2 型糖尿病与消化系统恶性肿瘤队列研究的 Meta 分析

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摘　要:[目的] 探讨 2 型糖尿病与消化系统恶性肿瘤的关系。[方法] 利用 Medline、Embase 与 Web of Science 检索 2012 年 10 月之前国外公开发表的关于 2 型糖尿病与消化系统恶性肿瘤关系的队列研究文献。利用 R 软件及其 Meta 程序包对检索结果进行综合分析。[结果] 纳入分析的文献共 41 篇。经 Meta 分析后结果显示,2 型糖尿病与消化系统恶性肿瘤间的相对危险度及 95%可信区间为 1.52 (95%CI:1.40~1.66)。2 型糖尿病与肝癌、食管癌、胃癌、胰腺癌、结直肠癌以及结肠癌的关联均有统计学意义，合并相对危险度分别为 1.79 (95%CI:1.61~1.99),1.16 (95%CI:1.07~1.27),1.34 (95%CI:1.11~1.61),1.56 (95%CI:1.49~1.64),1.32 (95%CI:1.23~1.40)和 1.24(95%CI:1.15~1.33)。2 型糖尿病与直肠癌合并相对危险度为 1.07 (95%CI:0.91~1.25),无统计学意义。[结论] 2 型糖尿病与消化系统恶性肿瘤密切相关,可能是肝癌、食管癌、胃癌、胰腺癌、结肠癌的危险因素之一。

关键词:2 型糖尿病;消化系统肿瘤;队列研究;Meta 分析
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A Meta-Analysis of Cohort Studies in Association with Type 2 Diabetes and Risk of Digestive System Cancer

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Abstract: [Purpose] To investigate the relationship between type 2 diabetes and risk of digestive system cancer. [Methods] The articles of association between type 2 diabetes and the risk of digestive system cancer from the cohort studies form Medline, Embase and Web of Science before October 2012 were selected. A Meta-analysis was conducted to estimate the pooled relative risks (RR) by R software and its Meta package. [Results] A total of 41 articles were included in the Meta-analysis. In total, the pooled relative risk (RR) for digestive system cancer among patients with type 2 diabetes was 1.52 (95%CI: 1.40~1.66) compared to those non-diabetes. The results showed significantly increased risks for the common cancer sites of digestive system such as liver, esophagus, stomach, pancreas, colorectum and colon with the pooled RRs of 1.79(95%CI: 1.61~1.99), 1.16(95%CI: 1.07~1.27), 1.34(95%CI: 1.11~1.61), 1.56(95%CI: 1.49~1.64), 1.32 (95% CI: 1.23~1.40) and 1.24 (95%CI: 1.15~1.33), respectively. Besides, a non-significant pooled RR of 1.07(95%CI: 0.91~1.25) was also estimated for type 2 diabetes and the risk of rectum cancer. [Conclusion] Type 2 diabetes is associated with an increased risk of digestive system cancer, and might be one of the risk factors for cancers of liver, esophagus, stomach, pancreas, and colon.
Key words: type 2 diabetes; digestive system cancer; cohort studies; Meta-analysis

随着人们的生活方式发生了重大改变,糖尿病(diabetes mellitus, DM)已成为继恶性肿瘤、心血管疾病之后的第 3 位慢性非传染性疾病[1]。近年来糖尿病与恶性肿瘤的关系逐渐被人们重视,有研究表明糖尿病患者恶性肿瘤的发病率是正常人群的 2 倍以上[2],其中消化道肿瘤占第 1 位,如糖尿病与结直肠癌、肝癌、胰腺癌等关系密切[3]。但不同国家或地区有关糖尿病与消化系统恶性肿瘤关系的研究结果也不尽相同。本研究对 2012 年 10 月之前国外公开发表的关于 2 型糖尿病与消化系统恶性肿瘤(肝癌、食管癌、胃癌、胰腺癌、结直肠癌、结肠癌和直肠癌)

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关系的文献进行了系统收集和整理，并开展综合分析，为探索2型糖尿病与消化系统恶性肿瘤发生之间的关系提供更多的基础数据。

1 材料与方法

1.1 文献来源

通过检索Medline、Embase与Web of Science数据库收集2型糖尿病与相关癌症关系的前瞻性研究文献，主题词包括：(1)“metabolic syndrome”、“diabetes mellitus”、“diabetes”、“hyperglycemia”；(2)“cancer”、“neoplasm”以及各部位的癌症名称；(3)“cohort study”、“prospective study”、“follow-up”、“longitudinal study”以及“nested case-control study”。为防止漏检，同时手工检查检索到的文献中列出的参考文献。

1.2 文献纳入标准

文献纳入标准必须同时满足下列2个条件：研究设计类型必须是队列研究（含巢式病例对照研究与病例队列研究）；至少可以提供2型糖尿病与癌症关系的相对危险度(relative risk，RR)或优势比(odds ratio，OR)或风险比(hazard ratio，HR)及其95%可信区间或标准误。对重复报告的文献进行剔除，如果是同一队列或研究人群不同观察时间点上的报道，则仅保留最新的研究报道。

1.3 文献信息的摘录与质量评价

两名研究者按照文献纳入和排除标准独立地评价文献的可用性，并依照事先设计好的统一表格摘录文献基本信息并建立数据库。如遇有分歧，通过与第三名研究者讨论解决，直至达成一致为止。由于结直肠癌文献的特殊性（有些文献单独研究结肠癌或直肠癌，有些文献把两者合并起来研究），因此等结直肠癌、结肠癌、直肠癌三者分开进行分析。

