

RESEARCH ARTICLE

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Diabetes History and Gastric Cancer Risk: Different Results by Types of Follow-Up Studies

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Abstract

Objective: The previous systematic reviews evaluating the association between diabetes history and gastric cancer risk showed inconsistent results. The aim was to check through a meta-epidemiological study that the conclusions of systematic reviews evaluating the association between diabetes history and gastric cancer risk might differ by the type of follow-up study. **Methods:** The potential study subjects were follow-up studies selected from the seven systematic reviews obtained by searching PubMed using diabetes and gastric cancer keywords. The selection criterion was defined as a follow-up study for evaluating the association between the history of type 2 diabetes mellitus and the incidence of gastric cancer. And the values of RR and its 95%CI, which adjusted for the most confounders in each paper, were extracted for meta-analysis. A random-effects model meta-analysis by types of the follow-up study and sex group was performed. **Results:** A total of 25 follow-up studies were finally selected for meta-analysis. They were classified into 16 retrospective and 9 prospective studies in types of follow-up study. The statistical significance between diabetes history and gastric cancer risk was found in retrospective studies (sRR=1.17, 95%CI: 1.02-1.34, I-squared =91.0%) but disappeared in prospective studies (sRR=1.09, 95%CI: 0.91-1.29, I-squared = 68.6%). Even in the analysis of subgroups by sex, statistical significance was not found in the prospective study, consistently. **Conclusion:** The main reason for the previous meta-analysis's diverse results for the association between diabetes history and gastric cancer risk was that the type of follow-up study was not reflected. According to the meta-analysis of prospective cohort studies, it could be concluded that there is no association between diabetes history and gastric cancer risk.

Keywords: Diabetes mellitus- Stomach neoplasm- Cohort studies- Meta-analysis

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Introduction

GLOBOCAN reported that gastric cancer is the fifth most diagnosed cancer and the third leading cause of cancer death worldwide in 2018 (Bray et al., 2018). As the prevalence of diabetes is also increasing (Cho et al., 2018), the relationship between diabetes and cancer has been continuously raised (Abudawood, 2019; Suh and Kim, 2019; Tanaka et al., 2019; Goto et al., 2020; Wang et al., 2020). Especially, potential links between diabetes and gastric cancer have been suggested in that both have shared risk factors such as smoking, obesity, physical activity, and insulin resistance (Hillon et al., 2010; Tseng and Tseng, 2014).

Table 1 summarizes the meta-analysis results of cohort studies in seven systematic reviews to evaluate the association between diabetes history and gastric cancer risk (Ge et al., 2011; Marimuthu et al., 2011; Tian et al., 2012; Shimoyama, 2013; Starup-Linde et al., 2013; Yoon et al., 2013; Miao et al., 2017). While I-squared values indicating the heterogeneity level were very high, over 75%, 4 out of 7 articles had statistical significance

for summary relative risk (sRR), but the other 3 articles showed no significance.

There may be various reasons for such inconsistent results, but it is necessary to guess that it might be an error due to types of follow-up study such as prospective and retrospective study (Sedgwick, 2014). Comparing to a prospective study, a retrospective cohort study, called a historical cohort study, has methodologically critical limitations in inferring an association in cases of unable to obtain information on potential confounders in advances (Sedgwick, 2013). Nevertheless, the previous systematic reviews in Table 1 did not consider the type of follow-up study. Therefore, it is necessary to determine whether it is due to the type of follow-up study as one of the reasons for inconsistent results among the existing systematic reviews. The aim was to check through a meta-epidemiological study (Bae, 2014) that the conclusions of systematic reviews evaluating the association between diabetes history and gastric cancer risk might differ by the type of follow-up study.

