Type 2 diabetes mellitus and risk of colorectal adenoma: a meta-analysis of observational studies

Feifei Yu†, Yibin Guo‡, Hao Wang§, Jian Feng‡, Zhichao Jin‡, Qi Chen‡, Yu Liu§ and Jia He‡*

Abstract

Background: To summarize the relationship between type 2 diabetes mellitus (T2DM) and risk of colorectal adenomas (CRA), we performed a meta-analysis of observational studies.

Methods: To find studies, we searched PubMed, Embase, the Cochrane Library, Web of Science and conference abstracts and related publications for American Society of Clinical Oncology and the European Society of Medical Oncology. Studies that reported relative risks (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs) for the association between T2DM and risk of CRA were included. The meta-analysis assessed the relationships between T2DM and risk of CRA. Sensitivity analyses were performed in two ways: (1) by omitting each study iteratively and (2) by keeping high-quality studies only. Publication bias was detected by Egger’s and Begg’s tests and corrected using the trim and fill method.

Results: This meta-analysis included 17 studies with 28,999 participants and 6798 CRA cases. We found that T2DM was a risk factor for CRA (RR: 1.52; 95% CI: 1.29–1.80), and also for the advanced adenoma (RR: 1.41; 95% CI: 1.06–1.87). Patients with existing T2DM (RR: 1.56; 95% CI: 1.16–2.08) or newly diagnosed T2DM (RR: 1.51; 95% CI: 1.16–1.97) have a risk of CRA. Similar significant results were found in retrospective studies (RR: 1.57; 95% CI: 1.30–1.89) and population based cross-sectional studies (RR: 1.46; 95% CI: 1.21–1.89), but not in prospective studies (RR: 1.27; 95% CI: 0.77–2.10).

Conclusions: Our results suggested that T2DM plays a risk role in the risk of developing CRA. Consequently, medical workers should increase the rate of CRA screening for T2DM patients so that they can benefit from behavioural interventions that can help prevent the development of colorectal cancer. Additional, large prospective cohort studies are needed to make a more convincing case for these associations.

Keywords: Type 2 diabetes mellitus, Colorectal adenoma, Meta-analysis

Background

Diabetes mellitus (DM) is the fourth or fifth leading cause of death in developed countries and one of the biggest threats to human health worldwide [1]. More than 90% of all DM is type 2 diabetes mellitus (T2DM) [2, 3]. Colorectal cancer (CRC) is the third most common cancer in the world. Colorectal adenoma (CRA) (also known as adenomatous polyp and always found by colonoscopy screen [4]) is a prevalent precancerous lesion that can lead to CRC through the adenoma–carcinoma sequence [5].

Research on risk factors for CRA has focused on several epidemiological factors, including smoking [6], alcohol consumption [5], body mass index [7], physical activity [8], and calcium intake [9]. Recent research on patients with diabetes suggested that insulin therapy and diabetes itself may increase the risk of CRC [10–12]. However, the association between T2DM and the risk of CRA risk has not yet been fully established. Some researchers asserted that there were no overall associations between T2DM and CRA risk [13–16], while others reported a higher risk [17–20]. To further examine these findings and provide evidence of association between...
T2DM and risk of CRA risk, we performed a meta-analysis about T2DM on the risk of CRA.

**Methods**

**Literature search**

Two investigators (FY and YG) independently conducted a systematic literature searches on January 10, 2016 in PubMed, Embase, the Cochrane Library and Web of Science without limiting the publication date range. The following search terms were used: (diabetes mellitus OR diabetes OR diabetic OR glucose) AND (colorectal OR colon OR rectal) AND (adenomas OR adenoma OR adenomatous OR polyp). No language restrictions and any other limitations were imposed. Conference abstracts on the websites of American Society of Clinical Oncology’s (ASCO) and the European Society for Medical Oncology’s (ESMO) annual meetings were also searched, along with the reference lists of the identified publications. Additional file 1 includes the complete searching process.

The titles and abstracts of all of the studies from the searches were screened independently by three reviewers (FY, YG and JF). To be included in this meta-analysis, studies had to be at least one of the following criteria: (1) retrospective or perspective observational study of the association between diabetes mellitus and CRA, or (2) a study reporting the relative risks (RRs) or odds ratios (ORs) for T2DM on CRA with 95 % confidence intervals (95 % CIs) adjusted for gender, age, or other factors. Studies reporting on the CRA recurrence were excluded.

