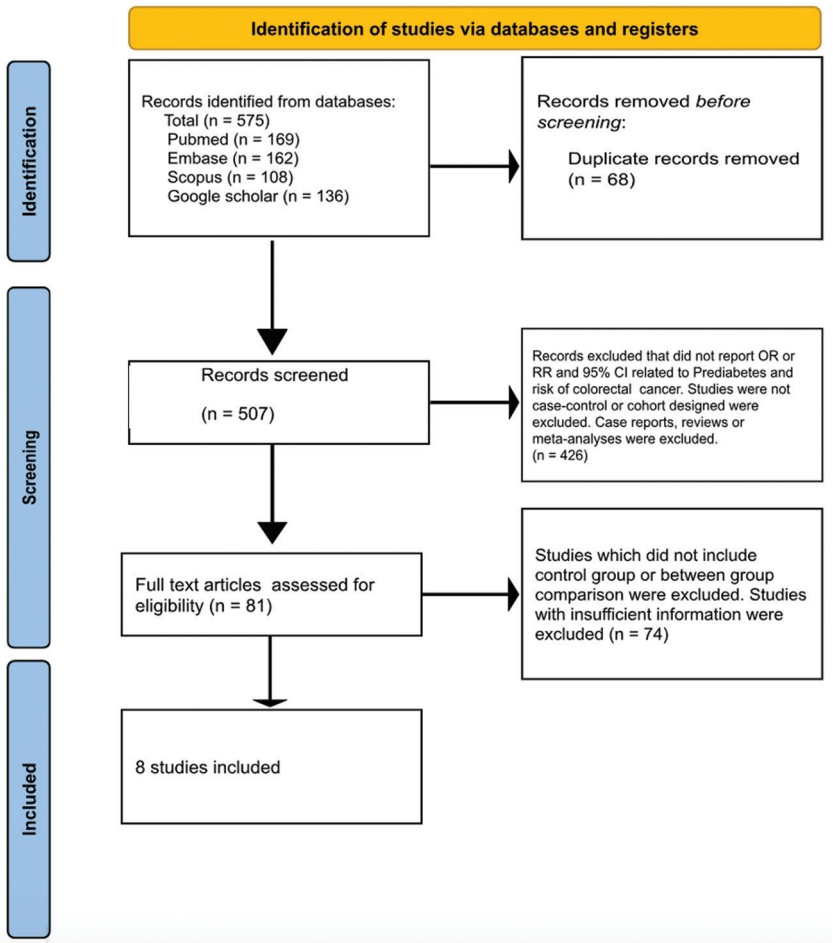

Fig. 1. PRISMA flow diagram for study selection

Selection of Studies

Abstracts and full texts were screened by following the PICO [1 - population, 2 - intervention, 3 - comparison group, 4 - outcome] criteria. Inlusions criteria were: 1) study was conducted in prediabetic adult population defined by fasting blood glucose between 100 and 125 mg/dl or 2 hours postprandial glucose between 140 and 199 mg/dl or Hemoglobin A1C between 5.7 and 6.5% or reported as prediabetes; 2) screening/follow-up for prediabetes was the intervention/exposure that was noted in the study; 3) study included a comparison group of normoglycemic adults (without prediabetes/impaired fasting glucose/DM); 4) study reported CRC as the outcome. All the studies that meet the PICO criteria, observational studies, case control and cohort studies, and studies where outcomes were reported for patients with the prevalence, incidence, odds ratios (ORs) / RRs / hazard ratios (HRs) of CRC in prediabetes were included. Case reports, case series, letter to editor, correspondence, animal studies, in-vitro studies and systematic reviews, meta-analyses are excluded from the study design. Screening was done by 4 authors to assess the included 7 prospective and 1 retrospective studies (2 Japan, 2 Korea, 1 Sweden, 1 UK, 1 China, and 1 USA). Newcastle Ottawa Scale Tool for the critical appraisal of studies can be seen in Supplementary file (Table I).