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Materials and Methods

Seven systematic reviews presented in Table 1 mentioned in the introduction were obtained by searching PubMed (<https://pubmed.ncbi.nlm.nih.gov>) using diabetes and gastric cancer keywords. The potential study subjects of this study were 27 follow-up studies selected from the 7 systematic reviews (Ragozzino et al., 1982; Adami et al., 1991; Wideroff et al., 1997; Zendehdel et al., 2003; Coughlin et al., 2004; Batty et al., 2004; Jee et al., 2005; Swerdlow et al., 2005; Inoue et al., 2006; Khan et al., 2006; Rapp et al., 2006; Hsieh et al., 2012; Kuriki et al., 2007; Ogunleye et al., 2009; Ikeda et al., 2009; Chodick et al., 2010; Hemminki et al., 2010; Lin et al., 2011; Atchison et al., 2011; Tseng, 2011; Wotton et al., 2011; Attner et al., 2012; Carstensen et al., 2012; Joshu et al., 2012; Kao et al., 2013; Chen et al., 2013; Xu et al., 2015). Considering that the most recently published year among them is in 2015 (Xu et al., 2015), it was necessary to secure additional papers to be selected until April 30, 2021. Therefore, a list of articles published by citing previously selected 27 articles applying the ‘cited by’ option provided by PubMed (Bae and Kim, 2016) was made.

Next, the author appraised whether each article satisfies the selection criterion defined as ‘a follow-up study for evaluating the association between the history of type 2 diabetes mellitus and the incidence of gastric cancer’. Among the articles satisfying the selection criteria, the author checked whether the cohort participants overlap. Through these processes, articles for meta-analysis were finally selected.

The types of follow-up study in the final selected articles were classified according to the following steps. The first step was to determine whether there were any mentions such as ‘prospective’, ‘retrospective’, or ‘historical’ on the method. If the words were not found, the author checked whether collecting information on potential confounders to participants was implemented at

the cohort construction. If the information on the variables was collected individually, it was decided as a prospective study. Lastly, the time of cohort construction and the follow-up period were compared to determine.

And the values of RR and its 95%CI, which adjusted for the most confounders in each paper, were extracted for meta-analysis. This process confirmed whether smoking status, alcohol habit, body mass index, and physical activity were adjusted. The I-squared value determined the heterogeneity among articles, and a random-effects model meta-analysis by types of the follow-up study and sex group was performed (Harris et al., 2008). Publication bias was confirmed by Egger’s test [49]. The level of statistical significance was set at 0.05.

Results

A total of 15 follow-up studies met the selection criterion among 27 studies selected by 7 systematic reviews in Table 1 (Ragozzino et al., 1982; Adami et al., 1991; Wideroff et al., 1997; Swerdlow et al., 2005; Inoue et al., 2006; Khan et al., 2006; Hsieh et al., 2012; Chodick et al., 2010; Hemminki et al., 2010; Lin et al., 2011; Atchison et al., 2011; Wotton et al., 2011; Carstensen et al., 2012; Chen et al., 2013; Xu et al., 2015). And a total of 1,164 cited 27 articles as of April 30, 2021, of which 12 satisfied the selection criterion (Lai et al., 2013; Nakamura et al., 2013; Oberaigner et al., 2014; Sekikawa et al., 2014; Sakitani et al., 2015; Wang et al., 2015; Dankner et al., 2016; Pan et al., 2018; Rastad et al., 2019; Zheng et al., 2019; Li et al., 2020; Yang et al., 2020). In a total of 27 follow-up studies, duplicating cohort participants were reviewed. The follow-up subjects of Hsieh et al. (2012) vs Chen et al. (2013), and Lin et al. (2011) vs Lai et al. (2013) were overlapped so that Hsieh et al. (2012) and Lin et al. (2011) with reporting more detail information were selected. Therefore, a total of 25 follow-up studies were finally selected for meta-analysis (Figure 1).