**Data extraction**

Data extraction was performed by three reviewers (FY, YG and WH), and verified independently for accuracy by a forth reviewer (JH). The following information was collected for each study: title and author, publication year, population, location, sample size, proportion of males and covariates controlled for by matching or multivariate analysis. For studies that reported several multivariate adjusted ORs, the effect estimate that adjusted for the maximum potential confounders was selected. Two investigators (FY and ZJ) conducted a quality assessment using the 9-star Newcastle-Ottawa Scale (NOS) [21], which was verified by a third investigator (YG). We considered studies with a NOS score of seven or more to be high-quality studies. The study selection process was based on the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [22] and is described in Additional file 2.

**Statistical analysis**

We examined the relationship between T2DM and CRA risk on the basis of the adjusted RRs and ORs and corresponding 95 % CI published in each study. A fixed-effects model was used to estimate the pooled RR and OR with 95 % CIs if there was no evidence of heterogeneity; otherwise, a random effect model was used [23, 24]. Because the incidence of CRA is low, the ORs in retrospective studies approximate the RRs [25, 26]. Heterogeneity between the studies was evaluated by the chi-square test and I-squared ($I^2$) statistic [23]. Statistical heterogeneity was considered significant when $p < 0.10$ [27].

Several methods were used to test and adjust for potential publication bias. Visual inspection of funnel plots was performed, and the Egger’s regression test [28] and Begg’s test [29] were used. Where publication bias existed, we used the trim and fill method to correct it [30]. Subgroups analyses by gender, adenoma subsite, and study type were performed to explore the potential heterogeneity among the included studies. Sensitivity analyses were performed in two ways: (1) by excluding each study iteratively from the meta-analysis and (2) by keeping high-quality studies only.

All statistical tests were two-sided and regarded as statistically significant at $p < 0.05$ Stata (Version 11.0; Stata Corp, College Station, TX) was used for all analyses.

**Results**

**Study characteristics**

Until January 10, 2016, 2522 records were retrieved by using our search strategy. After reviewing the titles and abstracts, 113 articles were further evaluated by reviewing the full texts. Of those remaining articles, we excluded studies that: (1) reported the data of adenoma recurrence were excluded [31, 32], (2) did not reported the RRs of getting CRA separately but mixed CRC and CRA patients [31], and (3) discussed the relationship between metformin [33] or insulin use [34] and CRA. We identified 17 studies that met all of our criteria [13–20, 35–44], including four conference abstracts [36, 37, 43, 44]. Figure 1 provides a flow chart of study selection. The final studies included 28,999 participants and 6798 CRA cases and 11 were rated as high-quality. Four of the conference abstracts rated less than seven stars due to insufficient information about their research. Table 1 includes the general characteristics of the included studies.

**Diabetes and risk of colorectal adenoma**

The summary RR of diabetes on CRA was statistically significant (RR: 1.52; 95 % CI: 1.29–1.80). Evidence of the heterogeneity was identified ($I^2 = 65.6 \%$, $P < 0.001$). Figure 2 shows the results.

**Subgroup analysis**

As shown in Table 2, we conducted subgroup analyses based on multiple factors, including sub-site of adenoma, geographic region, gender, and study type. The
results showed that advanced adenoma was significantly associated with T2DM (RR: 1.41; 95 % CI: 1.06–1.87). However, a similar effect was not detected for proximal, distal, or colon adenoma. No evidence indicated significant associations between T2DM and CRA by gender, i.e., males (RR: 1.36; 95 % CI: 0.99–1.80) or females (RR: 1.29; 95 % CI: 0.76–2.17). The relationships between T2DM and CRA risk was significant in Europe (RR: 1.27, 95 % CI: 1.02–1.57), the USA (RR: 1.69; 95 % CI: 1.14–2.51) and Asia (RR: 1.57; 95 % CI: 1.21–2.05). A significant increase in risk was found in retrospective studies (RR: 1.57; 95 % CI: 1.30–1.89) and not in prospective studies (RR: 1.27; 95 % CI: 0.77–2.10).

Sensitivity analysis
Sensitivity analysis indicated that no single study dramatically influenced the pooled RR. The results are shown in Fig. 3. Regardless of which study was omitted, the summary RRs were always greater than one. Similarly, Table 2 shows that excluding low-quality studies yielded results comparable with including all studies (RR: 1.64; 95 % CI: 1.26–2.14).

Publication bias
The Begg’s rank correlation test ($p = 0.001$) and Egger’s regression test ($p = 0.003$) results showed potential publication bias that is described in Fig. 4. Once corrected by the trim and fill method [30], the result indicated that the pooled effect size did not change.