纳入文献质量的评分标准按照NOS(Newcastle-Ottawa Scale)[4]执行。该标准主要从3个方面综合衡量纳入meta分析文献的质量：暴露组与非暴露组的选取；暴露组与非暴露组的可比性；暴露与结局的测量。满分为9分，本次分析中的高质量文献被定义为评分≥7分，具体可参见相应量表[4]。由于肝癌和结直肠癌的特殊性，为综合考虑混杂、测量偏倚等影响，肝癌与结直肠癌的文献质量评分按以下标准执行，其中肝癌[5]的标准为：(1)DM的确诊来源于临床或实验室诊断得1分，其余不得分；(2)有(或绝大部分有)明确的肝癌病理学诊断得2分，来源于死因登记或者肿瘤登记系统得1分，其余不得分；(3)非洲或者亚洲(日本除外)地区的研究调整了HBV，或者欧美地区、日本的研究调整了HCV得2分，除此之外，研究进一步调整了饮酒再得1分；(4)队列研究的失访率<20%得1分。结直肠癌参照杨万水等[6]的标准为：(1)DM的确诊来源于临床或实验室诊断得1分，其余不得分；(2)结直肠癌病例的确定来源于明确的医学证明或病理组织学诊断得2分，来源于死亡证明或肿瘤登记系统等得1分，其余不得分；(3)调整的混杂因素方式：年龄+饮食(膳食因素中任一种或以上)得1分，除此之外，研究进一步调整了阿司匹林或非甾体抗炎药用药史或多种维生素再得2分；(4)队列人群失访率<20%得1分。故肝癌与结直肠癌的文献满分为7分，得5分及以上者被定义为高质量文献。

文献质量评分的程序同文献信息摘录，均由两名研究者独立完成，并通过与第三名研究者讨论解决存在的分歧。

1.4 统计学处理

各研究间异质性的检测采用统计量Q和I^2，Q统计量对应的P值<0.10(鉴于Q统计量对应的检验效能较低，故将检验水准调整为0.10)或I^2>50%则认为纳入的研究之间存在显著异质性[7]，此时RR值的合并采用随机效应模型中的D-L法(DerSimonian-Laird method)[8]；反之RR值的合并采用固定效应模型中的倒方差法[9]。

为评价潜在的发表偏倚，本次分析采用Begg's检验(秩相关法)[10]，其对应的P值<0.05即可判断为存在显著发表偏倚，此时采用Duval和Tweetdie推荐的对称填补法[11]对综合后的RR值及其可信区间进行重新计算，以纠正发表偏倚对结果的影响。反之，若秩相关法对应的P值>0.05，则认为发表偏倚不显著。

为检测潜在的异质性，判断所获结果是否稳健，本次分析对性别、是否调整BMI、随访时间、研究地区、DM诊断方式进行了分组分析，以便发现影响meta结果的主要因素与产生原因。本次meta分析通过R软件(version 2.15.3，来源：www.r-project.org)及

其 Meta 程序包与 Epicalc 程序包实现 (R Development Core Team,2012)。

2 结 果

2.1 文献资料基本情况

共收集到符合要求的文献 2052 篇 (肝癌 592 篇,食管癌 55 篇,胃癌 179 篇,胰腺癌 759 篇,结直肠癌 467 篇)。其中重复文献筛去 535 篇,通过标题阅读筛去 973 篇,通过摘要阅读筛去 358 篇,通过阅读全文筛去 148 篇(其中无置信区间 12 篇,无 RR、HR 及 OR 66 篇,计算肿瘤生存率 64 篇,文献质量差 6 篇),通过阅读参考文献增加 3 篇,最后符合纳入标准的文献为 41 篇[12~52](肝癌 16 篇,食管癌 8篇,胃癌 12 篇,胰腺癌 18 篇,结直肠癌 19 篇,其中重复文献 32 篇)(Table 1)。

2.2 2 型糖尿病与消化系统恶性肿瘤的关系

对提供合计结果的28篇文献[12-14,16,20-24,26-28,30-38,40-42,45-47,51]进行了异质性检验,I^2=67.1%,P<0.0001,说明研究之间存在异质性, 因而采用随机效应模型进行效应值合并分析,合并 RR 为 1.52 (95%CI:1.40~1.66)(Figure 1)。提示 2 型糖尿病与消化系统恶性肿瘤有一定的关系,是消化系统恶性肿瘤的危险因素。