Data Extraction and Meta-analysis

Data was extracted by 6 authors and then independently assessed by 2 reviewers. Data was analyzed using Open[Meta] Analyst software. We used a Binary random-effects model to analyze the data with unadjusted and adjusted effect size (ES) (HR or OR) with 95%CI. Unadjusted and adjusted (multivariable regression analysis) ORs were extracted. If the studies reported multiple ORs, they were entered separately in the meta-analysis. Heterogeneity was assessed using the I2 statistic. The p-values less than 0.05 were considered statistically significant.

RESULTS

The analysis comprised seven prospective [15-21] and one retrospective studies [22] (2 Japan, 2 Korea, 1 Sweden, 1 UK, 1 China, and 1 USA) with 15 groups and a total of 854,876 cases and 219,0511 controls (Table I). Analysis revealed statistically significant increase in unadjusted (OR=1.62; 95%CI: 1.35-

Table I. Baseline characteristics of included study population

Study	Country/ region	Definition of pre diabetes/Impaired fasting glucose/Impaired glucose tolerance	Total sample size	Number of Colorectal cancer cases	Age(years) Mean/ Median	Follow-up duration in years	Study design	Adjusted confounders
Itoh et al. [22]	Japan	High normal FPG - FPG 100-109; IFG - FPG 110-125 mg/dl	1,441,311	5,318	46	3.1	Retrospective	Age, gender, obesity, high waist circumference, hypertension, dyslipidemia, cigarette smoking, alcohol consumption, and physical inactivity
Ke et al. [15]	China	IFG - FPG 110-125 mg/dL IGT= 2h plasma glucose 140-199 mg/L IFG and IGT categorized as prediabetes	9,224	31	58	7.5	Prospective	Age and gender
Parekh et al [16]	USA	FPG > 110 mg/dL	4,615	136	67	37	Prospective	Age, gender, alcohol, smoking, and BMI
Stocks et al. [17]	Sweden	IFG (6.1–6.9 mmol/L) and IGT (8.9–12.1 mmol/L)	647	306	59	20	Prospective	BMI
Jung et al. [18]	Korea	High normal FPG - FPG 100-109; IFG - FPG 110-125 mg/dl	144,527	280	41	5.3	Prospective	Age and gender
Goto et al. [19]	Japan	HbA1c 5.7-6.4%	29,629	247	63	8.5	Prospective	Age, public health center area, BMI (continuous), smoking status, sports and physical activity, alcohol consumption, energy-adjusted vegetable intake (quartiles), total energy intake (quartiles), coffee consumption
Jee et al. [20]	Korea	FPG 110-125 mg/dl	1,298,385	NA	47.45	10	Prospective	Age, age squared, amount of smoking, and alcohol use
Rentsch et al. [21]	UK	HbA1c 6-6.4%	378,253	2,358	61	7.1	Prospective	Age, gender, ethnicity, deprivation, BMI, physical activity, cardiovascular and diabetes diagnoses at baseline, smoking status, and alcohol consumption.

FPG: fasting plasma glucose; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; BMI: body mass index.

1.95, p< 0.01, Fig. 2a) and adjusted (OR=1.16; 95%CI: 1.08-1.25, p<0.01, Fig. 2b) odds of having CRC with prediabetes. Sensitivity analysis utilizing the leave-one-out approach confirmed the increased risk of CRC in prediabetes (Fig. 3). Heterogeneity analysis for unadjusted OR had statistically significant heterogeneity with an overall I2 of 85.72% (p<0.01) whereas for adjusted OR it showed moderate heterogeneity with an overall I2 of 56.06% (p<0.01). Depending on the type of study, subgroup analysis showed an OR of 1.175 for having CRC in prospective studies (12 groups, 95%CI: 1.065-1.298, p=0.001) The OR in the only available retrospective studies was 1.162 (2 groups, 95%CI: 1.033-1.306, p=0.012) (Fig. 4c). Though subgroup analysis based on age did not show increased CRC risk in people over 60 (2 groups, OR=1.446; 95%CI: 0.887-2.356, p=0.139), it was increased in those under 60 years (11 groups, OR=1.124, 95%CI: 1.066-1.186, p<0.001) (Fig. 4a). Subgroup analysis was also performed on the basis of the duration of follow-up since prediabetes diagnosis. All the 3 sub-groups had statistically significantly higher CRC diagnosis risk in prediabetes than normoglycemic, i.e., 1.162 for less than 5 years (2 groups, 95%CI: 1.033-1.306, p=0.012), 1.257 for 5-10 years follow-up (5 groups, 95%CI: 1.029-1.534, p=0.025), 1.149 for more than 10 years (7 groups, 1.026-1.286, p=0.016) (Fig. 4b). The risk of bias was assessed using a funnel plot (Fig. 5).

