CARING (CAncer Risk and INsulin analoGues): The Association of Diabetes Mellitus and Cancer Risk with Focus on Possible Determinants - A Systematic Review and a Meta-Analysis

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Abstract: Background: Patients suffering from diabetes mellitus (DM) may experience an increased risk of cancer; however, it is not certain whether this effect is due to diabetes per se.

Objective: To examine the association between DM and cancers by a systematic review and meta-analysis according to the PRISMA guidelines.

Data Sources: The systematic literature search includes Medline at PubMed, Embase, Cinahl, Bibliotek.dk, Cochrane library, Web of Science and SveMed+ with the search terms: “Diabetes mellitus”, “Neoplasms”, and “Risk of cancer”.

Study Eligibility Criteria: The included studies compared the risk of cancer in diabetic patients versus non-diabetic patients. All types of observational study designs were included.

Results: Diabetes patients were at a substantially increased risk of liver (RR=2.1), and pancreas (RR=2.2) cancer. Modestly elevated significant risks were also found for ovary (RR=1.2), breast (RR=1.1), cervix (RR=1.3), endometrial (RR=1.4), several digestive tract (RR=1.1-1.5), kidney (RR=1.4), and bladder cancer (RR=1.1). The findings were similar for men and women, and unrelated to study design. Meta-regression analyses showed limited effect modification of body mass index, and possible effect modification of age, gender, with some influence of study characteristics (population source, cancer- and diabetes ascertainment).

Limitations: Publication bias seemed to be present. Only published data were used in the analyses.

Conclusions: The systematic review and meta-analysis confirm the previous results of increased cancer risk in diabetes and extend this to additional cancer sites. Physicians in contact with patients with diabetes should be aware that diabetes patients are at an increased risk of cancer.

Keywords: Cancer risk, diabetes mellitus, meta-analysis, neoplasm, systematic review.

INTRODUCTION

Rationale

The CAncer Risk and INsulin analoGues (CARING) project aims to assess the possible carcinogenic effect of insulin. As part of this project evaluation of the background risk of developing cancer in diabetes patients was performed in this systematic review and meta-analysis.

Diabetes Mellitus is associated with increased morbidity and mortality. Diabetes is the 8th leading cause of mortality in high-income countries; whereas colorectal and breast cancer are the 7th and 10th leading causes, respectively [1]. Associations between diabetes and cancer have already been established for specific cancer sites in several meta-analyses.
Associations between diabetes and cancer have been described in several meta-analyses including only studies of an observational design (case control and/or cohort). All meta-analyses reporting a significant increased risk among diabetes patients for pancreatic cancer between 1.8 to 2.1 [2-4] and liver cancer between 1.8 to 3.6 [5-8, 24]. Subgroup analyses stratified by gender or statistical adjustment for Body Mass Index (BMI), smoking and alcohol did not influence the risk for pancreatic cancer [2]. However, results were conflicting on whether a duration of diabetes of 10 years was associated with an increased risk of pancreatic cancer [2, 3], while duration of diabetes appeared not to influence risk of liver cancer [5]. Furthermore, diabetes treatment modulated the risk of liver cancer with greater risk estimates for insulin or sulfonylurea users than for metformin users [5]. Several observational studies have examined the relationship between diabetes and gastrointestinal cancers. Results were conflicting in the meta-analyses on gastric cancer [15,16], while an increased risk of esophageal cancer was reported [13]. In addition, diabetes has been associated with an increased risk of colorectal cancer [17-19, 21-23] after adjustment for BMI and smoking [20]. Both endometrial cancer [7] and breast cancer [25-28] were reported to be increased in diabetes, while prostate cancer was found to be decreased in men with diabetes by 10 % [9,10]. The association with prostate cancer was independent of BMI [10]. Diabetes was also associated with increased risk of kidney cancer [11] and bladder cancer [12]; however, this last association was not significant when using estimates adjusted for BMI due to wider confidence intervals. Last of all an increased risk among diabetes patients for non-Hodgkin lymphoma and leukemia but not multiple myeloma has also been reported in a meta-analysis [14].