对 21 篇报道男性[12~14,17~19,25,28~31,37,38,45~50,43,52]和 20

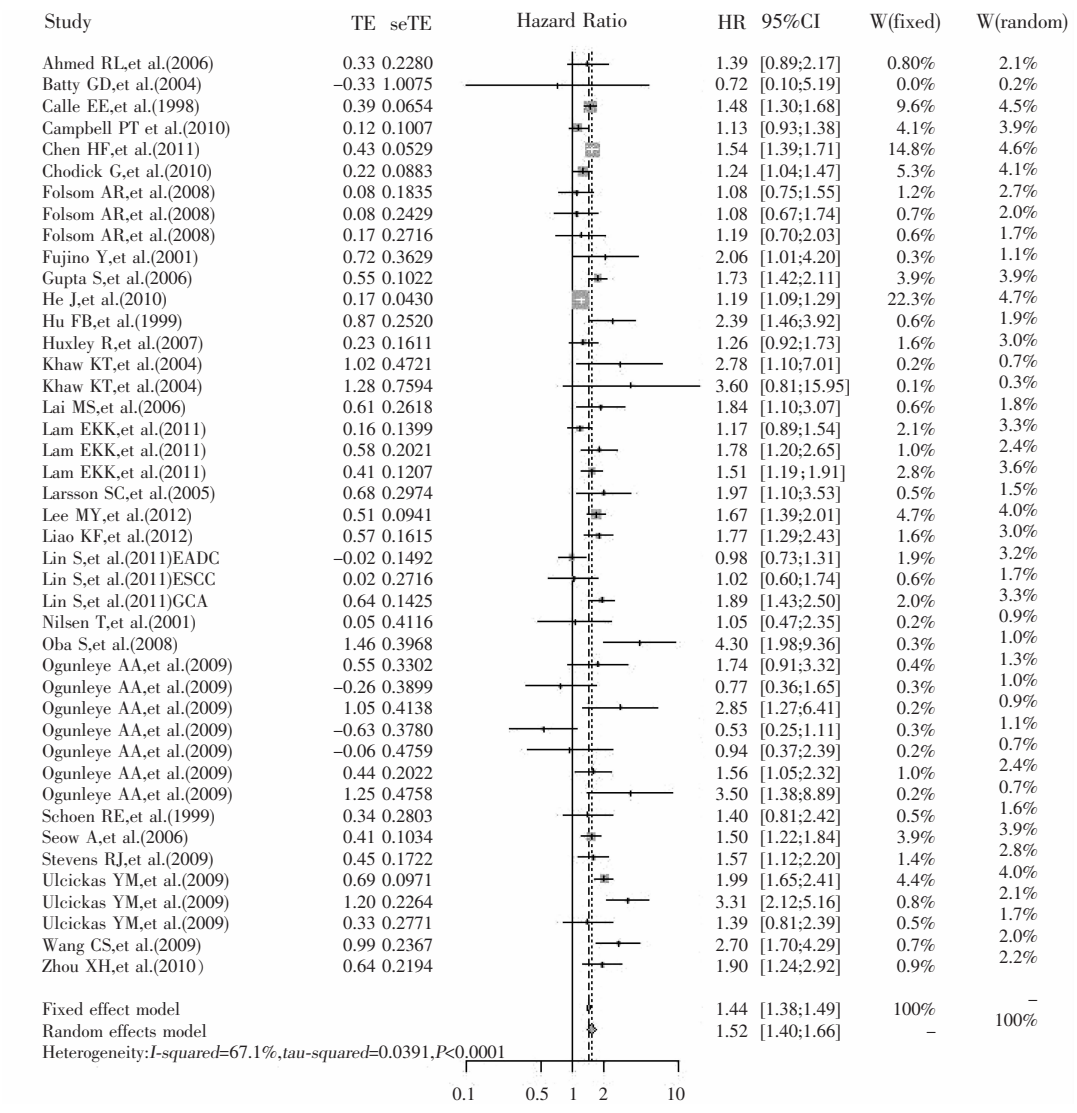

Figure 1 Summary estimates of association between type 2 diabetes and digestive system cancer

Table 1 General characteristics of included studies

The first author and publication time①	Cancer type	Study region	Cohort participants	Gender②	RR,HR/OR(95%CI)③	Confounding adjusted④
Batty GD (2004)[12]	Liver	England	18006	M	M:9.22(2.66~31.9)	Age, occupation, smoking, SBP⑤, physical activity, disease history, and others
Campbell PT (2012)[13]	Liver	America	1053831	T	M:2.26(1.89~2.70);W:1.40(1.05~1.86)	Age, education, BMI⑥, smoking, drinking, and others
Chodick G (2010)[14]	Liver	Israel	100595	T	M:1.83(0.86~3.89);W:2.42(1.00~5.84)	Age, region, BMI, cardiovascular disease, and others
Coughlin SS(2004)[15]	Liver	America	1056243	T	M:2.19(1.76~2.72);W:1.37(0.94~2.00)	Age, gender, race, education, BMI, smoking, drinking, and others
Fujino Y(2001)[16]	Liver	Japan	6944	T	T:2.06(1.01~4.19)	Age, gender, drinking, and smoking
Inoue M(2006)[17]	Liver	Japan	97771	T	M:2.30(1.49~3.55);W:1.84(0.79~4.30)	Age, region, cardiovascular disease, smoking, drinking, BMI, and others
Jee SH(2005)[18]	Liver	Korea	1298385	T	M:1.66(1.53~1.79);W:1.28(1.00~1.66)	Age, smoking, and drinking
Khan M ,et al.(2006)[19]	Liver	Japan	56881	T	M:2.09(1.26~3.47);W:2.55(1.07~6.10)	Age, drinking, smoking, and BMI
Lam EKK,et al.(2011)[20]	Liver	Asia-Pacific	343801	T	T:1.51(1.19~1.91)	Age, gender, and others
Lai MS(2006)[21]	Liver	Taiwan	54979	T	T:1.84(1.10~3.07)	Age, gender, HBV⑦, HCV⑧, smoking, drinking, and others
Lee MY(2012)[22]	Liver	Taiwan	881472	T	T:1.67(1.39~2.01)	Age, gender, hypertension, gout, and dyslipidemia
Oba S(2008)[23]	Liver	Japan	27862	T	T:4.3(1.98~9.38)	Age
Ogunleye AA(2009)[24]	Liver	Scotland	28731	T	T:3.50(1.38~8.91)	Unknown
Osaki Y(2012)[25]	Liver	Japan	15386	T	W:3.67(1.78~7.57);M:1.89(1.11~3.22)	Age, smoking, and others
Ulcickas YM(2009)[26]	Liver	America	251489	T	T:1.39(0.81~2.40)	Age, gender, HBV, HCV, smoking, drinking, and others
Wang CS(2009)[27]	Liver	Taiwan	5929	T	T:2.7(1.7~4.3)	Age, gender, smoking, BMI,HBV, HCV, and drinking
Batty GD(2004)[12]	Esophagus	England	18006	M	M:3.02(0.72~12.60)	Age, occupation, smoking, SBP, physical activity, and disease history
Campbell PT(2012)[13]	Esophagus	America	1053831	T	M:1.14(0.93~1.40);W:1.26(0.83~1.92)	Age, education, BMI, smoking, drinking, and others
Chodick G(2010)[14]	Esophagus	Israel	100595	T	M:1.06(0.42~2.72);W:2.66(0.77~9.21)	Age, region, BMI, cardiovascular disease, and others
Coughlin SS(2004)[15]	Esophagus	America	1056243	M	M:1.20(0.94~1.53)	Age, gender, race, education, BMI, smoking, drinking, and others
Inoue M(2006)[17]	Esophagus	Japan	97771	M	M:0.96(0.45~2.09)	Age, region, cardiovascular disease, smoking, drinking, BMI, and others
Jee S H(2005)[18]	Esophagus	Korea	1298385	M	M:1.11(0.90~1.37)	Age, smoking, and drinking
Lin S(2011)[28] ESCC	Esophagus	America	469448	T	T:1.02 (0.60 ~1.74);M:1.08 (0.59 ~1.98); W:0.87(0.27~2.82)	Age, gender, calories, drinking, smoking, consumption of fruits and vegetables, ethnicity, education, and physical activity
Lin S(2011)[28] EADC	Esophagus	America	469448	T	T:0.98 (0.73 ~1.31);M:1.00 (0.74 ~1.34); W:0.68(0.16~2.85)	Age, gender, calories, drinking, smoking, consumption of fruits and vegetables, ethnicity, education, and physical activity
Ogunleye AA(2009)[24]	Esophagus	Scotland	28731	T	T:1.74(0.91~3.32)	Unknown