DISCUSSION

Previous studies show that both DM and prediabetes are reported as metabolic risk factors for cancer incidence and prevalence. DM has been studied at length for its association with CRC, but there is a lack of data to prove the impact of prediabetes on CRC incidence. Our novel and unique meta-analysis utilizing publicly available databases with a systematic approach investigated the link between prediabetes and CRC. The results of our analysis are 1) a positive association between CRC and prediabetes; 2) young population i.e. age < 60 showed a statistically significant association than age > 60, for prediabetes & CRC; 3) individuals with prediabetes requiring both short & long-term follow-ups had a higher risk for a CRC diagnosis.

Several researchers contributed to developments in connecting DM and CRC. In 1995, Giovannucci et al. [23] hypothesized that DM might be a risk factor for developing CRC [23]. Later in 2014, Huang et al. [14] researched the risk of CRC in prediabetes in their meta-analysis. Following this, the growing interest worldwide led to studying not just DM but also hyperglycemia in relation to various cancers and their incidence. Systematic reviews by Shen et al. [24] in 2021 and Teymoori et al. [25] in 2022, investigated and reported a higher risk of CRC in metabolic syndrome and a positive association between CRC mortality and higher dietary insulin load.

In our meta-analysis, we included all recent studies from 2013 onwards except Jee et al. [20] from 2005. GLOBOCON 2018 stated that developed countries are at the highest risk of CRC. For colon cancer, Southern Europe, Australia/New Zealand, and Northern Europe are the regions of highest incidence and for rectal cancer, incidence was higher in Eastern Europe, Australia/New Zealand, and Eastern Asia [26]. GLOBOCON 2020

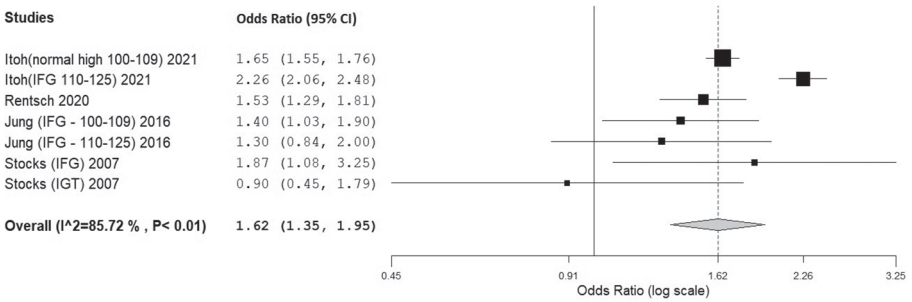

Fig. 2a. Unadjusted pooled odds of colorectal cancer in patients with prediabetes vs. normoglycemic population.

