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ORIGINAL ARTICLE

Diabetes mellitus increases the risk of colorectal neoplasia: An updated meta-analysis

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Summary
Objective: Recent studies proved that patients with diabetes were at significantly higher risk of developing colorectal cancer. However, the association between diabetes mellitus and the risk of colorectal adenoma remains undefined. Thus we conducted an updated meta-analysis to identify the association between diabetes mellitus and the risk of colorectal neoplasia including adenoma and cancer.
Methods: We conducted a search in databases including Pubmed, Web of Science, EMBASE Databases, Cochrane CENTRAL, Wanfang Data, and CNKI database. Case-control and cohort studies were included. All articles were published before January 2015 and the quality of each study was evaluated by the Newcastle-Ottawa Scale. Odds ratios (ORs) or relative risks (RRs) and its corresponding 95% confidence intervals (CIs) for each study were calculated and summary relative risk estimates with corresponding 95% CIs were generated using the random-effects model. Heterogeneity and publication bias were assessed.
Results: Twenty-nine articles including ten case-control studies and nineteen cohort studies were included in this meta-analysis. In a pooled analysis of all studies, diabetes mellitus was

Abbreviations: DM, Diabetes mellitus; CRN, Colorectal neoplasia; CRC, Colorectal cancer; IGF-1, Insulin-like growth factor-1; MOOSE, Meta-analyses of Observational Studies in Epidemiology; RR, Relative risk; OR, Odds ratio; CI, Confidence interval; NOS, Newcastle-Ottawa Scale.

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associated with increased risk of colorectal neoplasia (RR = 1.35, 95% CI = 1.28—1.42). The risk increased significantly for both colorectal cancer (RR = 1.37, 95% CI = 1.30—1.45) and adenoma (RR = 1.26, 95% CI = 1.11—1.44). Subgroup analyses on study design, gender, geographical region, and type of diabetes mellitus further evidenced these findings.
Conclusions: Diabetes mellitus was associated with an increased risk of colorectal neoplasia. Not only the increased risk of colorectal cancer but also the higher risk of adenoma was identified in patients with diabetes mellitus.

Introduction

Diabetes mellitus (DM) is a serious and growing health problem worldwide nowadays. It is estimated that the global prevalence of DM among adults will increase to 7.7% and affect 439 million adults by 2030 [1]. Colorectal neoplasia (CRN) is defined as low-grade dysplasia, high-grade dysplasia, adenoma, and colorectal cancer (CRC). As it is known, CRC is one of the most common cancers around the world as well as the most common malignancy of the gastrointestinal tract [2]. And low-grade dysplasia, high-grade dysplasia, and adenoma are precancerous lesions which will progress to CRC. Previous studies identified that obesity, physical inactivity, visceral adiposity, hyperglycemia, and hyperinsulinemia were risk factors for CRC [3]. Moreover, plenty evidences showed that DM shares several similar risk factors with CRC including western diet, obesity, and physical inactivity, which led to the hypothesis that they might be pathophysiologically associated with each other [4—6].

The hypothesis that DM might be a risk factor for CRC based on hyperinsulinemia was first stated in the 1990s [7,8]. According to this hypothesis, high levels of insulin could enhance mitogenic effects and promote tissue growth and energy metabolism, which increased the risk of CRC. Further studies suggested that elevated levels of insulin and free insulin-like growth factor-1 (IGF-1) promoted proliferation of colon epithelial cells, ultimately resulting in CRC. It was confirmed that insulin enhanced the expression of insulin cognate receptor and the IGF-1 receptor, which led to the proliferation of colon epithelial cells. Compared with normal colon epithelial cells, insulin receptor density in colon cancer cells increased significantly [9,10]. In addition, β-catenin accumulation with altered phosphorylation was proven to be correlated with the proliferation of colorectal epithelium in DM patients [11]. These findings indicated that DM might promote the proliferation of colorectal epithelial cells therefore increased the risk of CRN.

A meta-analysis conducted by Larsson et al. in 2005 suggested that DM was associated with an increased risk of CRC [12]. Since then, several studies have been conducted to examine the association between DM and the risk of CRC and not surprisingly, most of their findings were consistent with the results reported by Larsson et al. Moreover, a few studies also addressed the potential association between DM and colorectal adenoma. However, no meta-analysis was conducted to examine the association between DM and the risk of adenoma or CRN in recent years.

To identify and update the association between DM and risk of CRN, we performed this meta-analysis. We also conducted the subgroup studies based on the study design, CRN type, gender, geographical region, and DM type to further analyze the risk of CRN in DM patients.

Methods

We conducted this meta-analysis in accordance with the Meta-analyses of Observational Studies in Epidemiology (MOOSE), which served as guidelines [13].

Search strategies

We conducted a search in databases including Pubmed, Web of Science, EMBASE Databases, Cochrane CENTRAL, Wanfang Data, and CNKI database. All the articles were published before January 2015. The keywords of search strategies included (''diabetes'', or ''diabetes mellitus'', or ''DM'', or ''insulin resistance'') and (''colorectal'', or ''colon'', or ''rectal'', or ''rectum'') and (''neoplasm'', or ''neoplasia'', or ''cancer'', or ''tumor'', or ''carcinoma'', or ''adenoma'', or ''polyps'', or ''hyperplasia'', or ''dysplasia''). The languages of included articles were strictly limited in English and Chinese. We excluded review articles, commentaries, and book chapters. Each titles and abstracts of studies were checked for relevance and full texts were reviewed if the abstracts referred to the associations between DM and the risk of CRN. We also checked the reference lists of the relevant articles to identify additional studies manually.

Study selection

Studies were included if they met all the following criteria: all studies were designed as observational studies including case-control or cohort studies. Study was considered eligible if it evaluated the risk of CRN in patients with DM or involved the content of evaluating the risk of CRN in patients with DM. The control population should be the non-diabetic population. In addition, original and sufficient data could be extracted to enabling us to calculate relative risks (RRs) or odds ratios (ORs) with their 95% confidence intervals (CIs).

We excluded the studies which were duplication of the previous publications. Articles published by the same authors with overlapping data were taken into comparison