It is uncertain whether the relationship between diabetes and cancer is direct (e.g., due to hyperglycemia), whether diabetes is a marker of underlying biologic factors that alter cancer risk (e.g., insulin resistance and hyperinsulinemia), or whether the association between diabetes and cancer is indirect and due to common risk factors such as obesity. Duration of diabetes has been found to be of importance in the development of cancer among insulin using type 2 diabetes (T2D) patients [29]; however, whether cancer risk was influenced by the duration of diabetes is a critical and complex issue and may be complicated further by the multidrug therapy often necessary for diabetes treatment. The incidence of cancer increases with age, and as age increases with duration of diabetes, this may confound the association between diabetes and cancer. However, an association between diabetes and cancer was present for several cancer sites. Few studies take into account duration of diabetes, medication use or age of the participants. Furthermore, a meta-analysis reported an association between obesity and several cancer types including colorectal, kidney, breast and endometrial cancer, and also an independent association between obesity and T2D [30]. Therefore, it is important both to take obesity into account and to distinguish between type 1 diabetes (T1D) and T2D, which have not been done in previous reports. Except from Ge et al. [16] (using three databases), none of the meta-analyses described in the introduction have used more than two databases in their search (Medline at PubMed and Embase/ Medline at PubMed and Cochrane database of systematic reviews), and many only used Medline at PubMed leaving them with a possible publication bias.

Objectives

In an attempt to evaluate the risk of cancer in diabetes patients and taking possible determinants into account this thorough systematic review and meta-analysis was conducted. The primary objective was to study the effects of diabetes per sé, by collating observational studies that compared diabetes patients to non-diabetes. A secondary objective was to examine the effects that type of diabetes, body weight, metabolic control, diet as well as study design had on the risk of cancer.

METHODS

Protocol and Registration

The systematic review and meta-analysis was developed according to the Cochrane Collaboration (http://www.cochrane.org/training/cochrane-handbook), and PRISMA guidelines [31] (http://www.prisma-statement.org/) and was registered on PROSPERO (http://www.crd.york.ac.uk/prospero/) with the registration number: CRD42012002310.

Eligibility Criteria

The eligibility criteria for the studies were those studies that evaluated the association between diabetes and cancer (incidence, odds or prevalence) as the outcomes. Studies evaluating solely cancer mortality were excluded. The studies needed to compare diabetes patients with a non-diabetes reference group. All types of observational study designs (e.g. case control, cohort and cross-sectional studies) were included. Studies assessing the effect of a specific intervention compared to no intervention were excluded. Studies only published as conference abstracts were excluded. Studies were not excluded due to language or publication year.

Information Sources

The systematic literature search included 7 databases: Medline at PubMed, Embase, Cinahl, Bibliotek.dk, Cochrane library, Web of Science, and SveMed+. The first search was performed 11th of January 2012, and updated with the last search on the 9th November 2012. Additional studies were added after assessment of the reference list in meta-analyses and reviews found in the search. Furthermore, studies were retrieved from the literature search of a systematic review of insulin use and cancer risk also performed by the CARING project group (PROSPERO registration number: CRD42012002428).

Search

The search terms included: “Diabetes mellitus”, “diabetes”, “Neoplasms”, “cancer”, “Prospective study”, “statistics”, “cancer statistics”, and “Risk of cancer”. Other search terms
such as statistics and cancer statistics were also used but gave to few results and were not used as the final result. The search was performed using the thesaurus if available in the respective databases. Limitations were used to refine the search if available in the databases (“biochemistry”, “cancer”, “physiology and endocrinology”, “cochrane review”, “controlled clinical trial”, “systematic review”, “clinical trial”, “randomized controlled trial”, “review”, “meta-analysis”), qualifiers (“analysis”, “blood”, “classification”, “epidemiology”, “statistics and numerical data”), categories (“endocrinology metabolism”, “oncology”) and research areas (“endocrinology metabolism”, “oncology”, “biochemistry molecular biology”). Search terms, limitations, qualifiers, categories and research areas used differently by database dependent on the functions available at the database. The search from Embase is listed below. The search was performed using the thesaurus if available in the respective databases. Limitations were used to refine the search if available in the databases (“biochemistry”, “cancer”, “physiology and endocrinology”, “cochrane review”, “controlled clinical trial”, “systematic review”, “clinical trial”, “randomized controlled trial”, “review”, “meta-analysis”), qualifiers (“analysis”, “blood”, “classification”, “epidemiology”, “statistics and numerical data”), categories (“endocrinology metabolism”, “oncology”) and research areas (“endocrinology metabolism”, “oncology”, “biochemistry molecular biology”). Search terms, limitations, qualifiers, categories and research areas used differently by database dependent on the functions available at the database. The search from Embase is listed below. The search was