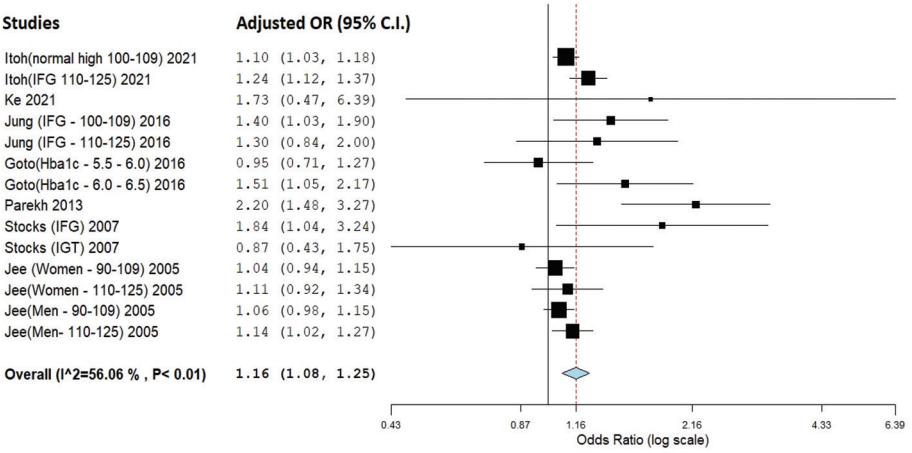

Fig. 2b. Adjusted pooled odds of colorectal cancer in patients with prediabetes vs. normoglycemic population.

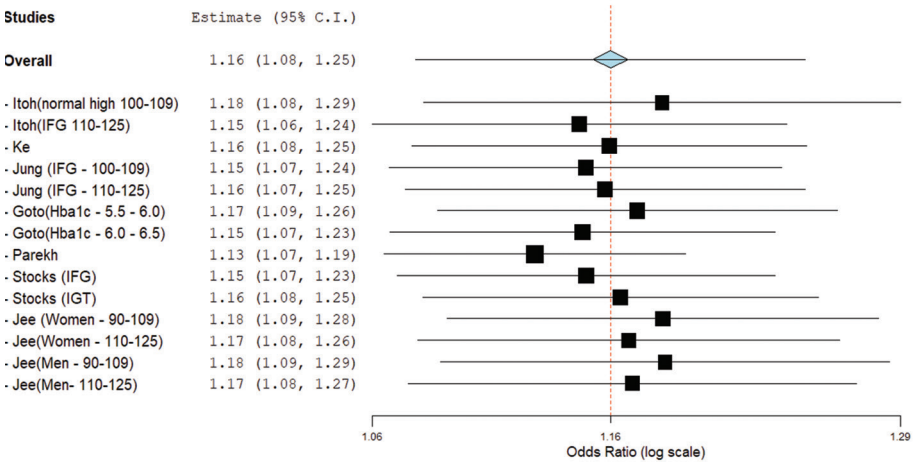

Fig. 3. Sensitivity analysis using leave-one-out method confirming equivalent results.

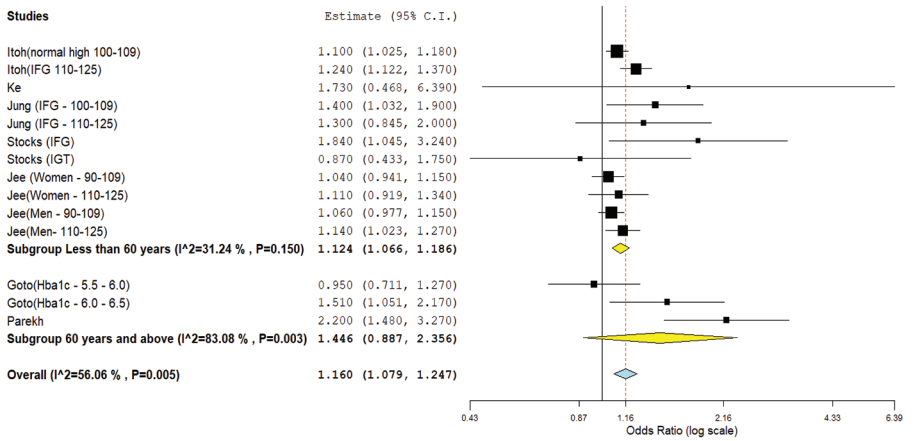

Fig. 4a. Subgroup analysis by mean/median age of population (age ≥ 60 years vs age < 60 years).

