2 型糖尿病患者罹患生殖系统恶性肿瘤危险性的 Meta 分析

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摘　要:[目的]探讨 2 型糖尿病与生殖系统恶性肿瘤发生风险的关系。[方法]检索 1979 年 1 月至 2012 年 10 月 Medline、Embase 和 Web of Science 数据库公开发表的有关 2 型糖尿病与生殖系统恶性肿瘤关系的队列研究文献,按纳入和排除标准进行筛选,利用 R 软件及其 Meta 程序包对检索结果进行综合分析。[结果]共纳入 39 篇文献,包括 10 778 543 名观察对象。与非糖尿病人群相比,2 型糖尿病患者发生生殖系统恶性肿瘤的合并相对危险度 (RR) 为 1.15 (95%CI:1.03~1.28)。2 型糖尿病与女性生殖系统恶性肿瘤发生的相对危险度 RR 为 1.39(95% CI:1.23~1.57)。2 型糖尿病可以增加子宫内膜癌、宫颈癌和女性乳腺癌的发病风险,合并 RR 分别为 1.83 (95%CI:1.58~2.12)、2.13 (95%CI:1.86~2.43)和 1.16 (95%CI:1.03~1.32)。卵巢癌风险的增加接近临界(RR=1.21,95%CI:0.99~1.48);与前列腺癌的发病风险无关(RR=0.92,95%CI:0.78~1.09)。亚组分析提示,在欧美人群中 2 型糖尿病患者发生前列腺癌的风险降低,RR 为 0.80 (95%CI:0.74~0.87)。[结论]2 型糖尿病可能是子宫内膜癌、宫颈癌、乳腺癌的危险因素之一,可能是欧美人群前列腺癌保护因素。

关键词:2 型糖尿病;生殖系统恶性肿瘤;队列研究;流行病学;Meta 分析
中图分类号:R737.25;R737.3　　**文献标识码**:A　　**文章编号**:1004-0242(2014)04-0265-10
doi:10.11735/j.issn.1004-0242.2014.04.A001

Meta-Analysis of Type 2 Diabetes and the Risk of Reproductive System Malignancy

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Abstract: [Purpose] To investigate the relationship between type 2 diabetes and the risk of reproductive system malignancy. [Methods] A Meta-analysis was conducted to evaluate the association between type 2 diabetes and the risk of reproductive system malignancy from cohort studies, which were identified through electronic search of Medline, Embase and Web of Science database within the time limit of January 1979 to June 2012 to estimate the pooled relative risks (RRs). [Results] A total of 39 studies, involving 10 778 543 participants met the inclusion criteria. In total, the pooled RR of reproductive system malignancy was 1.15(95%CI: 1.03~1.28) for subjects with type 2 diabetes compared to those without diabetes. The pooled RR of reproductive system malignancy including ovarian, endometrial, cervical and breast cancer was 1.39 (95% CI: 1.23~1.57) for female subjects with type 2 diabetes. The results showed that type 2 diabetes increased the risk of endometrial cancer, cervical cancer and breast cancer with the pooled RRs of 1.83 (95% CI: 1.58~2.12), 2.13(95%CI: 1.86~2.43) and 1.16(95%CI: 1.03~1.32). A borderline increase for ovarian cancer with the pooled RR of 1.21(95%CI: 0.99~1.48) was observed. There was a significant statistical risk of prostate cancer with the pooled RR of 0.92(95%CI: 0.78~1.09). A reduced risk, RR of 0.80 (95%CI: 0.74~0.87) was observed for prostate cancer among European and American population in subgroup analysis. [Conclusion] The Type 2 diabetes might be associated with the increased risk of endometrial, cervical and breast cancer, and decreased risk of prostate cancer among European and American population.

Key words: type 2 diabetes; reproductive system malignancy; cohort study; epidemiology; Meta-analysis

大量流行病学调查显示,2 型糖尿病与恶性肿瘤的发生存在一定的关联。早在 20 世纪初,Maynard[1]和 Wilson 等[2]提出 2 型糖尿病可能与肿瘤的发生有关。近 30 年来流行病学研究显示,2 型糖尿病与恶性肿瘤的发生存在关联,但不同国家或地区的结果