Discussion
This study indicated that patients with diabetes, especially type 2, have about 50 % increased relative risk of developing CRA than non-diabetic individuals, regardless of their geographic location. Although sample size was small in the newly diagnosed T2DM subgroup, the heterogeneity was also small and a significant risk relationship between T2DM and CRA was still detected. A similar result was only found in the advanced adenoma subgroup, not in the proximal, distal, colon or multiple adenoma subgroups. When low-quality studies were excluded, the positive association still existed. These results suggested that T2DM patients should pay more attention to their risk of CRA.

The positive relationship between T2DM and CRA may be linked to insulin resistance or an increased
### Table 1 Characteristic of studies included in the meta-analysis

| Author                        | Year | Country   | Study type | Mean age | Male (%) | Sample size | Category of exposure (N) | Outcome | Adjusted variable                                                                 | NOS |
|-------------------------------|------|-----------|------------|----------|----------|-------------|------------------------|---------|-----------------------------------------------------------------------------------|-----|
| Chiranjeev Dash [13]          | 2014 | US        | retrospective | 54.6 (8.5) | 0 (0)  | 3668        | T2DM (804)             | CRA (917) | age, educational status, body mass index (weight (kg)/height (m)^2), physical activity, family history of colorectal cancer in a first-degree relative, smoking status, alcohol intake, total energy intake, red meat intake, fruit and vegetable intake, and regular aspirin use | 8   |
| Heike Ursula [14]             | 2012 | German    | prospective | 61.5     | 667 (62) | 1554        | T2DM (166)             | Colorectal neoplasia (389) | age and sex | hospital, rank in the Self Defense Forces, alcohol use, and cigarette smoking | 8   |
| Tomomi Marugame [15]          | 2002 | Japan     | retrospective | 52.4     | 1389 (100) | 1389        | Newly diagnosed T2DM (41) | CRA (560), Proximal adenomas (254), Distal adenomas (306) | ethnicity, body mass index, smoking, and alcohol use | 7   |
| Hongta T Vu [20]              | 2014 | USA       | retrospective | 46       | 92 (36.8) | 250         | T2DM (125)             | CRA (56) | Age, Sex, TG, LDL, HDL, Smoking, Family history of CRC, Aspirin, NSAID, Statins | 7   |
| Rodney Eddi [18]              | 2012 | USA       | retrospective | 71       | 442 (56.4) | 783         | T2DM (89)              | Adenomatous polyps (261) | Age, Sex, TG, LDL, HDL, Smoking, Family history of CRC, Aspirin, NSAID, Statins | 7   |
| Mehulkumar K. Kanadiya [19]   | 2013 | American  | retrospective | 60.63 (9.20) | 1697 (49) | 3465        | T2DM (405)             | CRA (852) | NA                                                                                | 3   |
| Joseph Carl Anderson [35]     | 2011 | USA       | retrospective | NA       | 76 (38.0) | 290         | T2DM (46)              | Any Sessile Serrated Adenomas (90) | NA | 7 |
| Bouwens, M [36]               | 2011 | NA        | retrospective | 60       | 863        | 1836        | T2DM                  | Combined adenoma-serrated phenotype (139) | NA | 5a |
| de Kort, S [37]               | 2013 | Netherlands | retrospective | NA       | NA         | 3335        | T2DM (326)             | CRA (1112) | age, gender, BMI and other relevant risk factors | 4a |
| Jill E. Elwing [38]           | 2006 | US        | retrospective | 59.2     | 0 (0)  | 600         | All diabetics (100)    | Any Adenoma (159), Advanced adenoma (46) | age, race, hypertension, hypercholesterolemia, BMI, and NSAID status | 7   |
| Kazushige Kawai [39]          | 2012 | Japan     | prospective  | 63.1 (10.5) | 109 (61.9) | 176         | T2DM (3888)            | Polyp (69) | NA                                                                                | 7   |
| Suminori Kono [40]            | 1998 | Japan     | retrospective | 50–54    | 5193 (100) | 5193        | T2DM (166)             | Sigmoid colon adenomas (821) | body mass index (wt [kg]/ht [m]^2), cigarette smoking, alcohol use, rank of the Self Defense Forces, and hospital. | 7   |
| Takasei Nishii [41]           | 2001 | Japan     | retrospective | 48.4     | 951 (100) | 951         | T2DM (43)              | Colon Adenomas (233) | Age- and BMI | 6   |
| Sungwhwan Suh [42]            | 2011 | Korea     | retrospective | 55.9     | 2528 (72.1) | 3505        | T2DM (509)             | Multiple Adenomatous Polyps (509) | sex, age, BMI, TC, HDL, TG, Fasting plasma glucose, HbA1c | 7   |
| Thomas R [43]                 | 2012 | NA        | retrospective | 58.4     | 1230 (95) | 1295        | T2DM (350)             | Advanced adenoma (243) | NA | 3a |
| Wang, JH [44]                 | 2013 | China     | retrospective | NA       | NA        | 470         | T2DM                  | CRA (235) | abdominal circumference, daily calories & fat intake, increased diastolic blood pressure, history of hypertension or fatty liver, family history of cancer in | 6a |
insulin-like growth factor 1 (IGF-1) might take effect in the adenoma–carcinoma process. High insulin levels could promote tumor growth [31, 45, 46]. Also, diabetes may lead to slower bowel transit, which would increase the probability of exposure to potential carcinogens for colonic mucosa [47–49]. It is worth noting that there might be some confounding effects because of the similar risk factors for both T2DM and CRA, such as physical inactivity, obesity, and an unhealthy diet habit [12, 50]. For example, a case–control study reported that higher red meat intake could significantly increase the risk of colon adenoma [51]. At the same time, obese people also tend to consume more red meats and have a higher risk of diabetes. Therefore, dietary habits might be a confounding factors. Finally, some researchers also report that obesity might be a confounder in the association between T2DM and colorectal disease [52]. Some studies reported a difference in risk between males and females [12, 39, 53–55]; however, the results of our subgroup analysis showed no difference. One possible explanation involves the redistribution of body fat that can occur when women experience menopause. The increase in visceral body mass fat could lead to hyperinsulinemia so that women, especially post-menopausal women, are more susceptible to colorectal diseases. However, the existence of menopause in some women cannot explain the different CRC risks for males and females [56–59]. Discrepancies among these studies