Search from the 09th of November 2012

| No. | No. Query                                                                 | Results          |
|-----|---------------------------------------------------------------------------|------------------|
| #1  | ‘Diabetes Mellitus’/exp                                                   | 526,730          |
| #2  | ‘Neoplasm’/exp                                                           | 3,165,370        |
| #3  | #1 AND #2                                                                | 34,949           |
| #4  | #1 AND #2 (([biochemistry]/lim OR [cancer]/lim OR [physiology and endocrinology]/lim) | 15,064           |
| #5  | ‘Cancer statistics’/exp                                                  | 2,034            |
| #6  | #4 AND #5                                                                | 7                |
| #7  | ‘Cancer statistics’/exp                                                  | 272,379          |
| #8  | #4 AND #5                                                                | 36               |
| #9  | #1 AND #2([biochemistry]/lim OR [cancer]/lim OR [physiology and endocrinology]/lim) AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [systematic review]/lim) | 634              |

Study Selection and Data Collection Process

Studies were assessed for eligibility using the criteria above. Reviewer one (JSL) performed the literature search in collaboration with a research librarian. Reviewer one and reviewer two (ØK) added additional studies from the insulin and cancer literature search, and studies were added from other meta-analyses and reviews by reviewer one. Reviewer one and reviewer two examined all studies by screening title and abstract. Studies passing this round were retrieved in full text and independently assessed for eligibility by reviewer one and two. Records for which both reviewers agreed on were included in the systematic review and meta-analysis. Disagreement were settled by discussion or if necessary by reviewer three (PV). No supplementary data were collected from the authors of the studies.

Data Items

From each study information was extracted on cancer risk (prevalence ratio, risk ratio, odds ratio, incidence ratio, standardized incidence ratio, hazard ratio), cancer site, patient characteristics including type of diabetes mellitus (type 1, type 2 or unspecified), age (mean/median/not reported), duration of diabetes (mean/median/not reported), HbA1c level (mean/median/not reported), BMI (mean/median/not reported), follow up years (mean/median/not reported), and on study design (case control/cohort/cross-sectional), population (population based/hospital based), confounders used to adjust for, and specific comorbidities. Data was extracted by reviewer one and validated by reviewer two. Any disagreement was solved by discussion. Studies that used the same study population as other studies were excluded by reviewer one and reviewer two to secure that no duplicate estimates were used in the meta-analysis.

Risk of Bias in Individual Studies

The risk of bias in individual studies was assessed using the Newcastle Ottawa Scale (NOS) [32]. The user-defined items required in the NOS score were defined as follows: age was the most important adjustment factor; the exposed patients in cohorts should be representative of the average “diabetic population”, minimum follow up time as 5 years, and loss to follow-up less than 10%. A scale modified for cross-sectional studies were produced for the quality score of these studies (the NOS are available in the Supplementary Material 1).

Reviewer one and reviewer two scored the studies based on the NOS. If the reviewers scored differently it was solved by discussion and if this was not possible reviewer three decided the score.

Summary Measures and Synthesis of Results

Prevalence ratios, risk ratios (RR), odds ratios, incidence ratios, standardized incidence ratios (in general standardized by age and sex using a reference population from same cancer registry, same district or the entire population of a country) and hazard ratios including 95% CI comparing the risk of cancer in diabetes patients compared to a non-diabetes group were the summary measures. A random effects model, Der Simonian and Laird, was used in all analyses [33]. The random effects model considers both in within study variability and between study variability.