收稿日期:2013-05-13;修回日期:2013-07-30
基金项目:国家科技重大专项基金(2008ZX10002-015, 2012ZX10002008-002)
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不尽相同。本研究对 1979 年 1 月至 2012 年 10 月公开发表的关于 2 型糖尿病与前列腺癌、子宫内膜癌、宫颈癌、卵巢癌、女性乳腺癌等生殖系统恶性肿瘤关系队列研究的英文文献进行了系统收集和整理，并开展 Meta 分析，为探索 2 型糖尿病与生殖系统恶性肿瘤发生之间的关系提供更多的证据。

1 资料与方法

1.1 文献查阅

通过网络收集 1979 年 1 月至 2012 年 10 月 Medline、Embase 以及 Web of Science 数据库发表的文献资料，主题词包括 diabetes mellitus、diabetes、metabolic syndrome、prostate cancer、endometrial cancer、cervical cancer、ovarian cancer、breast cancer、cohort study、prospective study、follow-up study 和 nested case-control study。

1.2 文献纳入排除标准及质量评分标准

文献纳入标准：①公开发表的生殖系统恶性肿瘤(前列腺癌、子宫内膜癌、宫颈癌、卵巢癌、乳腺癌)发病危险因素的前瞻性队列研究的研究报道；②暴露因素和主要检验假设为 2 型糖尿病；③生殖系统恶性肿瘤(前列腺癌、子宫内膜癌、宫颈癌、卵巢癌、乳腺癌)诊断明确；④能够提供暴露因素的相对危险度(RR)及其 95%可信区间(95%CI)。

文献排除标准：①研究结局不为生殖系统恶性肿瘤(如肺癌、胃癌)；②重复报告或质量较差；③报告信息少，或不能提供效应值的 95%CI，或无法利用的文献。

质量评分标准：依据针对观察性研究应用较广的评价标准 Newcastle-Ottawa 质量评价标准对文献质量进行评价。文献质量评分满分为 9 分，其中：①暴露组是否有代表性：来源于随机抽样的一般人群得 1 分，来源于特殊群体如护士、志愿者等不得分；②非暴露组的选择：和暴露组来源于同一人群得 1 分，否则不得分；③暴露的确认：有明确的 2 型糖尿病诊断书或者有详细面试得 1 分，自报有 2 型糖尿病或者没有介绍的不得分；④随访之前的恶性肿瘤患者被排除在外得 1 分，否则不得分；⑤是否调整了相关混杂因素：调整体质指数(BMI)以及与该肿瘤相关的重要混杂因素得 2 分，只调整 BMI 或者只调整与该肿瘤相关的重要混杂因素得 1 分，均未调整的不得分；⑥结局的评价：产生的恶性肿瘤结局有明确病理诊断或肿瘤登记得 1 分，否则不得分；⑦随访年限：随访或回访超过 10 年得 1 分，否则不得分；⑧队列人群失访率：小于 25%得 1 分，否则不得分。各文献评分结果见 Table 1。

1.3 数据整理

根据文献的纳入与评分标准，对符合要求的文献，详细记录其 2 型糖尿病调整的 RR 值(即原始研究中调整了最多的、目前认为可能是潜在混杂因素的效应值)及其 95%CI。将文献作者、国家(或地区)等信息，原文献资料中调整了已知或潜在的混杂因素的相对危险度(RR)以及其他相关信息进行汇总，建立数据库。

1.4 统计学处理

本次 Meta 分析的各个研究效应值采用调整后的 RR 值。依据异质性检验(Q 检验法)的结果，选择相应的模型计算合并 RR。若异质性检验结果 $P>0.05$ 即不存在异质性，则表明各个研究结果之间一致性较好，采用固定效应模型的 M-H 法 (Mantel-Haenszel method) [3]；否则采用随机效应模型的 D-L 法 (DerSimonian-Laird method) [4]。为使研究更具针对性，同时对不同文献质量、是否调整 BMI 以及研究地区进行亚组分析。资料分析利用 R 软件 [5]与 Meta 程序包[6]来实现。

2 结 果

2.1 文献资料基本情况

共收集到符合要求的文献 39 篇[7~45]，其中前列腺癌 26 篇[7~32]，子宫内膜癌 9 篇[9,14,22,33~38]，宫颈癌 5 篇[9,14,15,17,32]，卵巢癌 7 篇[9,14,17,22,32,37,39]，乳腺癌 14 篇[9,14,15,17,18,22,24,32,40~45]；包括 10 778 543 名观察对象。各文献的基本特征详见 Table 2。