### Table 1

| Study                                | RR (95% CI)     | Weight(%) |
|--------------------------------------|-----------------|-----------|
| Heike Ursula 2012                    | 1.14 (0.88, 1.49) | 7.92      |
| Misciagna G 2004                     | 2.69 (0.71, 10.19) | 1.41      |
| Thomas R 2012                        | 1.30 (0.94, 1.81)  | 7.19      |
| Takasei Nishii 2001                  | 2.20 (1.10, 4.00)  | 4.08      |
| Jill E. Elwing 2006                  | 1.75 (1.05, 2.87)  | 5.29      |
| Chiranjeev Dash 2014                 | 0.83 (0.64, 1.09)  | 7.89      |
| Wang, J. H 2013                      | 1.15 (1.03, 1.91)  | 7.40      |
| Joseph Carl Anderson 2011            | 4.57 (2.36, 8.82)  | 3.98      |
| Sunghwan Suh 2011                    | 2.85 (1.83, 4.44)  | 5.90      |
| Rodney Eddi 2012                     | 1.45 (1.05, 2.01)  | 7.22      |
| Tomomi Marugame 2002                 | 1.53 (0.96, 2.46)  | 5.61      |
| Bouwens, M 2011                      | 1.20 (0.70, 2.30)  | 4.48      |
| Suminori Kono 1998                   | 1.40 (1.00, 2.00)  | 6.97      |
| Mehulkumar K. Kanadiya 2013          | 1.35 (1.08, 1.70)  | 8.33      |
| Hongha T Vu 2014                     | 3.10 (1.50, 6.40)  | 3.54      |
| Kazushige Kawai 2012                 | 1.56 (1.37, 3.66)  | 5.41      |
| de Kort S 2013                       | 1.39 (1.02, 1.90)  | 7.38      |
| Overall (I–squared = 67.9%, p = 0.000)| 1.52 (1.28, 1.80)  | 100.00    |

**Fig. 2** Forest plot of relative risk estimates of diabetes on risk of colorectal adenoma

---

DM diabetes mellitus, T2DM type 2 diabetes mellitus, CRA colorectal adenoma, NSAID nonsteroidal anti-inflammatory drugs, TG serum cholesterol and triglycerides, BMI body mass index, HDL-C high density lipoprotein cholesterol, LDL-C low density lipoprotein cholesterol, hsCRP high-sensitivity C-reactive protein, T2DM non-insulin dependent diabetes mellitus, TC total cholesterol, HDL high-density lipoprotein, NA not available

a conference abstract
Table 2 Subgroup analyses for the effect of diabetes on risk of colorectal adenoma