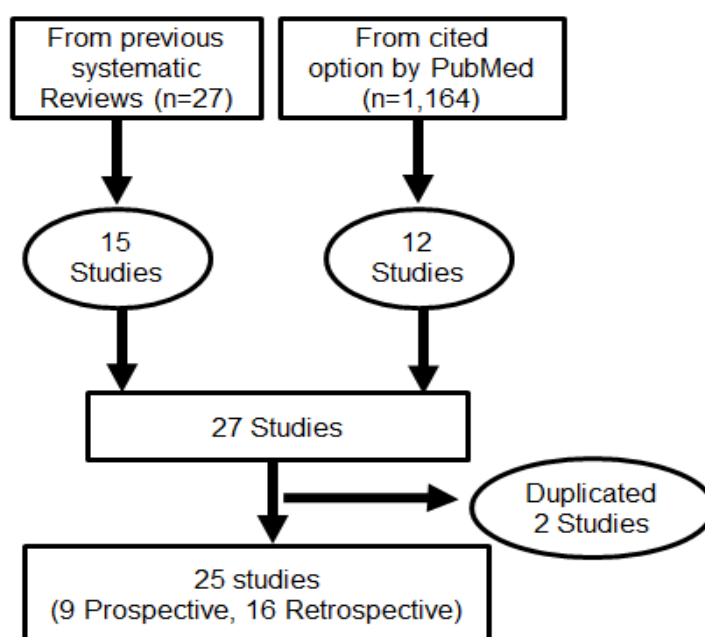


Figure 1. Flow Chart of Selection Process

Table 1. Summary Relative Risk (sRR) and Its 95% Confidence Intervals (CI) of Published Systematic Reviews

Author (year)	Search to	Selected studies	sRR (95%CI)	I-squared (%)
Ge (2011)	May-11	9 cohorts	1.16 (0.99-1.36)	81.2
Marimuthu (2011)	na	10 cohorts	1.01 (0.90-1.11)	75.6
Tian (2011)	Oct-11	14 cohorts	1.14 (1.01-1.30)	84.8
Yoon (2013)	Feb-12	11 cohorts	1.20 (1.08-1.34)	75.5
Starup-Linde (2013)	Nov-12	na	1.13 (1.02-1.24)	na
Shimoyama (2013)	Jan-13	10 cohorts + 2 case-control	1.41 (1.10-1.81)	95
Miao (2017)	na	15 cohorts	1.10 (0.94-1.29)	92.9

na, not available

(Ragozzino et al., 1982; Adami et al., 1991; Wideroff et al., 1997; Swerdlow et al., 2005; Inoue et al., 2006; Khan et al., 2006; Hsieh et al., 2012; Chodick et al., 2010; Hemminki et al., 2010; Lin et al., 2011; Atchison et al., 2011; Wotton et al., 2011; Carstensen et al., 2012; Nakamura et al., 2013; Oberaigner et al., 2014; Sekikawa et al., 2014; Sakitani et al., 2015; Wang et al., 2015;

Xu et al., 2015; Dankner et al., 2016; Pan et al., 2018; Rastad et al., 2019; Zheng et al., 2019; Li et al., 2020; Yang et al., 2020). The 25 articles were classified into 16 retrospective studies (Ragozzino et al., 1982; Adami et al., 1991; Wideroff et al., 1997; Swerdlow et al., 2005; Hsieh et al., 2012; Chodick et al., 2010; Hemminki et al., 2010; Atchison et al., 2011; Wotton et al., 2011; Carstensen et