2.2 2 型糖尿病与生殖系统恶性肿瘤的关系

对 39 篇文献所有研究结果进行异质性检验，Q=1283.92($P<0.001$)，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 1.15(95%CI：1.03~1.28)，该结果提示 2 型糖尿病与生殖系统恶性肿瘤有一定的关系。

Table 1 Study quality of selected articles in the Meta-analysis

First author	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Adjustment for important factor or additional factor	Outcome assessment	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total quality scores
Anderson, et al[34]	1	1	0	1	2	1	1	0	7
Atchison, et al[7]	1	1	1	1	2	1	1	1	9
Bjorge, et al(2010)[40]	1	1	1	1	2	1	1	0	8
Bjorge, et al(2011)[39]	1	1	1	1	2	1	1	0	8
Calton, et al[8]	1	1	0	1	2	1	0	0	6
Chodick, et al[9]	1	1	1	1	2	1	0	0	7
Coughlin SS, et al[10]	1	1	0	1	1	1	1	0	7
Darbinian, et al[11]	1	1	1	1	2	1	1	1	9
Folsom AR, et al[33]	0	1	1	1	2	1	1	1	8
Friberg, et al[35]	1	1	1	1	2	1	0	0	7
Giovannucci E, et al[12]	1	1	1	1	2	1	0	0	7
Grundmark, et al[13]	1	1	1	1	0	1	1	0	6
Inoue, et al[14]	1	1	0	1	2	1	1	1	8
Jee, et al[15]	1	1	1	1	2	1	0	1	8
Kasper, et al[16]	1	1	1	1	2	1	1	0	8
Khan, et al[17]	1	1	0	1	2	1	0	0	6
Lambe, et al[37]	1	1	1	1	2	1	1	1	9
Lee, et al[18]	0	1	1	1	2	1	1	0	7
Leitzmann, et al[19]	1	1	0	1	2	1	0	0	6
Li, et al[20]	1	1	0	1	2	1	0	1	7
Lindemann K, et al[36]	1	1	0	1	2	1	1	1	8
Lipscombe, et al[41]	1	1	1	1	2	1	0	1	8
Martin, et al[21]	1	1	0	1	2	1	0	1	7
Michels, et al[42]	0	1	0	1	2	1	1	1	7
Mink, et al[43]	1	1	1	1	2	1	0	1	8
Osaki Y, et al[44]	1	1	1	1	2	1	0	0	7
Ragozzino, et al[22]	1	1	1	1	1	0	1	0	6
Rapp, et al[45]	1	1	1	1	2	1	0	1	8
Rodriguez, et al[23]	1	1	0	1	2	1	0	0	6
Steenland, et al[24]	1	1	0	1	2	1	1	0	7
Tande, et al[25]	1	1	0	1	1	1	0	0	5
Terry, et al[38]	0	1	0	1	2	1	1	0	6
Tseng, et al[26]	1	1	0	1	1	1	1	0	6
Velicer, et al[27]	1	1	0	1	2	1	0	0	6
Wallner, et al[28]	1	1	0	1	1	1	1	0	7
Wallstrom, et al[29]	1	1	1	1	2	1	0	0	7
Waters, et al[30]	1	1	0	1	2	1	1	0	7
Will, et al[31]	1	1	0	1	1	1	1	0	7
Wotton, et al[32]	0	1	1	1	2	1	1	0	7