| Subgroup                  | Sample size | RR (95% CI)     | P value | Heterogeneity | P value |
|---------------------------|-------------|-----------------|---------|---------------|---------|
| Sub-site of adenoma       |             |                 |         |               |         |
| Advanced adenoma          | 2145        | 1.41 (1.06–1.87)| 0.018   | 1.50          | 0.0%    | 0.473   |
| Proximal adenoma          | 9343        | 1.28 (0.88–1.87)| 0.199   | 10.89         | 72.4%   | 0.012   |
| Distal adenoma            | 9343        | 1.11 (0.89–1.38)| 0.353   | 3.63          | 17.3%   | 0.305   |
| Colon adenoma             | 11201       | 1.06 (0.73–1.53)| 0.758   | 10.72         | 72.0%   | 0.013   |
| Multiple adenoma          | 6840        | 1.95 (0.97–3.94)| 0.061   | 6.73          | 85.2%   | 0.009   |
| Type of diabetes          |             |                 |         |               |         |
| Known T2DM                | 20326       | 1.56 (1.16–2.08)| 0.003   | 43.88         | 81.8%   | 0.000   |
| Newly diagnosed T2DM      | 1604        | 1.51 (1.16–1.97)| 0.002   | 0.00          | 0.0%    | 0.946   |
| Gender                    |             |                 |         |               |         |
| Male                      | 7839        | 1.33 (0.99–1.80)| 0.059   | 4.74          | 36.7%   | 0.192   |
| Female                    | 5135        | 1.29 (0.76–2.17)| 0.348   | 10.33         | 80.6%   | 0.006   |
| Area                      |             |                 |         |               |         |
| Europe                    | 13527       | 1.27 (1.02–1.57)| 0.032   | 2.18          | 0.0%    | 0.336   |
| USA                       | 5767        | 1.69 (1.14–2.51)| 0.009   | 32.18         | 84.5%   | 0.000   |
| Asia                      | 11684       | 1.57 (1.21–2.05)| 0.001   | 13.23         | 62.2%   | 0.021   |
| Study type                |             |                 |         |               |         |
| Prospective study         | 13871       | 1.27 (0.77–2.10)| 0.357   | 11.93         | 83.2%   | 0.003   |
| Retrospective study       | 17405       | 1.57 (1.30–1.89)| 0.000   | 25.40         | 60.6%   | 0.005   |
| Population based study    | 6122        | 1.46 (1.21–1.89)| 0.005   | 2.06          | 3%      | 0.357   |
| Studies with high quality | 26046       | 1.64 (1.26–2.14)| 0.000   | 45.78         | 78.2%   | 0.000   |

T2DM: type 2 diabetes mellitus

Fig. 3 Result of sensitivity analyses by omitting one study in each turn
and ours and the insignificant results by adenoma sub-site might be attributed to the limited sample sizes and insufficient statistical power. For the prospective studies, varied different follow-up procedures and mix of ethnicities different study populations might be the sources of heterogeneity.

Our analysis revealed that with T2DM have about a 5% higher risk of CRA than newly diagnosed diabetes patients, revealing the duration of T2DM as a risk factor for CRA. A possible explanation is that known T2DM patients’ bowels are exposed to hyperinsulinemia or a hyperglycemic environment for a longer time, and such hormonal or metabolic abnormalities (according to former study [60]) could affect tumour growth. However, some studies reported that metformin use was a protective factor of CRA [33] and cancer [61]. If this is true, diagnosed diabetes patients should have a lower risk of adenomas than new patients, which is counter to our results. On the other hand, the severity of T2DM, which was not confirmed in the included studies, may affect colorectal disease risk and contribute to the mixed results.

In sum, there might be a dose–response relationship between insulin and CRA, and further studies should include this as an important potential confounding factor.

Several limitations of in this meta-analysis that should be taken into consideration. First, results for several subgroups, such as gender and adenoma sub-site subgroup, were based on a limited number of studies. Therefore, we cannot rule out the possibility that insufficient statistical power is present. Second, in the present analysis, some small studies with inverse associations between T2DM and risk of CRA risk seemed to be suppressed. The presence of possible publication bias could have led to an overestimation of the effect of T2DM on CRA risk. However, the adjusted result was comparable after trim and fill method corrections. Third, we could not account for all of the confounding factors in the meta-analysis, though most confounders were adjusted in the original RRs. Many factors might induce the adenomas, such as age, ethnicity, inactivity, regular aspirin use, obesity, and family history of CRA, and menopausal status. We could not control for these covariates because of lack of relevant data. Relevant studies with additional data on these other factors may be found by searching by searching beyond the sources used for this study. Furthermore, we could not determine whether using insulin as a therapy for T2DM is an important factor because CRA risk might be altered by hyperinsulinemia, thought to be an important promoter of carcinogenesis [62, 63]. At the same time, metformin may have a direct anti-proliferative effect [64]. Finally, most of the existing studies did not discuss the influences of T2DM severity level on CRA risk. Thus, more cohort studies about these topics should be conducted.