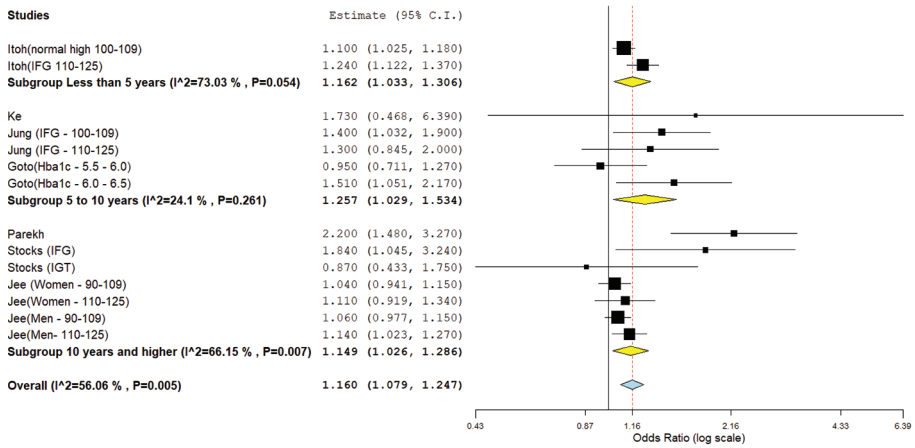

Fig. 4b. Subgroup analysis by Median Duration of Follow-up (years).

stated that China and the United States would have the highest estimated number of new CRC cases in the next 20 years [27]. Our included studies were reported from Japan, Korea (eastern Asia), the UK, China, the USA, and Sweden.

With the exception of the study by Rentsch et al. [21], all other research investigations provided adjusted ORs. Among these studies, the Japanese studies exhibited the most comprehensive adjustment for various factors. Specifically, Itoh et al. [22] reported HRs, which were adjusted for age, sex, obesity, high waist circumference, hypertension, dyslipidemia, cigarette smoking, alcohol consumption, and physical inactivity. In contrast, Gota et al. [19] additionally incorporated adjustments for public health centers and a history of cardiovascular disease into their analysis.

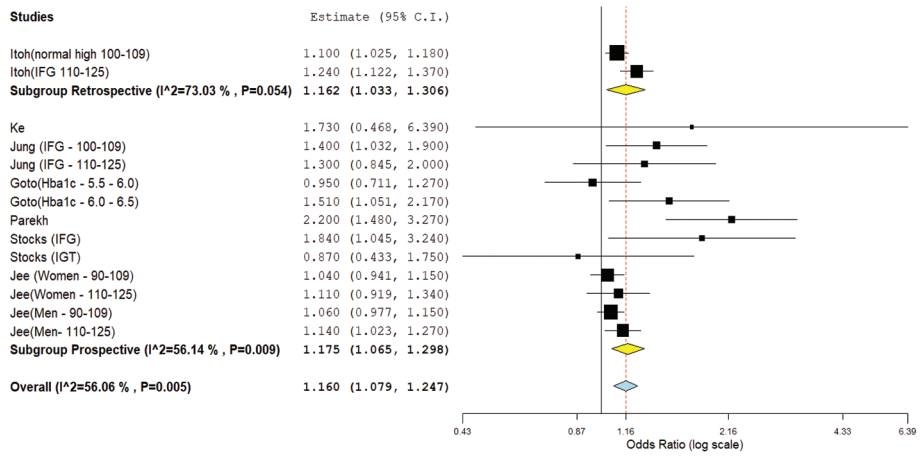

Fig. 4c. Subgroup analysis by study design i.e retrospective vs prospective.

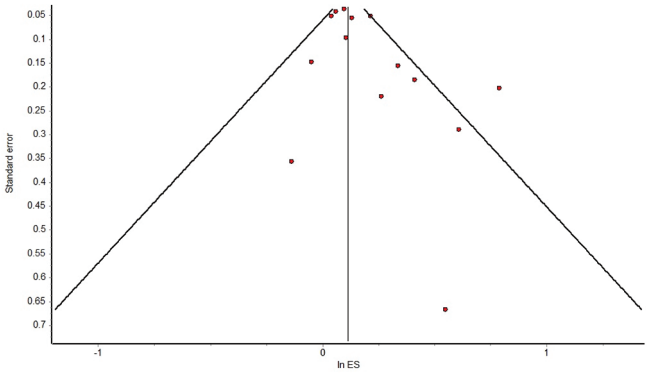

Fig. 5. Funnel plot of the included studies assessing risk of colorectal cancer in individuals with prediabetes.