Table 2 Characteristics of studies included in the meta-analysis

First author(Year)	Type of cancer	Region	Number of patients/cohorts	Gender	RR(95%CI)	Scores	Matched or adjusted variables
Atchison, et al(2011)[7]	Prostate cancer	USA	65463/4501578	Male	0.89(0.87~0.91)	9	Age, alcohol drinking, BMI, race
Calton, et al(2007)[8]	Prostate cancer	USA	11193/328316	Male	0.71(0.66~0.76)	6	Age, BMI, race, education, family history of prostate cancer, others
Chodick, et al(2010)[9]	Prostate cancer	Israel	1444/52913	Male	0.63(0.56~0.74)	7	Age, region, BMI, history of cardiovascular disease
Coughlin, et al(1996)[10]	Prostate cancer	USA	826/348874	Male	0.77(0.43~1.36)	7	Age
Darbinian, et al(2008)[11]	Prostate cancer	USA	2833/47209	Male	0.78(0.62~0.97)	9	Age, BMI, race
Giovannucci, et al(1998)[12]	Prostate cancer	USA	1369/351670	Male	0.75(0.59~0.95)	7	Age, BMI, race, others
Grundmark, et al(2010)[13]	Prostate cancer	Sweden	237/2322	Male	1.04(0.71~1.54)	6	Age
Inoue, et al(2006)[14]	Prostate cancer	Japan	284/46548	Male	0.82(0.51~1.33)	8	Age, region, smoking, alcohol drinking, BMI, fruits and vegetables intake, others
Jee, et al(2005)[15]	Prostate cancer	Korea	NA/829770	Male	0.80(0.64~0.99)	8	Age, smoking, alcohol drinking
Kasper, et al(2009)[16]	Prostate cancer	USA	4511/51529	Male	0.83(0.74~0.94)	8	Age, BMI, race, smoking, family history of prostate cancer, physical activity, height, others
Khan, et al(2006)[17]	Prostate cancer	Japan	98/23378	Male	0.98(0.47~2.03)	6	Age, smoking, alcohol drinking, BMI
Lee, et al(2012)[18]	Prostate cancer	Taiwan	2205/488778	Male	1.56(1.19~2.04)	7	Age, history of high blood pressure, others
Leitzmann, et al(2008)[19]	Prostate cancer	USA	2085/33088	Male	0.80(0.68~0.95)	6	Age, BMI, race, smoking, education, family history of prostate cancer, physical activity, aspirin use, height, others
Li, et al(2010)[20]	Prostate cancer	Japan	230/22458	Male	1.18(0.76~1.83)	7	Age, BMI, smoking, family history of prostate cancer, others
Martin, et al(2009)[21]	Prostate cancer	Norway	687/29364	Male	0.98(0.70~1.36)	7	Age, height, smoking, education, physical activity, others
Ragozzino, et al(1982)[22]	Prostate cancer	USA	9/1135	Male	1.30(0.60~2.30)	6	Age
Rodriguez, et al(2005)[23]	Prostate cancer	USA	5318/184192	Male	0.67(0.60~0.75)	6	Age, BMI, race, education, family history of prostate cancer, others
Steenland, et al(1995)[24]	Prostate cancer	USA	156/14407	Male	1.45(0.78~2.71)	7	Age, BMI, smoking, alcohol drinking, income, physical activity, menopausal status
Tande, et al(2006)[25]	Prostate cancer	USA	385/6429	Male	0.73(0.51~1.05)	5	Age, race
Tseng, et al(2011)[26]	Prostate cancer	Taiwan	889/494630	Male	5.83(5.10~6.66)	6	Age
Velicer, et al(2007)[27]	Prostate cancer	USA	827/35239	Male	0.83(0.64~1.07)	6	Age, PSA test
Wallner, et al(2011)[28]	Prostate cancer	USA	206/16209	Male	0.77(0.39~1.50)	7	Age
Wallstrom, et al(2009)[29]	Prostate cancer	Sweden	809/19564	Male	0.76(0.51~1.11)	7	Age, region, smoking, alcohol drinking, income, others
Waters, et al(2009)[30]	Prostate cancer	USA	5941/86303	Male	0.81(0.74~0.87)	7	Age, BMI, race, education
Will, et al(1999)[31]	Prostate cancer	USA	2523/305065	Male	1.13(0.88~1.45)	7	Age
Wotton, et al(2011)ORLS1 (1963~1998)[32]	Prostate cancer	England	73/15898	Male	0.59(0.46~0.74)	7	Age, region