Table 1 General characteristics of included studies(continue)

The first author and publication time①	Cancer type	Study region	Cohort participants	Gender②	RR,HR/OR(95%CI)③	Confounding adjusted④
Batty GD(2004)[12]	Stomach	England	18006	M	M:1.24(0.30~5.03)	Age, occupation, smoking, SBP, physical activity, disease history, and others
Campbell PT(2012)[13]	Stomach	America	1053831	T	M:0.99(0.79~1.22);W:1.24(0.95~1.63)	Age, education, BMI, smoking, drinking, and others
Chodick G(2010)[14]	Stomach	Israel	100595	T	M:1.44(0.98~2.11);W:0.99(0.55~1.80)	Age, region, BMI, cardiovascular disease, and others
Coughlin SS(2004)[15]	Stomach	America	1056243	T	M:0.99(0.77~1.27);W:1.25(0.90~1.73)	Age, gender, race, education, BMI, smoking, drinking, and others
Inoue M(2006)[17]	Stomach	Japan	97771	T	M:1.09(0.79~1.50);W:1.92(1.06~3.47)	Age, region, cardiovascular disease, smoking, drinking, BMI, and others
Jee SH(2005)[18]	Stomach	Korea	1298385	T	M:1.11(1.04~1.20);W:1.09(0.88~1.36)	Age, smoking, and drinking
Khan M(2006)[19]	Stomach	Japan	56881	T	M:0.72(0.40~1.09);W:0.26(0.08~0.82)	Age, drinking, smoking, and BMI
Lam EKK(2011)[20]	Stomach	Asia-Pacific	343801	T	T:1.17(0.89~1.54)	Age, gender, and others
Lin S(2011)[28] GCA	Stomach	America	469448	T	T:1.89 (1.43 ~2.50);M:1.89 (1.41 ~2.54); W:1.77(0.68~4.58)	Age, gender, calories, drinking, smoking, consumption of fruits and vegetables, ethnicity, education, and physical activity
Ogunleye AA(2009)[24]	Stomach	Scotland	28731	T	T:0.77(0.36~1.66)	Unknown
Osaki Y(2012)[25]	Stomach	Japan	15386	T	W:0.74(0.50~1.10);M:0.98(0.65~1.49)	Age, smoking, and others
Tseng CH.(2011)[29] 25~64y	Stomach	Taiwan	88694	T	M:4.49(3.93~5.12);W:3.65(3.11~4.28)	Age
Tseng CH.(2011)[29] 65~74y	Stomach	Taiwan	88694	T	M:1.58(1.40~1.78);W:1.95(1.67~2.27)	Age
Tseng CH.(2011)[29] ⩾75y	Stomach	Taiwan	88694	T	M:1.52(1.31~1.77);W:1.58(1.32~1.90)	Age
Batty GD(2004)[12]	Pancreas	England	18006	M	M:3.99(1.44~11.0)	Age, occupation, smoking, SBP, physical activity, disease history, and others
Campbell PT(2012)[13]	Pancreas	America	1053831	T	M:1.40(1.23~1.59)W:1.31(1.14~1.51)	Age, education, BMI, smoking, drinking, and others
Chen HF(2011)[30]	Pancreas	Taiwan	1230403	T	T:1.54 (1.39 ~1.71);M:1.66 (1.44 ~1.91); W:1.43(1.23~1.65)	Age, gender, region, HBV, HCV, and others
Chodick G(2010)[14]	Pancreas	Israel	100595	T	M:1.47(0.90~2.41);W:1.89(1.16~3.07)	Age, region, BMI, cardiovascular disease, and others
Coughlin SS(2004)[15]	Pancreas	America	1056243	T	M:1.48(1.27~1.73);W:1.44(1.21~1.72)	Age, gender, race, education, BMI, smoking, drinking, and others
Calle EE(1998)[31]	Pancreas	America	1089586	T	T:1.48 (1.30 ~1.68);M:1.49 (1.25 ~1.77); W:1.51(1.24~1.85)	Age, gender, race, smoking, BMI, family history of pancreatic cancer, and others
Gupta S(2006)[32]	Pancreas	America	1421794	T	T:1.73(1.42~2.12)	Age, education , drinking, smoking, and physical activity
Inoue M(2006)[17]	Pancreas	Japan	97771	T	M:1.97(1.01~3.88);W:1.32(0.41~4.28)	Age, smoking, drinking, BMI, consumption of vegetables and coffee, and others
Jee SH(2005)[18]	Pancreas	Korea	1298385	T	M:1.78(1.50~2.11);W:1.71(1.25~2.34)	Age, smoking, and drinking
Khan M(2006)[19]	Pancreas	Japan	56881	T	M:1.57(0.67~3.68);W:1.63(0.70~3.80)	Age, drinking, smoking, and BMI
Lam EKK(2011)[20]	Pancreas	Asia-Pacific	343801	T	T:1.78(1.20~2.65)	Age, gender, and others

Table 1 General characteristics of included studies(continue)