The American study conducted by Parekh et al. [16] adjusted for age, sex, alcohol consumption, smoking, and body mass index. Korean studies conducted by Jung et al. [18] and Jee et al. [20], as well as Chinese studies conducted by Ke et al. [15], focused their adjustments solely on age and gender. Meanwhile, a Swedish study by Stock et al. [17] reported body mass index-adjusted ORs for CRC risk after controlling for variables such as case-control status, sex, age, smoking status, and fasting time before blood draw.

Islami et al. [3] have provided valuable insights into the risk factors associated with CRC. The availability of adjusted effect sizes for various risk factors emphasizes the significance of our own research findings in this context.

Colorectal cancers emerge as a consequence of the clinical evolution of precancerous lesions, following a simplified morphological sequence that progresses from normal tissue to adenomatous polyps, then to dysplasia, and ultimately culminates in CRC. This transformation is primarily driven by genetic mutations, alterations in signal molecules, and changes in cytokines, collectively contributing to the shift in tissue morphology that promotes CRC development. The initiation of inflammation, followed by the establishment of chronic inflammation within the tissue microenvironment, further accelerates the genetic changes conducive to oncogenesis. Numerous studies have explored and reported on the potential association between DM and its role as a precursor, favoring inflammatory pathways that promote the onset of cancer [28].

Insulin resistance is a well-established characteristic of prediabetes. This condition leads to compensatory hyperinsulinemia, elevated insulin growth factors, chronic oxidative stress, and the accumulation of advanced glycation end-products, all of which collectively contribute to the proliferation of abnormal cells [7, 29]. As glycemic control worsens, an increasing amount of DNA damage caused by oxidative stress accumulates. If left untreated, prediabetes can advance to DM in approximately 4 years. However, lifestyle interventions alone have the potential to delay this progression by up to 10 years [30]. The time it takes for a precancerous lesion to develop into CRC can vary significantly between average-risk and high-risk individuals. In high-risk familial syndromes, this process can occur as quickly as 3 years, while in average-risk individuals, it may take up to 10 years for CRC to form. Murphy et al. [6] and Zhou et al. [7] have both documented a trend of CRC occurring at a younger age in recent years. This observation has piqued our interest in examining the interplay between underlying prediabetes, the variable duration for the progression from precancerous lesions to CRC, and the rising incidence of CRC among younger individuals. Consequently, we decided to subgroup our study for analysis based on age and the duration of follow-up years to further investigate these trends.

Strengths and Limitations

Our research study showcases several significant strengths that highlight its credibility. Firstly, our study incorporated a meticulously executed and systematic search process, ensuring that we comprehensively gathered all relevant data and minimized the risk of bias. Secondly, the inclusion of prospective studies in our research design enhances the reliability of our results. Finally, our analysis features accurately adjusted effect sizes, which account for various confounding variables and offer a more precise understanding of the association between prediabetes and CRC.

The studies included in our analysis predominantly originated from Asian countries, such as Japan, Korea, and China, with a smaller representation from Western nations such as the UK, Sweden, and the USA. Our meta-analysis revealed substantial heterogeneity among the included studies. Heterogeneity can potentially impact the reliability and

applicability of our results, and therefore we did the subgroup analysis. Although we conducted subgroup analyses based on the duration of follow-up since prediabetes diagnosis, we did not explore the underlying reasons for these variations in risk over time. Distinct subgroups were unavailable due to heterogeneous data and methods utilized in individual studies. Gaining a deeper understanding of the factors contributing to these temporal changes could further strengthen the conclusions drawn from our study.