Conclusions

In conclusion, the results of our meta-analysis indicated that patients with T2DM have higher risks for the development of CRA, which is an important inducement for colorectal cancer. Our study has important implications for clinical and public health. Because T2DM and CRA are prevalent in the developed and developing countries [65], medical workers should increase the rate of CRA screening for T2DM patients so that they can benefit from behavioural interventions that can help prevent CRA [38]. Large prospective studies that investigate the interactions among environmental and behavioral factors, medications, and functional polymorphisms are also needed to further clarify the etiology of CRA.
Additional files

Additional file 1: The detail searching process. (DOCX 14 kb)
Additional file 2: The MOOSE list of this meta-analysis. (DOCX 19 kb)

Funding

This work was supported by National Natural Science Foundation (81001287), Natural Science Foundation of Shanghai (15ZR1412300), Leading Talents of Science in Shanghai 2010 (022), and the Fourth Round of Three-year Action Plan on Public Health Discipline and Talent Program of Shanghai: Evidence-based Public Health and Health Economics in Shanghai (15GWZX0901).

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article and its additional files.

Authors’ contributions

FY, ZJ and JH discussed and developed the question for this review. FY and YG carried out the searches, FY, YG, HW and JF assessed the eligibility of the studies for inclusion, extracted data and carried out all analysis. All authors were involved in interpreted and discussed results. FY wrote the first draft of this paper and it was reviewed by JH. FY and YG revised the paper and the English was improved by JF and JH. QC and YL completed the figures and tables of the analysis. All authors agreed on the final draft of this study. JH is the guarantor.

Competing interests

The authors declare that they have no competing interests.

Author details

1Medical Service Research Division, Navy Medical Research Institute, Shanghai, China. 2Department of Health Statistics, Second Military Medical University, No. 800 Xiangyin Road, Shanghai 200433, China. 3Department of Colorectal Surgery, Changhai Hospital, Shanghai, China. 4College of Art & Science, University of San Francisco, San Francisco, USA.