The first author and publication time①	Cancer type	Study region	Cohort participants	Gender②	RR,HR/OR(95%CI)③	Confounding adjusted④
Larsson SC(2005)[33]	Pancreas	Sweden	83053	T	T:1.97(1.10~3.53)	Age, BMI, and others
Liao KF(2012)[34]	Pancreas	Taiwan	249015	T	T:1.77(1.29~2.43)	Age, chronic pancreatitis, gallstones, and HCV
Ogunleye AA(2009)[24]	Pancreas	Scotland	28731	T	T:2.85(1.27~6.43)	Unknown
Stevens RJ(2009)[35]	Pancreas	England	12900000	T	T:1.57(1.12~2.20)	Age, gender, family history of pancreatic cancer, physical exercise, smoking, and others
Ulcickas YM(2009)[26]	Pancreas	America	251489	T	T:3.31(2.12~5.15)	Age, gender, and others
Folsom AR(2008)[36]	Pancreas	America	13117	T	T:1.08(0.75~1.54)	Age, race, BMI, smoking, and drinking
Zhou XH(2010)[37]	Pancreas	Europe	44655	T	T:1.90 (1.24 ~2.93);M:1.67 (0.94 ~2.97); W:2.13(1.09~4.16)	Age, BMI, cholesterol, blood pressure, and smoking
Ahmed RL(2006)[38]	Colorectum	America	14109	T	T:1.39 (0.90 ~2.20);M:1.78 (1.00 ~3.60); W:1.16(0.60~2.20)	Age, gender, physical activity, family history of cancer, drinking, smoking, and others
Campbell PT(2010)[13]	Colorectum	America	154975	T	T:1.13 (0.93 ~1.38);M:1.24 (1.08 ~1.44); W:1.01(0.82~1.23)	Age, BMI, physical activity, family history of cancer, drinking, and others
Chodick G(2010)[14]	Colorectum	Israel	100595	T	T:1.24(1.04~1.47)	Age, BMI, race, and cardiovascular disease
Flood A(2010)[39]	Colorectum	America	41516	W	W:1.60(1.18~2.18)	Age, drinking, smoking, colories, education, and others
He J(2010)[40]	Colorectum	America	199143	T	T:1.19(1.09~1.29)	Age, gender, BMI, drinking, smoking, non-hormonal drug use, and others
Hu FB(1999)[41]	Colorectum	America	118072	T	T:1.43(1.10~1.87)	Age, BMI, drinking, smoking, non-hormonal drug use, and others
Jee SH(2005)[18]	Colorectum	Taiwan	1298385	T	T:1.13 (1.03 ~1.23);M:1.11 (1.00 ~1.24); W:1.17(0.98~1.40)	Age, smoking, and drinking
Khaw KT(2004)[42]	Colorectum	England	9605	T	T:2.78(1.10~7.00)	Age, gender, BMI, and smoking,
Larsson SC(2005)[43]	Colorectum	Sweden	45550	M	M:1.49(1.14~1.96)	Age, BMI, family history of cancer, smoking, non-hormonal drug use, and others
Limburg PJ(2005)[44]	Colorectum	America	34972	W	W:1.40(1.10~1.80)	Age
Nilsen T(2001)[45]	Colorectum	Norway	75219	T	T:1.05(0.48~2.41)	Age
Ogunleye AA(2009)[24]	Colorectum	Scotland	28731	T	T:0.94(0.37~2.39)	Age, and gender
Schoen RE(1999)[46]	Colorectum	America	1184	T	T:1.40(0.80~2.40);M:1.60(0.80~3.10); W:1.10(0.50~2.60)	Age
Seow A(2006)[47]	Colorectum	Singapore	61320	T	T:1.50 (1.20 ~1.80);M:1.50 (1.20 ~2.10); W:1.40(1.00~1.90)	Age, gender, BMI, family history of cancer, drinking, smoking, and others
Steenland K(1995)[48]	Colorectum	America	14407	T	M:1.43(0.61~3.31);W:1.40(0.64~3.10)	Age, gender, smoking, drinking, BMI, income, and others
Sturmer T(2006)[49]	Colorectum	America	22046	M	M:1.50(1.10~2.00)	Age, drinking, smoking, non-hormonal drug use, and others
Will J C(1998)[50]	Colorectum	America	863700	T	T:1.24(1.03~1.49)	Age, BMI, drinking, smoking, non-hormonal drug use, and others
Folsom AR(2008)[36]	Colorectum	America	13117	T	T:1.13(0.71~1.84)	Age, race, BMI, smoking, and drinking

Table 1 General characteristics of included studies(continue)

The first author and publication time①	Cancer type	Study region	Cohort participants	Gender②	RR,HR/OR(95%CI)③	Confounding adjusted④
Huxley R(2007)[51]	Colorectum	Asia-Pacific	539201	T	T:1.26(0.92~1.73)	Age, BMI, smoking, and drinking
Jee SH(2005)[18]	Colorectum	Taiwan	1298385	T	T:1.23 (1.05 ~1.45);M:1.11 (0.81 ~1.51); W:1.28(1.06~1.55)	Age, smoking, and drinking
Khaw KT(2004)[42]	Colorectum	England	9605	T	T:3.60(0.81~15.9)	Age, gender, BMI, and smoking
Will JC(1998)[50]	Colorectum	America	863669	T	T:1.02 (0.78 ~1.32);M:0.98 (0.70 ~1.37); W:1.07(0.71~1.62)	Age, BMI, drinking, smoking, non-hormonal drug use, and others
Hu FB(1999)[41]	Colorectum	America	118072	T	T:2.39(1.46~3.92)	Age, BMI, drinking, smoking, non-hormonal drug use, and others
Chodick G(2010)[14]	Colon	Israel	100595	T	M:1.14(0.91~1.44);W:1.52(1.19~1.95)	Age, region, BMI, and cardiovascular disease
Inoue M(2006)[18]	Colon	Japan	97771	T	M:1.36(1.00~1.85);W:0.83(0.42~1.61)	Age, region, smoking, drinking, BMI, consumption of fruits and vegetables, and others
Khan M(2006)[19]	Colon	Japan	56881	T	M:1.39(0.80~2.43);W:1.02(0.44~2.33)	Age, smoking, drinking, and BMI
Ogunleye AA(2009)[24]	Colon	Scotland	28731	T	T:1.56(1.05~2.32)	Age, and gender
Osaki Y(2012)[25]	Colon	Japan	15386	T	W:1.08(0.63~1.85);M:0.80(0.44~1.78)	Age, smoking, and others
Coughlin SS(2004)[15]	Colon	America	1056243	T	M:1.20(1.06~1.37);W:1.24(1.07~1.43)	Age, gender, BMI, smoking, drinking, non-hormonal drug use, and others
Bowers K(2006)[52]	Colon	Finland	28983	T	T:1.09(0.66~1.80)	Age, and smoking
Folsom AR(2008)[36]	Colon	America	13117	T	T:1.19(0.70~2.03)	Age, race, BMI, smoking, and drinking
Batty GD(2004)[12]	Colon	England	18006	T	T:0.72(0.10~5.19)	Age, occupation, BMI, smoking, and physical activity
Chodick G(2010)[14]	Rectum	Israel	100595	T	M:1.10(0.74~1.61);W:1.08(0.69~1.69)	Age, region, BMI, and cardiovascular disease
Inoue M(2006)[17]	Rectum	Japan	97771	T	M:0.80(0.47~1.36);W:1.65(0.80~3.39)	Age, region, smoking, drinking, BMI, consumption of fruits and vegetables, and others
Khan M(2006)[19]	Rectum	Japan	56881	T	M:1.21(0.61~2.40);W:2.70(0.94~7.71)	Age, smoking, drinking, and BMI
Ogunleye AA(2009)[24]	Rectum	Scotland	28731	T	T:0.53(0.25~1.10)	Age, and gender
Osaki Y(2012)[25]	Rectum	Japan	15386	T	W:0.86(0.35~2.14);M:2.04(0.84~4.93)	Age, smoking, and others
Coughlin SS(2004)[15]	Rectum	America	1056243	T	M:1.07(0.75~1.51);W:0.90(0.57~1.42)	Age, gender, BMI, smoking, drinking, non-hormonal drug use, and others
Bowers K(2006)[52]	Rectum	Finland	28983	T	T:1.23(0.65~2.32)	Age, and smoking