Table 2(Continued) Characteristics of studies included in the meta-analysis

First author(Year)	Type of cancer	Region	Number of patients/cohorts	Gender	RR(95%CI)	Scores	Matched or adjusted variables
Wotton, et al(2011)ORLS2 (1999~2008)[32]	Prostate cancer	England	48/7771	Male	0.66(0.49~0.88)	7	Age, region
Anderson, et al(2001)[34]	Endometrial cancer	USA	346/24664	Female	1.43(0.98~2.09)	7	Age, BMI, family history of high blood pressure, others
Chodick, et al(2010)[9]	Endometrial cancer	Israel	177/47682	Female	2.00(1.41~2.84)	7	Age, region, BMI, history of cardiovascular disease
Folsom, et al(2003)[33]	Endometrial cancer	USA	415/23335	Female	2.12(1.52~2.89)	8	Age, BMI, family history of high blood pressure, alcohol drinking, smoking, menopausal status, others
Friberg, et al(2007)[35]	Endometrial cancer	Sweden	225/36773	Female	1.94(1.23~3.08)	7	Age, BMI, physical activity
Inoue, et al(2006)[14]	Endometrial cancer	Japan	89/51223	Female	1.68(0.61~4.64)	8	Age, region, smoking, alcohol drinking, BMI, fruits and vegetables intake, others
Lambe, et al(2011)[37]	Endometrial cancer	Sweden	1070/230737	Female	1.46(1.09~1.96)	9	Age, race, others
Lindemann, et al(2008)[36]	Endometrial cancer	Norway	222/36761	Female	3.13(1.92~5.11)	8	Age, physical activity, family history of high blood pressure, alcohol drinking
Ragozzino, et al(1982)[22]	Endometrial cancer	USA	3/1135	Female	1.30(0.30~3.80)	6	Age
Terry, et al(1999)[38]	Endometrial cancer	Sweden	133/12186	Female	1.60(0.20~11.30)	6	Age, physical activity, weight, race
Chodick, et al(2010)[9]	Cervical cancer	Israel	42/47682	Female	1.43(0.59~3.47)	7	Age, region, BMI, history of cardiovascular disease
Inoue, et al(2006)[14]	Cervical cancer	Japan	133/51223	Female	0.61(0.15~2.48)	8	Age, region, smoking, alcohol drinking, BMI, fruits and vegetables intake, others
Jee, et al(2005)[15]	Cervical cancer	Taiwan	NA/468615	Female	2.20(1.90~2.54)	8	Age, smoking, alcohol drinking
Khan, et al(2006)[17]	Cervical cancer	Japan	26/33503	Female	0.99(0.13~7.38)	6	Age, smoking, alcohol drinking, BMI
Wotton, et al(2011)ORLS1 (1963~1998)[32]	Cervical cancer	England	27/15898	Female	2.07(1.33~3.10)	7	Age, region
Wotton, et al(2011)ORLS2 (1999~2008)[32]	Cervical cancer	England	2/7771	Female	1.51(0.18~5.83)	7	Age, region
Bjorge, et al(2011)[39]	Ovarian cancer	Australia, Norway, Sweden	644/288834	Female	1.09(0.86~1.40)	8	Age, BMI, smoking, others
Chodick, et al(2010)[9]	Ovarian cancer	Israel	88/47682	Female	2.39(1.43~4.00)	7	Age, region, BMI, history of cardiovascular disease
Inoue, et al(2006)[14]	Ovarian cancer	Japan	74/51223	Female	2.42(0.96~6.09)	8	Age, region, smoking, alcohol drinking, BMI, fruits and vegetables intake, others
Khan, et al(2006)[17]	Ovarian cancer	Japan	30/33503	Female	1.82(0.42~7.87)	6	Age, smoking, alcohol drinking, BMI