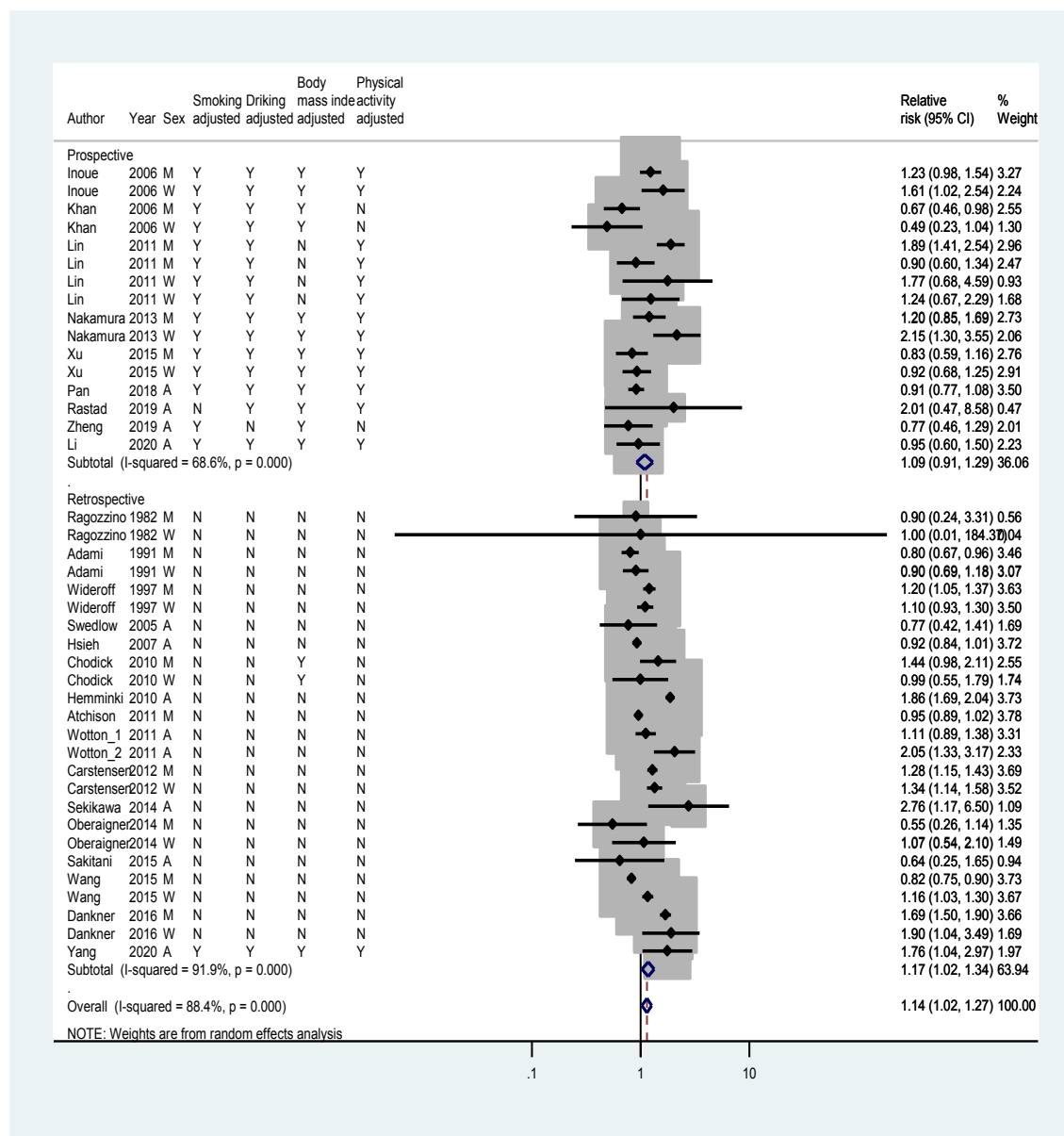


Figure 2. Forest Plot of Estimating Summary Relative Risk by Types of Follow-up Studies. A(sex-adjusted) M(men), N(no), W(women), Y(yes)

Table 2. Summary Relative Risk (sRR) of Subgroup analyses by Kinds of Follow-up Studies, Sites and Sex*

Sex	Prospective cohorts	Retrospective cohorts	Cardia	Non-Cardia
All	1.09 (0.91-1.29) [68.6] <16>	1.17 (1.02-1.34) [91.0] <25>	1.45 (0.87-2.42) [67.8] <3>	0.99 (0.71-1.39) [0.0] <2>
Men	1.07 (0.81-1.43) [79.1] <6>	1.07 (0.88-1.31) [93.9] <9>	-	-
Women	1.24 (0.84-1.83) [68.3] <6>	1.16 (1.04-1.29) [27.4] <8>	-	-
Both	0.91 (0.78-1.06) [0.0] <4>	1.33 (0.95-1.88) [94.2] <8>	-	-

* Summary relative risk (95% confidence intervals) [I-squared value(%)] <numbers of cohorts>

al., 2012; Oberaigner et al., 2014; Sekikawa et al., 2014; Sakitani et al., 2015; Zheng et al., 2019; Li et al., 2020; Yang et al., 2020) and 9 prospective studies (Inoue et al., 2006; Khan et al., 2006; Lin et al., 2011; Nakamura et al., 2013; Wang et al., 2015; Xu et al., 2015; Dankner et al., 2016; Pan et al., 2018; Rastad et al., 2019) in types of the follow-up study. The 16 retrospective studies were organized into 25 cohorts by sex, such as 9 cohorts of men, 8 cohorts of women, and 8 sex-adjusted cohorts. On the other hand, the 9 prospective studies consisted of 6 men, 6 women, and 4 sex-adjusted cohorts.