Notes:①The first author and publication time;ESCC:esophageal squamous cell carcinoma,EADC:esophageal adenocarcinoma,GCA:gastric cardia adenocarcinoma;②Gender:T:total,M:man,W:woman; ③RR,HR/OR (95%CI):T:total,M:man,W:woman; ④Confounding adjusted:Others:refers to physical activity,education,economic status,ethnicity and other factors; ⑤SBP:systolic blood pressure;⑥BMI:body mass index;⑦HBV:hepatitis B virus;⑧HCV:hepatitis C virus.

篇报道女性[13,14,17~19,25,28~31,37~39,41,44~48,50]的研究进行异质性检验,结果发现各研究之间存在异质性,故采用随机效应模型进行效应值合并分析后,男、女性合并RR分别为1.42(95%CI:1.31~1.55)和1.38(95%CI:1.26~1.51),提示2型糖尿病是男女性消化系统恶性肿瘤的危险因素。

2.2.1 2型糖尿病与肝癌的关系

对提供结果的16篇相关肝癌文献[12~27]的一致性检验的I^2=65.6%,P<0.0001,可见研究之间存在异质性,因而采用随机效应模型进行效应值合并分析,合并RR为1.79(95%CI:1.61~1.99),表明2型糖尿病是肝癌的危险因素。发表偏倚Begg's检验Z=2.1954(P=0.0281),提示存在发表偏倚。亚组分析显示各亚组文献一致性均较好(Table 2)。

2.2.2 2型糖尿病与食管癌的关系

对提供结果的8篇食管癌文献[12~15,17,18,24,28]的一致性检验的I^2=0,P=0.75,可见研究之间不存在异质性,因而采用固定效应模型进行效应值合并分析,合并RR为1.16(95%CI:1.07~1.27);表明2型糖尿病是食管癌的危险因素。发表偏倚Begg's检验Z=0.6303(P=0.5285),提示发表偏倚不显著。亚组分析显示是否调整体质指数(BMI)亚组和研究地区亚组的文献一致性均较好(Table 3)。

2.2.3 2型糖尿病与胃癌的关系

对提供结果的12篇胃癌文献[12~15,17~20,24,25,28,29]的一致性检验的I^2=95.4%,P<0.0001,可见研究之间存在异质性,因而采用随机效应模型进行效应值合并分析,合并RR为1.34(95%CI:1.11~1.61),固定效应模型结果为1.46(95%CI:1.41~1.51),两者结果相似。表明2型糖尿病是胃癌的危险因素。发表偏倚Begg's检验Z=-0.2371(P=0.8126),提示发表偏倚不显著。亚组分析显示是否调整BMI、研究地区、DM诊断方式亚组文献一致性均较好(Table 4)。

Table 2 Subgroup analysis (RR and 95%CI) and heterogeneity of type 2 diabetes and liver cancer

Category	Study number	RR(95%CI)	Heterogeneity I^2(%)	Heterogeneity P
Liver cancer	16	1.79(1.61~1.99)	65.6	<0.001
High quality literature	4	2.10(1.65~2.67)	33.7	0.197
Gender				
Male	8	1.94(1.68~2.23)	70.1	<0.001
Female	7	1.49(1.22~1.82)	49.9	0.052
Adjusted with BMI				
Yes	6	2.03(1.83~2.25)	32.6	0.138
No	10	1.65(1.45~1.86)	66.2	0.002
Follow time				
<10 years	8	1.87(1.60~2.19)	35	0.128
≥10 years	8	1.72(1.52~1.94)	73.9	<0.001
Study region				
Europe	9	1.77(1.55~2.03)	75.6	<0.001
Asia	7	1.76(1.56~1.99)	0	0.496
DM diagnosis				
Self-report	7	2.08(1.71~2.52)	55.4	0.013
Clinical or laboratory diagnosis	8	1.61(1.45~1.79)	56.6	0.005

Table 3 Subgroup analysis (RR and 95%CI) and heterogeneity of type 2 diabetes and esophageal cancer

Category	Study number	RR(95%CI)	Heterogeneity I^2(%)	Heterogeneity P
Esophageal cancer	8	1.16(1.07~1.27)	0	0.750
High quality literature	4	1.14(1.01~1.27)	0	0.683
Gender				
Male	7	1.18(1.06~1.30)	0	0.721
Female	3	1.25(0.87~1.79)	0	0.479
Adjusted with BMI				
Yes	5	1.21(1.05~1.39)	0	0.693
No	3	1.13(1.01~1.27)	0	0.577
Follow time				
<10 years	2	1.62(1.00~2.65)	0	0.484
≥10 years	6	1.15(1.05~1.26)	0	0.804
Study region				
Europe	6	1.13(1.02~1.26)	0	0.791
Asia	2	1.23(1.05~1.43)	7.2	0.357
DM diagnosis				
Self-report	4	1.10(0.97~1.24)	0	0.838
Clinical or laboratory diagnosis	4	1.24(1.09~1.40)	0	0.497