While our meta-analysis identified a statistically significant risk of CRC in patients with prediabetes compared to normoglycemic population, the relatively small risk (OR 1.16 - 1.62) identified by our study necessitates cautious interpretation of the results in terms of direct causality. This cautious interpretation is in line with the established criteria for causality and GRADE recommendations, which emphasizes considering factors beyond just statistical significance.

Heterogeneity among studies and potential confounding factors highlight the complexity in relationship between CRC risk and prediabetes. Although our study provides valuable insight into the association between CRC and prediabetes, further high quality studies would be necessary to further clarify the nature of this association and underlying mechanisms.

CONCLUSIONS

In our comprehensive meta-analysis including studies spread globally, we report a 16% higher risk of CRC in patients with prediabetes as compared to those with normal blood sugar levels. High mortality, morbidity, and rise of incidence in younger individuals of CRC demand better understanding and insights into the risk factors of CRC. Efforts must be directed not only on early detection and aggressive management of prediabetes but also conscientious efforts to screen for CRC in these patients. Researchers and policymakers should focus on addressing the gaps and healthcare initiatives addressing prediabetes and CRC. Further research should be directed on the pathophysiology of insulin resistance/prediabetes in the initiation and progression of colorectal carcinoma and possible therapeutic targets.

Conflicts of interest: None to declare.

Authors' contributions: A.G., P.R.K. and R.D. conceived the study. A.G. and P.R.K. designed the study. Y.S.P, R.R.K. and A.T collected the data. A.G., P.R.K. and R.D analysed and interpreted the data. A.G. and P.R.K. drafted the manuscript. All the authprs revised the manuscript and approved the final version of the manuscript.

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://dx.doi.org/10.15403/jgld-5527.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-249. doi:10.3322/caac.21660
2. Siegel RL, Wagle NS, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2023. CA Cancer J Clin, 2023;73:233-254. doi:10.3322/caac.21772
3. Islami F, Goding Sauer A, Miller KD, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin 2018;68:31-54. doi:10.3322/caac.21440
4. Winawer SJ, Zauber AG. The advanced adenoma as the primary target of screening. Gastrointest Endosc Clin N Am 2002;12:1-9. doi:10.1016/s1052-5157(03)00053-9
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30. doi:10.3322/caac.21590
6. Murphy CC, Singal AG, Baron JA, Sandler RS. Decrease in Incidence of Young-Onset Colorectal Cancer Before Recent Increase. Gastroenterology 2018;155:1716-1719.e4. doi:10.1053/j.gastro.2018.07.045
7. Zhou XH, Qiao Q, Zethelius B, et al. Diabetes, prediabetes and cancer mortality. Diabetologia 2010;53:1867-1876. doi:10.1007/s00125-010-1796-7
8. Done JZ, Fang SH. Young-onset colorectal cancer: A review. World J Gastrointest Oncol 2021;13:856-866. doi:10.4251/wjgo.v13.i8.856
9. Myers EA, Feingold DL, Forde KA, Arnell T, Jang JH, Whelan RL. Colorectal cancer in patients under 50 years of age: a retrospective analysis of two institutions' experience. World J Gastroenterol 2013;19:5651-5657. doi:10.3748/wjg.v19.i34.5651
10. Kim TJ, Kim ER, Hong SN, Chang DK, Kim YH. Long-Term Outcome and Prognostic Factors of Sporadic Colorectal Cancer in Young Patients: A Large Institutional-Based Retrospective Study. Medicine (Baltimore) 2016;95:e3641. doi:10.1097/MD.0000000000003641
11. Wang M, Yang Y, Liao Z. Diabetes and cancer: Epidemiological and biological links. World J Diabetes 2020;11:227-238. doi:10.4239/wjd.v11.i6.227
12. Habib SL, Rojna M. Diabetes and risk of cancer. ISRN Oncol 2013;2013:583786. doi:10.1155/2013/583786
13. Yuhara H, Steinmaus C, Cohen SE, Corley DA, Tei Y, Buffler PA. Is diabetes mellitus an independent risk factor for colon cancer and rectal cancer? Am J Gastroenterol 2011;106:1911-1921. doi:10.1038/ajg.2011.301
14. Huang Y, Cai X, Qiu M, et al. Prediabetes and the risk of cancer: a meta-analysis. Diabetologia 2014;57:2261-2269. doi:10.1007/s00125-014-3361-2
15. Ke J, Lin T, Liu X, et al. Glucose Intolerance and Cancer Risk: A Community-Based Prospective Cohort Study in Shanghai, China. Front Oncol 2021;11:726672. doi:10.3389/fonc.2021.726672
16. Parekh N, Lin Y, Vadiveloo M, Hayes RB, Lu-Yao GL. Metabolic Dysregulation of the Insulin–Glucose Axis and Risk of Obesity-Related Cancers in the Framingham Heart Study-Offspring Cohort (1971-2008). Cancer Epidemiol Biomarkers Prev 2013;22:1825-1836. doi:10.1158/1055-9965.EPI-13-0330
17. Stocks T, Lukanova A, Johansson M, et al. Components of the metabolic syndrome and colorectal cancer risk; a prospective study. Int J Obes (Lond) 2008;32:304-314. doi:10.1038/sj.ijo.0803713
18. Jung KJ, Kim MT, Jee SH. Impaired fasting glucose, single-nucleotide polymorphisms, and risk for colorectal cancer in Koreans. Epidemiol Health 2016;38:e2016002. doi:10.4178/epih/e2016002
19. Goto A, Noda M, Sawada N, et al. High hemoglobin A1c levels within the non-diabetic range are associated with the risk of all cancers. Int J Cancer 2016;138:1741-1753. doi:10.1002/ijc.29917

20. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting Serum Glucose Level and Cancer Risk in Korean Men and Women. JAMA 2005;293:194-202. doi:10.1001/jama.293.2.194
21. Rentsch CT, Farmer RE, Eastwood SV, et al. Risk of 16 cancers across the full glycemic spectrum: a population-based cohort study using the UK Biobank. BMJ Open Diabetes Res Care 2020;8:e001600. doi:10.1136/bmjdrc-2020-001600
22. Itoh H, Kaneko H, Okada A, et al. Fasting Plasma Glucose and Incident Colorectal Cancer: Analysis of a Nationwide Epidemiological Database. J Clin Endocrinol Metab 2021;106:e4448-e4458. doi:10.1210/clinem/dgab466
23. Giovannucci E. Insulin and colon cancer. Cancer Causes Control 1995;6:164-179. doi:10.1007/BF00052777
24. Shen X, Wang Y, Zhao R, et al. Metabolic syndrome and the risk of colorectal cancer: a systematic review and meta-analysis. Int J Colorectal Dis 2021;36:2215-2225. doi:10.1007/s00384-021-03974-y
25. Teymoori F, Mokhtari E, Bahrami A, et al. The association of dietary insulin load and index with the risk of cancer and cancer mortality: a systematic review and meta-analysis. J Diabetes Metab Disord 2022;21:1105-1118. doi:10.1007/s40200-022-01013-3
26. Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. Prz Gastroenterol 2019;14:89-103. doi:10.5114/pg.2018.81072
27. Xi Y, Xu P. Global colorectal cancer burden in 2020 and projections to 2040. Transl Oncol 2021;14:101174. doi:10.1016/j.tranon.2021.101174
28. Zhang C, Le A. Diabetes and Cancer: The Epidemiological and Metabolic Associations. Adv Exp Med Biol 2021;1311:217-227. doi:10.1007/978-3-030-65768-0_16
29. Abe R, Yamagishi Si. AGE-RAGE system and carcinogenesis. Curr Pharm Des 2008;14:940-945. doi:10.2174/138161208784139765
30. Tuso P. Prediabetes and Lifestyle Modification: Time to Prevent a Preventable Disease. Perm J 2014;18:88-93. doi:10.7812/TPP/14-002