Table 2(Continued) Characteristics of studies included in the meta-analysis

First author(Year)	Type of cancer	Region	Number of patients/cohorts	Gender	RR(95%CI)	Scores	Matched or adjusted variables
Lambe, et al(2011)[37]	Ovarian cancer	Sweden	783/230787	Female	0.99(0.64~1.53)	9	Age, race, others
Ragozzino, et al(1982)[22]	Ovarian cancer	USA	3/1135	Female	1.20(0.20, 3.40)	6	Age
Wotton, et al(2011)ORLS1 (1963~1998)[32]	Ovarian cancer	England	37/15898	Female	1.28(0.89, 1.78)	7	Age, region
Wotton, et al(2011)ORLS2 (1999~2008)[32]	Ovarian cancer	England	8/7771	Female	0.93(0.40, 1.88)	7	Age, region
Bjorge, et al(2010)[40]	Breast cancer	Australia, Norway, Sweden	4862/288834	Female	0.83(0.76~0.90)	8	Age, smoking, BMI
Chodick, et al(2010)[9]	Breast cancer	Israel	1167/47682	Female	1.00(0.86~1.19)	7	Age, region, BMI, history of cardiovascular disease
Inoue, et al(2006)[14]	Breast cancer	Japan	451/51223	Female	0.93(0.44~1.98)	8	Age, region, smoking, alcohol drinking, BMI, fruits and vegetables intake, others
Jee, et al(2005)[15]	Breast cancer	Korea	NA/468615	Female	1.51(1.26~1.80)	8	Age, smoking, alcohol drinking
Khan, et al(2006)[17]	Breast cancer	Japan	120/33503	Female	1.27(0.51~3.14)	6	Age, smoking, alcohol drinking, BMI
Lee, et al(2012)[18]	Breast cancer	Taiwan	3911/497037	Female	1.01(0.74~1.37)	7	Age, family history of high blood pressure, others
Lipscombe, et al(2006)[41]	Breast cancer	Canada	6107/465510	Female	1.08(1.01~1.16)	8	Age, income
Michels, et al(2003)[42]	Breast cancer	USA	5605/116488	Female	1.17(1.01~1.35)	7	Age, family history of breast cancer, BMI, menopausal status, others
Mink, et al(2002)[43]	Breast cancer	USA	187/7894	Female	1.39(0.86~2.23)	8	Age, region, BMI, menarche age, menopausal status, the firstborn age, family history of breast cancer, alcohol drinking, smoking
Osaki, et al(2012)[44]	Breast cancer	Japan	119/15386	Female	2.87(1.67~4.94)	7	Age, smoking, others
Ragozzino, et al(1982)[22]	Breast cancer	USA	14/1135	Female	1.30(0.70~2.20)	6	Age
Rapp, et al(2006)[45]	Breast cancer	Australia	872/77228	Female	1.38(1.02~1.86)	8	Age, BMI, occupation, smoking
Steenland, et al(1995)[24]	Breast cancer	USA	163/14407	Female	1.40(0.70~2.78)	7	Age,BMI,smoking,alcoholdrinking,income,physical activity, menopausal status
Wotton, et al(2011)ORLS1 (1963~1998)[32]	Breast cancer	England	149/15898	Female	1.05(0.88~1.24)	7	Age, region
Wotton, et al(2011)ORLS2 (1999~2008)[32]	Breast cancer	England	52/7771	Female	0.96(0.71~1.27)	7	Age, region

2.2.1 2型糖尿病与女性生殖系统恶性肿瘤

对21篇女性生殖系统恶性肿瘤文献的研究结果进行异质性检验，Q=241.12(P<0.001)，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1.39(95%CI：1.23~1.57)，该结果提示2型糖尿病与女性生殖系统恶性肿瘤有一定的关系。

2.2.2 2型糖尿病与前列腺癌

对26篇文献研究结果进行异质性检验的Q值为906.92（*P*<0.001），表明不同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0.92（95%CI：0.78~1.09）。亚组分析发现，高质量文献、调整BMI、欧美地区组结果提示2型糖尿病对前列腺癌有保护作用(Table 3)。

2.2.3 2型糖尿病与子宫内膜癌

对9篇文献研究结果进行异质性检验的Q值为9.96（*P*=0.268），提示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1.83（95%CI：1.58~2.12）。亚组分析结果表明，除低质量文献组未发现2型糖尿病增加子宫内膜癌危险性的关系外，高质量文献组、调整或不调整BMI组以及欧美和亚洲地区合并结果均支持2型糖尿病增加子宫内膜癌发病的危险(Table 4)。

2.2.4 2型糖尿病与宫颈癌

对5篇文献研究结果进行异质性检验的Q值为4.74（*P*=0.448），说明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2.13（95%CI：1.86~2.43）。因低质量文献仅1篇，排除低质量文献后高质量文献分析结果表明，高质量文献组2型糖尿病患者罹

Table 3 Summary risk estimates of the association between type 2 diabetes and the risk of prostate cancer

Index	No. of studies	RR(95%CI)	Heterogeneity test	
			P	*Q*
Total	26	0.92(0.78~1.09)	<0.001	906.92
High-quality studies				
Yes	17	0.84(0.77~0.92)	<0.001	72.71
No	9	1.07(0.60~1.91)	<0.001	821.1
Matched or adjusted BMI				
Yes	12	0.76(0.71~0.82)	0.003	28.22
No	14	1.01(0.68~1.49)	<0.001	784.81
Region				
Europe/America	19	0.80(0.74~0.87)	<0.001	86.21
Asia	7	1.24(0.52~2.96)	<0.001	581.95

Table 4 Summary risk estimates of the association between type 2 diabetes and the risk of reproductive malignancy in females