2.2.4 2型糖尿病与胰腺癌的关系

对提供结果的18篇胰腺癌文献[12~15,17~20,24,26,30~37]的一致性检验的 I^2=26.5%，P=0.087，研究之间存在异质性，因而采用随机效应模型进行效应值合并分析，合并RR为1.56(95%CI：1.49~1.64)，固定效应模型结果为1.54(95%CI：1.48~1.60)，两者结果相似。表明2型糖尿病是胰腺癌的危险因素。发表偏倚Begg's检验 Z=2.1081(P=0.0350)，提示发表偏倚显著。亚组分析显示各亚组文献一致性均较好(Table 5)。

2.2.5 2型糖尿病与结直肠癌的关系

对提供结果的19篇结直肠癌文献[13,14,18,24,36,38~51]的一致性检验的 I^2=47.2%，P=0.001，研究之间存在异质性，因而采用随机效应模型进行效应值合并分析，合并RR为1.32(95%CI：1.23~1.40)。固定效应模型结果为1.27 (95% CI：1.22~1.32)，两者结果相似，且均有统计学意义。表明2型糖尿病是结直肠癌的危险因素。发表偏倚Begg's检验 Z=1.4083(P=0.159)，提示发表偏倚不显著。亚组分析显示各亚组文献一致性均较好(Table 6)。

2.2.6 2型糖尿病与结肠癌的关系

对提供结果的10篇结肠癌文献[12,14,15,17~19,24,25,36,52]的一致性检验的 I^2=0，P=0.825，研究之间不存在异质性，因而采用固定效应模型进行效应值合并分析，合并RR为1.24(95%CI：1.15~1.33)。随机效应模型结果为1.24 (95%CI：1.15~1.33)，两者结果相似。表明2型糖尿病是结肠癌的危险因素。发表偏倚Begg's检验 Z=−1.2372(P=0.216)，提示发表偏倚不显著。亚组分析显示除了是否调整BMI亚组外，其他亚组文献一致性均较好(Table 6)。

2.2.7 2型糖尿病与直肠癌的关系

对提供结果的7篇直肠癌文献[14,15,17,19,24,25,52]的一致性检验的 I^2=9.2%，P=0.356，研究之间不存在异质性，因而采用固定效应模

Table 4 Subgroup analysis (RR and 95%CI) and heterogeneity of type 2 diabetes and gastric cancer

Category	Study number	RR(95%CI)	Heterogeneity I^2(%)	Heterogeneity P
Gastric cancer	12	1.34(1.11~1.61)	95.4	<0.001
High quality literature	5	1.17(1.11~1.22)	64.9	<0.001
Gender				
Male	10	1.35(1.03~1.78)	96.9	<0.001
Female	9	1.33(0.99~1.79)	93.6	<0.001
Adjusted with BMI				
Yes	6	1.12(0.97~1.29)	41.6	0.072
No	6	1.51(1.19~1.92)	97.0	<0.001
Follow time				
<10 years	5	0.93(0.73~1.18)	50.8	0.047
≥10 years	7	1.53(1.24~1.90)	96.5	<0.001
Study region				
Europe	8	1.13(1.03~1.24)	61.6	0.001
Asia	4	1.60(1.24~2.07)	97.5	<0.001
DM diagnosis				
Self-report	6	1.59(1.21~2.07)	95.5	<0.001
Clinical or laboratory diagnosis	6	1.12(1.06~1.17)	0	0.574

Table 5 Subgroup analysis (RR and 95%CI) and heterogeneity of type 2 diabetes and pancreatic cancer

Category	Study number	RR(95%CI)	Heterogeneity I^2(%)	Heterogeneity P
Pancreatic cancer	18	1.56(1.49~1.64)	26.5	0.087
High quality literature	8	1.61(1.52~1.70)	28.4	0.132
Gender				
Male	10	1.57(1.47~1.67)	10.3	0.346
Female	9	1.45(1.34~1.56)	1.33	0.743
Adjusted with BMI				
Yes	12	1.47(1.40~1.55)	0	0.586
No	6	1.68(1.54~1.84)	43.7	0.059
Follow time				
<10 years	10	1.61(1.52~1.72)	25.9	0.176
≥10 years	8	1.50(1.42~1.57)	19.7	0.218
Study region				
Europe	12	1.52(1.40~1.65)	36.4	0.054
Asia	6	1.62(1.53~1.71)	0	0.805
DM diagnosis				
Self-report	6	1.44(1.35~1.54)	0	0.592
Clinical or laboratory diagnosis	12	1.60(1.52~1.68)	27.5	0.120

Table 6 Subgroup analysis (RR and 95%CI) and heterogeneity of type 2 diabetes and colorectal cancer