Received: 1 November 2014 Accepted: 5 August 2016

References

1. Tripathi BK, Srivastava AK. Diabetes mellitus: complications and therapeutics. Med Sci Monit. 2006;12(7):Ra130–47.
2. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nat Rev Endocrinol. 2012; 8(4):229–36.
3. Wu Y, Ding Y, Tanaka Y, Zhang W. Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. Int J Med Sci. 2014;11(1):1185–200.
4. Adenoma. http://en.wikipedia.org/wiki/Adenoma. Accessed 10 Oct 2014.
5. Ben Q, Wang L, Liu J, Qian A, Wang Q, Yuan Y. Alcohol drinking and the risk of colorectal adenoma: a dose–response meta-analysis. Eur J Cancer Prev. 2015;24(4):286–95.
6. Bottet E, Iodice S, Raimondi S, Maisonneuve P, Lowenfels AB. Cigarette smoking and adenomatous polyps: a meta-analysis. Gastroenterology. 2008; 134(2):388–95.
7. Ben Q, An W, Jiayang Z, Zhan X, Du Y, Cai QC, Gao J, Li Z. Body mass index increases risk for colorectal adenomas based on meta-analysis. Gastroenterology. 2012;142(4):762–72.
8. Wolin KY, Yan Y, Colditz GA. Physical activity and risk of colon adenoma: a meta-analysis. Br J Cancer. 2011;104(5):882–5.
9. Keum N, Lee DH, Greenwood DC, Zhang X, Giovannucci EL. Calcium intake and colorectal adenoma risk dose–response meta-analysis of prospective observational studies. Int J Cancer. 2015;136(7):1680–7.
10. Auburger G, Gispert S, Lahut S, Omur D, Dannath E, Heck M, Basak N. 12q24 locus association with type 1 diabetes. H2B3 or ATXN2? World J Diabetes. 2014;5(3):316–27.
11. Yin S, Bai H, Jing D. Insulin therapy and colorectal cancer risk among patients with type 2 diabetes mellitus patients: a systemic review and meta-analysis. Diagn Pathol. 2014;9,911.
12. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst. 2005;97(22):1679–87.
13. Dash C, Palmer JR, Boggs DA, Rosenberg L, Adams-Campbell LL. Type 2 diabetes and the risk of colorectal adenomas: Black Women's Health Study. Am J Epidemiol. 2014;179(1):112–9.
14. Kramer HIU, Muller H, Stegmaier C, Rothenbacher D, Raum E, Brenner H. Type 2 diabetes mellitus and gender-specific risk for colorectal neoplasia. Eur J Epidemiol. 2012;27(5):341–7.
15. Marugame T, Lee K, Eguchi H, Oda T, Shinichi K, Kono S. Relation of impaired glucose tolerance and diabetes mellitus to colorectal adenomas in Japan. Cancer Causes Control. 2002;13(10):917–21.
16. Mischagnia G, De Michele G, Gueira V, Cisternino AM, Di Leo A, Freudenheim JL. Serum fructosamine and colorectal adenomas. Eur J Epidemiol. 2004;19(5):425–32.
17. Chung YW, Han DS, Park YK, Son BK, Paik CH, Lee HL, Jeon YC, Sohn JH. Association of obesity, serum glucose and lipids with the risk of advanced colorectal adenoma and cancer: a case–control study in Korea. Dig Liver Dis. 2006;38(9):668–72.
18. Eddi R, Kari A, Shah A, DeBari VA, DePasquale JR. Association of type 2 diabetes and colon adenomas. J Gastrointest Cancer. 2012;43(1):87–92.
19. Kanaditka MK, Goehl TD, Sanaka MR, Thota PN, Shubbrook JR. Type 2 diabetes mellitus and use of metformin with risk of colorectal adenoma in an American population receiving colonoscopy. J Diabetes Complications. 2013;27(7):463–6.
20. Yu HT, Ufere N, Yan Y, Wang JS, Early DS, Elwing JE. Diabetes mellitus increases risk for colorectal adenomas in younger patients. World J Gastroenterol. 2014;20(22):6946–52.
21. OECD WGS. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa, Canada: Department of Epidemiology and Community Medicine, University of Ottawa. http://www. ohri.ca/programs/clinical_epidemiology/needgen.pdf
22. Stroup DF, Berlin JA, Morton SC, Olkin I, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008–12.
23. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177–88.
24. Higgins JPT GSe, Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org/
25. Greenland S. Quantitative methods in the review of epidemiologic literature. Epidemiol Rev. 1987;9:1–30.
26. Zhang J, Yu KF. What’s the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA. 1998;280(19):1690–1.
27. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539–58.
28. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clin Res ed). 1997;315(7109):629–34.
29. Egger CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088–101.
30. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000;56(2):455–63.
31. Acedo VA, Diaz Y, Perez CM, Carau M, Baron J, Cruz-Correa M. Diabetes mellitus and colorectal neoplasia. J Cancer Ther. 2012;3(6a):859–63.
32. Flood A, Mai V, Pfeiffer R, Kahle L, Remaley AT, Lanza E, Schatzkin A. Elevated serum concentrations of insulin and glucose increase risk of recurrent colorectal adenomas. Gastroenterology. 2007;133(5):1423–9.
33. Marks AR, Petritofa RA, Jensen CD, Zebrowski A, Corley DA, Doubeni CA. Metformin use and risk of colorectal adenoma after polypectomy in patients with type 2 diabetes mellitus. Cancer Epidemiol Biomarkers Prev. 2015;24(11):1692–8.
34. Yong WC, Dong SH, Park KH, Chang SE, Yoo KS, Park CK. Insulin therapy and colorectal adenoma risk among patients with Type 2 diabetes mellitus: a case–control study in Korea. Dis Colon Rectum. 2008;51(5):593–7.
35. Anderson JC, Rangasamy P, Rustagi T, Myers M, Sanders M, Vaziri H, Wu G, Birk JW, Protiva P. Risk factors for sessile serrated adenomas. J Clin Gastroenterol. 2011;45(8):694–9.
36. Bouwens M, Rondagh E, Weijenberg M, Winkens B, Maschele A, Sandeuleau S. Risk factors for the combined adenoma-serated phenotype: a population-based study. Gastroenterology. 2011;140(5):S346.
37. De Kort S, Bouwens M, Weijenberg M, Van Den Brandt PA, Redli R, Masleev A, Sanduleanu S. Increased prevalence of proximal and multiple adenomas in patients with diabetes mellitus. Gastroenterology. 2013;144(5):S382.

38. Elwing JE, Gao F, Davidson NO, Early DS. Type 2 diabetes mellitus: the impact on colorectal adenoma risk in women. Am J Gastroenterol. 2006;101(8):1866–71.

39. Kawai K, Sunami E, Tsuno NH, Kitayama J, Watanabe T. Polyp surveillance after surgery for colorectal cancer. Int J Colorectal Dis. 2012;27(8):1087–93.

40. Kono S, Honjo S, Todoroki I, Nishiwaki M, Hamada H, Nishikawa H, Koga H, Ogawa S, Nakagawa K. Glucose intolerance and adenomas of the sigmoid colon in Japanese men. Cancer Causes Control. 1998;9(4):441–6.