Index	No. of studies	RR(95%CI)	Heterogeneity test	
			P	*Q*
Endometrial cancer	9	1.83(1.58~2.12)	0.268	9.96
High-quality studies*				
Yes	7	1.84(1.59~2.13)	0.14	9.66
No	2	1.38(0.47~4.04)	0.86	0.03
Matched or adjusted BMI				
Yes	6	1.75(1.50~2.04)	0.456	4.68
No	3	2.72(1.74~4.24)	0.39	1.88
Region				
Europe/America	7	1.80(1.53~2.12)	0.14	9.65
Asia	2	1.96(1.41~2.73)	0.75	0.1
Cervical cancer	5	2.13(1.86~2.43)	0.448	4.74
High-quality studies				
Yes	4	2.13(1.87~2.44)	0.381	4.19
No	1	0.99(0.13~7.46)		
Matched or adjusted BMI				
Yes	2	0.71(0.23~2.26)	0.7	0.15
No	3	2.16(1.89~2.47)	0.78	1.1
Region				
Europe/America	1	2.03(1.35~3.07)	0.73	0.12
Asia	4	2.14(1.86~2.47)	0.21	4.57
Ovarian cancer	7	1.21(0.99~1.48)	0.056	15.16
High-quality studies				
Yes	5	1.21(0.97~1.51)	0.023	14.68
No	2	1.47(0.53~4.06)	0.69	0.16
Matched or adjusted BMI				
Yes	4	1.19(0.91~1.55)	0.025	11.11
No	3	1.30(0.97~1.74)	0.479	2.48
Region				
Europe/America	4	1.04(0.93~1.16)	0.831	2.13
Asia	3	2.34(1.52~3.60)	0.94	0.12
Breast cancer	14	1.16(1.03~1.32)	<0.001	65.52
High-quality studies				
Yes	11	1.15(1.01~1.31)	<0.001	63.29
No	3	1.38(0.93~2.05)	0.9486	0.11
Matched or adjusted BMI				
Yes	8	1.10(0.92~1.33)	<0.001	28.81
No	6	1.25(1.03~1.53)	<0.001	25.9
Region				
Europe/America	11	1.15(1.00~1.32)	<0.001	51.03
Asia	3	1.27(0.83~1.94)	0.0012	13.48

Note：*：Quality scores=7，8，9

患宫颈癌的危险性增加，无论是否调整 BMI 以及不同研究地区均支持 2 型糖尿病患者增加其罹患宫颈癌的危险(Table 4)。

2.2.5　2 型糖尿病与卵巢癌

对 7 篇文献研究结果进行异质性检验的 Q 值为 15.16(P=0.056)，由于研究结果数目较少，且 P 值接近临界统计学意义，故采用随机效应模型进行效应值合并分析，合并 RR 为 1.21(95%CI：0.99~1.48)。亚组分析提示，亚洲组结果提示 2 型糖尿病患者增加其罹患卵巢癌危险性的证据。

2.2.6　2 型糖尿病与乳腺癌

对 14 篇文献研究结果进行异质性检验的 Q 值为 65.52(P<0.001)，说明不同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 1.16(95%CI：1.03~1.32)。亚组分析提示，高质量文献组、未调整 BMI 组、欧美组均提示 2 型糖尿病会增加其罹患卵巢癌的风险(Table 4)。

3　讨　论

本研究分析结果显示，2 型糖尿病与生殖系统恶性肿瘤的关系密切，危险性约增加 15%，有统计学意义。文中同时分析了 2 型糖尿病与女性生殖系统恶性肿瘤的数据，发现其危险性约增加高达 39%，有统计学意义。其中 2 型糖尿病可以提高子宫内膜癌、宫颈癌和乳腺癌的发病风险，合并 RR 分别为 1.83 (95%CI：1.58~2.12)、2.13 (95%CI：1.86~2.43) 和 1.16(95%CI：1.03~1.32)，均有统计学意义；前列腺癌和卵巢癌的 RR 分别为 0.92　(95%CI：0.78~1.09) 和 1.21 (95%CI：0.99~1.48)，没有统计学意义。但亚组分析提示，2 型糖尿病与欧美人群前列腺癌发生风险降低有关。