Category	Study number	RR(95%CI)	Heterogeneity I^2(%)	Heterogeneity P
Colorectal cancer	19	1.32(1.23~1.40)	47.2	0.001
High quality literature	4	1.20(1.10~1.30)	0	0.432
Gender				
Male	9	1.23(1.15~1.32)	22.9	0.299
Female	8	1.25(1.15~1.35)	0.9	0.432
Adjusted with BMI				
Yes	12	1.30(1.22~1.39)	37.3	0.0048
No	7	1.33(1.15~1.52)	60.3	0.002
Follow time				
<10 years	7	1.38(1.22~1.55)	64.3	<0.001
≥10 years	12	1.24(1.18~1.31)	19.4	0.218
Study region				
Europe	16	1.36(1.24~1.49)	50.1	0.002
Asia	3	1.22(1.15~1.30)	33.9	0.157
DM diagnosis				
Self-report	9	1.29(1.18~1.40)	34.6	0.092
Clinical or laboratory diagnosis	10	1.34(1.22~1.48)	55.5	0.002
Colon cancer	10	1.24(1.15~1.33)	0	0.825
High quality literature	2	1.29(1.12~1.49)	34.5	0.205
Gender				
Male	6	1.20(1.08~1.32)	0	0.773
Female	5	1.27(1.13~1.43)	6.8	0.368
Adjusted with BMI				
Yes	7	1.24(1.15~1.34)	0	0.832
No	3	1.21(0.94~1.55)	8	0.353
Follow time				
<10 years	5	1.25(1.11~1.41)	0	0.540
≥10 years	5	1.23(1.12~1.34)	0	0.842
Study region				
Europe	6	1.21(1.11~1.33)	0	0.819
Asia	4	1.28(1.13~1.45)	0	0.548
DM diagnosis				
Self-report	6	1.22(1.12~1.33)	0	0.962
Clinical or laboratory diagnosis	4	1.28(1.11~1.49)	19.9	0.284
Rectal cancer	7	1.07(0.91~1.25)	9.2	0.356
High quality literature	2	1.07(0.84~1.37)	0	0.466
Gender				
Male	6	1.10(0.89~1.34)	0	0.628
Female	5	1.12(0.86~1.46)	20.4	0.285
Adjusted with BMI				
Yes	4	1.08(0.91~1.28)	0	0.517
No	3	1.01(0.69~1.49)	48.5	0.120
Follow time				
<10 years	4	1.15(0.93~1.42)	5.9	0.385
≥10 years	3	0.97(0.76~1.23)	14.2	0.321
Study region				
Europe	4	1.01(0.80~1.26)	19	0.290
Asia	3	1.13(0.91~1.41)	7.5	0.368
DM diagnosis				
Self-report	4	1.09(0.89~1.34)	5.4	0.386
Clinical or laboratory diagnosis	3	1.04(0.81~1.33)	29.6	0.224

型进行效应值合并分析，合并 RR 为 1.07 (95%CI：0.91~1.25)，随机效应模型结果为 1.07(95%CI：0.90~1.27)，两者结果相似。发表偏倚 Begg's 检验 Z = 1.2343(P=0.2171)，提示发表偏倚不显著。亚组分析显示各亚组文献一致性均较好，且各亚组分析的结果均无统计学意义(Table 6)。

3 讨 论

本研究分析结果显示，2 型糖尿病约可增加50%的消化道恶性肿瘤发生风险，其中肝癌、食管癌、胃癌、胰腺癌、结直肠癌和结肠癌发生风险分别增加了 79%、16%、34%、56%、32%和 24%，且均有统计学意义，提示 2 型糖尿病与消化系统恶性肿瘤关系密切。但直肠癌的合并 RR=1.07，95%CI：0.91~1.25，无统计学意义。本次荟萃分析进一步开展了敏感性分析，通过比较随机效应模型和固定效应模型的结果，发现两者均接近，提示 meta 分析的结果较可靠。

敏感性分析显示，有些亚组存在明显的异质性，异质性的来源可能与各研究控制的混杂因素的种类及数目不同有关。肝癌亚组分析后，性别亚组显示男性比女性更容易患肝癌，合并 RR 分别为1.94

(95%CI:1.68~2.23)和 1.49(95%CI:1.22~1.82),与有关研究结果相一致[53]。胃癌亚组分析后,从性别、是否调整 BMI、随访时间来看,女性、调整组、随访<10 年均无统计学意义,可能与女性更注意生活方式和随访时间短导致癌症结局未产生有关。食管癌亚组分析后,从性别、随访时间、诊断方式来看,女性、随访<10 年、自报结果均无统计学意义,可能与女性更注意生活方式、随访时间短导致癌症结局未产生和自报质量差有关,且食管癌纳入文献数目较少(仅 8 篇),结果稳健性不好。

Meta 分析本身属于观察性研究,在研究设计、资料收集和统计分析过程中不可避免存在偏倚,资料质量评判与取舍时也会产生偏倚,其中最突出的是发表偏倚[54]。要控制偏倚,惟一的方法是尽可能收集全部研究资料,由多人进行盲法评判决定资料的取舍,然后对所有合格资料进行合并分析,以尽可能地减少漏检及选择偏倚。由于罕见疾病的巢式病例对照研究 OR 值近似等于队列研究 RR 值,因此可以直接合并。本研究收集了 2 型糖尿病与消化系统恶性肿瘤关系的巢式病例对照研究与病例队列研究,尽可能地减小了选择偏倚。并且本研究摘录调整混杂因素最多的效应值做综合分析,尽量减少混杂对分析结果的影响。而且本研究在收集文献时由两位作者同时独立开展收集,由第三位作者进行核实和补充,矛盾和不一致的地方大家共同讨论和确定入选文献。纳入的文献均为英语,可能会导致语种的选择偏倚。由于每项研究都是相互独立的,并不是按照统一的标准和格式开展研究的,我们必须根据实际情况进行效应指标的综合和分析。因此本研究在收集资料时尽可能按照国际标准将相关资料和信息提供给读者。

2 型糖尿病导致消化系统恶性肿瘤的确切发病机制尚不清楚,主要有以下几种观点:①高血糖刺激糖酵解的增强,充分代偿呼吸酶系统的损伤,使正常细胞恶变为肿瘤细胞[55];②高胰岛素血症使胰岛素样生长因子(IGF-1)分泌增加,后者通过酪氨酸激酶级联途径刺激上皮细胞的增生,最终可能导致癌症的发生[56];③糖尿病患者存在细胞免疫调节功能紊乱,T 淋巴细胞亚群比例失调,免疫功能受损,进而诱发恶性肿瘤[57];④血管内皮生长因子(vascular endothelial growth factors,VEGF)为肿瘤细胞的生长和新生毛细血管网建立营养条件,对恶性肿瘤的发生、发展和侵袭均有促进作用[58,59]。

综上所述,本研究结果提示 2 型糖尿病可能是大多数消化系统恶性肿瘤的危险因素,糖尿病患者需警惕消化系统恶性肿瘤的发生,但是这一结论还需要大样本的前瞻性研究和干预实验结果来验证。

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