41. Nishii T, Kono S, Abe H, Eguchi H, Shimazaki K, Hatano B, Hamada H. Glucose intolerance, plasma insulin levels, and colon adenomas in Japanese men. Jpn J Cancer Res. 2001;92(8):836–40.

42. Suh S, Kang M, Kim MY, Chung HS, Kim SK, Hur KY, Kim JH, Lee MS, Lee MK, Kim KW. Korean type 2 diabetes patients have multiple adenomatous polyps compared to non-diabetic controls. J Korean Med Sci. 2011;26(9):1196–200.

43. Thomas RA, Rao DS, Oni OA, Bansal A, Sharma P, Pandya PK, Rastogi A. Risk factors for advanced adenomas in veterans undergoing screening colonoscopy. Gastroenterology. 2012;142(5):S775–6.

44. Wang JH, Gu F, Lv YM. Retrospective case–control study on risk factors of colorectal adenoma. J Gastroenterol Hepatol. 2013;28:S58.

45. Ezzat VA, Duncan ER, Wheatcroft SB, Kearney MT. The role of IGF-I and its binding proteins in the development of type 2 diabetes and cardiovascular disease. Diabetes Obes Metab. 2008;10(3):198–211.

46. Onitilo AA, Berg RL, Engel JM, Glurich I, Stankowski RV, Williams G, Doi SA. Increased risk of colon cancer in men in the pre-diabetes phase. PLoS One. 2013;8(8), e70426.

47. Rafter JJ, Eng WW, Furrer R, Medline A, Bruce WR. Effects of calcium and pH on the mucosal damage produced by deoxycholic acid in the rat colon. Gut. 1986;27(11):1320–9.

48. Will JC, Galuzka DA, Vinicor F, Calle EE. Colorectal cancer, another complication of diabetes mellitus? Am J Epidemiol. 1998;147(9):816–25.

49. Yang R, Arendt R, Chan L. Gastrointestinal tract complications of diabetes mellitus. Pathophysiology and management. Arch Intern Med. 1994;144(6):1251–6.

50. Giovannucci E. Insulin and colon cancer. Cancer Causes Control. 1995;6(2):164–79.

51. Amutha R, Mimalini K. Food intake and colorectal adenomas: a case–control study in Malaysia. Asian Pac J Cancer Prev. 2009;10(5):925–32.

52. Steele RJC, Anderson AS, Macleod M, Craigie AM, Caswell S, Belch J, Treweek S. Colorectal adenomas and diabetes: implications for disease prevention. Colorectal Dis. 2015;17:589–94.

53. Campbell PT, Deka A, Jacobs EJ, Newton CC, Hildebrand JS, McCullough ML, Limburg PJ, Gapstur SM. Prospective study reveals associations between colorectal cancer and type 2 diabetes mellitus or insulin use in men. Gastroenterology. 2010;138(4):1138–46.

54. Nilsen TI, Vatten LJ. Prospective study of colorectal cancer risk and physical activity, diabetes, glucose and BMI: exploring the hyperinsulinaemia hypothesis. Br J Cancer. 2001;84(3):417–20.

55. Sandhu MS, Luben R, Khaw KT. Self reported non-insulin dependent diabetes, family history, and risk of prevalent colorectal cancer: population based, cross sectional study. J Epidemiol Community Health. 2001;55(11):804–5.

56. Kang HW, Kim D, Kim HJ, Kim CH, Kim YS, Park MJ, Kim JS, Cho SH, Sung MW, Jung HC, et al. Visceral obesity and insulin resistance as risk factors for colorectal adenoma: a cross-sectional, case–control study. Am J Gastroenterol. 2010;105(1):178–87.

57. Smullovicz ED, Stuenkel CA, Seely EW. Influence of menopause on diabetes and diabetes risk, Nat Rev Endocrinol. 2009;5(10):553–8.

58. Yamaji T, Iwasaki M, Satazuki S, Tsugane S. Interaction between adiponectin and leptin influences the risk of colorectal adenoma. Cancer Res. 2010;70(13):5430–7.

59. Yamamoto S, Nakagawa T, Matsushita Y, Kusano S, Hayashi T, Irokawa M, Aoki T, Korogi Y, Mizoue T. Visceral fat area and markers of insulin resistance in relation to colorectal neoplasia. Diabetes Care. 2010;33(1):184–9.

60. Mao Y, Tao M, Xia X, Xu H, Chen K, Tang H, Li D. Effect of diabetes mellitus on survival in patients with pancreatic cancer: a systematic review and meta-analysis. Sci Rep. 2015;5:17102.