糖尿病患者多发生胰岛素抵抗，致使胰岛素出现代偿性增加，但此时并不能发挥其生理功能，满足机体需要，从而导致机体高血糖与内源性高胰岛素血症同时存在。文献研究表明，胰岛素可以上调血管内皮生长因子的表达，促进肿瘤的生长[46]。此外，胰岛素能降低胰岛素生长因子结合蛋白 (IGF-BP1 或 IGF-BP2)水平，导致胰岛素样生长因子-1(IGF-1)水平升高，IGF-1 是公认的肿瘤促进因子，在肿瘤细胞的浸润、转移中发挥重要作用[47]。同时，IGF-1 还通过促进有丝分裂，诱导细胞分化，进而加快细胞增殖，增加细胞恶变的可能[48]。近年来，人们还发现 IGF-1 可以抑制细胞的凋亡[49]。由此可见，内源性高胰岛素血症可能是导致糖尿病时肿瘤发生的一个重要因素。另外，糖尿病患者高血糖本身也可能是导致肿瘤的一个重要因素。长期的高血糖刺激，可引起毛细血管基底膜增厚，通透性下降，导致细胞线粒体上的呼吸酶受损，细胞呼吸发生障碍，无氧酵解增加，正常细胞为适应这种状态而选择性的发生恶变，成为糖酵解能力较强的肿瘤细胞[50]。此外，研究提示糖尿病患者 T 淋巴细胞亚群比例严重失调[51]。糖尿病患者普遍存在免疫调节功能紊乱，致使机体免疫监测作用减弱，所以即使发生恶变转化的细胞免疫原性很高，也仍能逃逸宿主的免疫监视而继续存活、增生，导致恶性肿瘤的发生。

异质性分析显示，各个亚组存在明显的异质性，异质性的来源可能与各个研究对象来自不同的总体以及控制的混杂因素的种类及数目不同有关，以及与作者对一些要素定义的不同如随访时间、失访率等有关。宫颈癌亚组分析后，各亚组结果与主要结果有一定差异，稳健性较差，这可能与不同地区的人群可能存在病因学差异，以及由于宫颈癌病例数目较少导致检验效能较低有关。本次研究发现高质量文献组、调整 BMI 组以及欧美组的 2 型糖尿病与前列腺癌发病率呈负相关，而与其他生殖系统恶性肿瘤却基本呈正相关，该结果验证了 2 型糖尿病患者患前列腺癌危险降低的假说[52]。假说认为总睾酮和游离睾酮含量较高的男性前列腺癌发病的风险会相对更大。而 2 型糖尿病患者的总睾酮及游离睾酮均减少，使得患前列腺癌风险也降低。Waters 等[53]在基因学水平上探讨糖尿病与前列腺癌的相关性，结果提示糖尿病高风险等位基因多态性与前列腺癌的发生没有关联。

国内关于 2 型糖尿病与生殖系统恶性肿瘤关系的 Meta 分析鲜有报道，且发表的 Meta 分析中所采用的 RR 指标可能存在一定的局限性，分析中绝大部分文献提供的统计指标均为非调整的 RR 值，本研究则利用纳入文献中调整的 RR 值作为 Meta 分析的效应值，进行综合分析，其结果可能更有价值。众所周知，队列研究比病例对照研究在病因学的推断上更具说服力，纳入本次分析的文献均为国外前

瞻性研究或大规模队列研究，得出的 Meta 分析结果应更可靠。此外，本次 Meta 分析是通过 R 软件及其 Meta 程序包实现的。目前有关 R 软件及其程序包在流行病学数据统计分析上的应用在国内很少报道，因此值得在研究中加以应用。

Meta 分析分析本身属于观察性研究，需要特别注意发表偏倚[54]的问题。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。因此Meta 分析原则上应尽可能收集各种研究类型的资料，这样才会尽可能的减少漏检及选择偏倚。本研究摘录调整混杂因素最多的效应值做综合分析，尽可能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，并且相互进行核实和补充，矛盾和不一致的地方大家共同讨论和确定入选文献。此外，评估有无明显的发表偏倚也是 Meta 分析工作的一个重要方面。本次分析乳腺癌资料时发现存在发表偏倚，其他肿瘤均未发现明显的发表偏倚，Begg 检验值均大于 0.05。但这并不能完全排除发表偏倚的存在，由于语言的差异，纳入的文献均为英语，未收集其他语种的文献，这可能会导致语种的选择偏倚。当纳入 Meta 分析的肿瘤部位和研究的地区较多时，可能会给研究带来一些困难，例如样本大小不一，可提供的亚组资料不同，各研究控制的混杂因素种类和数量可能不等。因为每个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，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把相关资料和信息提供给读者，并归纳和罗列在 Table 2 中。

综上所述，本次研究结果提示 2 型糖尿病可能与子宫内膜癌、宫颈癌和乳腺癌等主要生殖系统恶性肿瘤的发生相关，可能与欧美人群前列腺癌发生风险降低有关。但是这些结论还需要得到大样本的前瞻性研究和干预实验结果的验证。

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