Figure 2 shows the results of the meta-analysis by types of the follow-up study. Excluding Yang et al., (2020), the other retrospective studies did not adjust for the major confounders such as smoking status, drinking history, body mass index, and physical activity. The meta-analysis result of 25 cohorts of retrospective studies showed that diabetes history significantly increased gastric cancer risk under high heterogeneity (sRR=1.14, 95%CI: 1.02-1.27). On the other hand, the meta-analysis result of 16 prospective cohorts showed that the I-squared value was 68.6%, which had lower heterogeneity, and there was no association between diabetes history and risk of gastric cancer (sRR=1.09, 95%CI: 0.91-1.29). Egger's test showed that neither prospective study nor retrospective study had statistical significance in publication error (P=0.63 in prospective, =0.67 in retrospective).

Table 2 shows the results of subgroup analysis by sex and gastric site. When analyzed by sex, prospective studies showed no statistical significance. There was also no statistical significance in either 3 cardia cohorts or 2 non-cardia cohorts.

Discussion

The main results were that the statistical significance between diabetes history and gastric cancer risk was found in retrospective studies but disappeared in prospective studies. Even in the analysis of subgroups by sex, statistical significance was not found in the prospective study, consistently.

Most of the selected retrospective studies presented results with age-standardized incidence ratios without adjusting for potential confounders. On the other hand, prospective studies reported results with adjusted hazard ratios for smoking status, drinking history, body mass index, and physical activity. When reflecting on this research design's difference, it is possible to interpret that the existing systematic reviews' diverse conclusion would be due to not considering the type of follow-up studies. Thus, it can be concluded that there was no association

between diabetes history and risk of gastric cancer, based on the results of the prospective studies.

Of the 27 articles selected by the 7 systematic reviews in Table 1, 12 were excluded because they did not satisfy the selection criterion. The reasons for exclusion were 4 studies for the exposure on type 1 diabetes or pre-diabetic status (Zendehdel et al., 2003; Rapp et al., 2006; Carstensen et al., 2012; Joshu et al., 2012), 4 for the outcome as the death of gastric cancer instead of occurrence (Coughlin et al., 2004; Batty et al., 2004; Jee et al., 2005; Tseng, 2011), and 4 for another research designs other than the follow-up study (Kuriki et al., 2007; Ogunleye et al., 2009; Attner et al., 2012; Nakamura et al., 2013). Therefore, it can be inferred that the conflict of results among the existing systematic reviews would be due to the difference in the selection criteria. This study confirmed that despite applying the more stringent selection criteria, different results were derived depending on the type of follow-up study. Based on this fact, it is necessary to select only prospective cohort studies among follow-up studies to derive more valid and consistent results from future systematic reviews.

The main strength is that by applying a more stringent selection criterion, several factors among the reasons for conflicting meta-analysis results could be controlled in the selection process. It could also be another advantage of this study that meta-analysis was performed by including nine new cohort studies that were not selected in the systematic reviews of Table 1 using the 'cited by' option provided by PubMed.

The main limitation of this meta-epidemiological study was that the process of confirming diabetes history varies by type of follow-up study. Most retrospective studies used databases of clinical management records to check diabetes history so that reverse causation increasing the probability of cancer diagnosis due to diabetes diagnosis could be intervened (Carstensen et al., 2012). On the other hand, prospective cohort studies mainly confirmed diabetes history by self-response at the time of cohort construction. There might involve an error that there would be no association between diabetes history and cancer risk because of long-term use of insulin or oral hypo-glycemic agents during a long follow-up period (Carstensen et al., 2012; Cignarelli et al., 2018). To overcome the above errors and to derive valid conclusions, it would be necessary to reflect the window period in the retrospective cohort studies and to perform an analysis that reflects the treatment information for follow-up intervals in the prospective cohort studies.

In conclusion, the main reason for the previous meta-analysis's diverse results for the association between

diabetes history and gastric cancer risk was that the type of follow-up study was not reflected. According to the meta-analysis of prospective cohort studies that presented the results of adjusting for the confounders, it could be concluded that there is no association between diabetes history and gastric cancer risk. To derive more valid and consistent results from future systematic reviews. While it is necessary to select only prospective cohort studies among follow-up studies to derive more valid conclusion from future systematic reviews, analytic strategies reflecting treatment information by follow-up intervals would be necessary for prospective studies, too.

Author Contribution Statement

Bae JM designed the study, searched and selected articles, conducted the statistical analysis, and wrote the draft.

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None.

Conflicts of interest

No conflicts of interest.

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