Subgroup analyses were performed for cancer sites, study design and gender. Meta-regression analyses were performed to assess whether any of the extracted characteristics were determinants of cancer risk. For the meta-regression the

Risk of Publication Bias

Risk of publication bias across studies was assessed using Egger’s regression analysis [34] in STATA 8.

Additional Analyses

Subgroup analyses were performed for cancer sites, study design and gender. Meta-regression analyses were performed to assess whether any of the extracted characteristics were determinants of cancer risk. For the meta-regression the
covariates were coded as follows: gender (0 = female, 1 = male), diabetes type (0 = unspecified, 1 = T1D, 2 = T2D), study design (0 = case control, 1 = cohort, 2 = cross-sectional), source (1 = population, 2 = hospital, 3 = other), adjustment factor (0 = no age adjustment, 1 = age + other, 2 = BMI / obesity / waist hip ratio + other, 3 = Age, BMI + other, 4 = Age, Sex, BMI, Smoking + other, 5 = Age, BMI and duration of diabetes), diabetes ascertainment (1 = registry, 2 = questionnaire / interview, 3 = biochemical analysis or criteria, 4 = other), cancer ascertainment (1 = registry with confirmation, 2 = questionnaire / interview, 3 = pathology / histology / imaging / criteria, 4 = other) and NOS (0-9). Other covers mixed ascertainment and other types of ascertainment. Age (years) was calculated as the difference of the age between cases and controls in case control studies and between diabetes cohort and non-diabetes cohort in cohort studies. The same applied for BMI (kg/m²). Sub analysis for age and BMI were performed by study design. For age, BMI and follow up years only mean or median estimates were used in the meta-regression. Age BMI and follow up years where treated as numerical outcomes in the meta-regression, whereas other variables were treated as categorical outcomes. Only analyses with the use of three or more populations were included in the meta-regression. HbA1c and duration of diabetes were extracted from the records, but too few values (two studies report on mean HbA1c and 4 studies report mean duration of diabetes) were available to perform a meaningful analysis.

RESULTS

Study Selection

The selection process is depicted in Fig. (1). 1,849 records were identified from the database search. An

![PRISMA Flow Diagram](image_url)
additional 172 records were identified from the reference list in meta-analyses and reviews identified in the search, and from the systematic literature search (PROSPERO registration number: CRD42012002428) on insulin and cancer also performed by the CARING group. In total, 2,021 records were identified. The RefWorks (RefWorks, RefWorks-COS, ProQuest RefWorks 2.0, 2010) functions exact duplicates and close duplicates were used to remove duplicates. In total, 1,785 unique records were retrieved. Screening by title and abstract by reviewer one and two excluded 1,534 records, thus 251 records remained. Of these records, 193 records (106 cohort studies, 80 case-control studies, 6 cross-sectional studies and 1 combined case-control and cross-sectional study [35]) were included in the systematic review, while 66 records were excluded after assessing for full-text eligibility (21 were excluded due to duplicate data with other studies, 3 were excluded due to lack of data, 11 were excluded because diabetes was not the exposure, 4 were excluded because they did not compare to a non-diabetes reference, 1 record was excluded due to intervention study design and 16 studies were excluded because the outcome was not incident or prevalent cancer). 190 records were included in the meta-analysis. Two studies were excluded from this analysis due to lack of information on the outcome to an extent that made analysis impossible [36, 37]. One study was the only to report on head and neck cancer [38] and was not included in the meta-analysis.

Study Characteristics and Risk of Bias within Studies

Tables 1-3 present the study characteristics and NOS score of the included studies in the systematic review for cohort and cross-sectional studies and case-control studies, respectively. Additional study information is available in the electronic Supplementary Material 2. The study quality ranged from as low as 3 to the highest score of 9, although most of studies (84%) were of fair quality (NOS 6-9). NOS is part of the meta-regression presented below.

Results of Individual Studies

The results of the individual studies are presented in the electronic Supplementary Material 3. Stott-Miller et al. [38] was the only study specifically addressing head and neck cancer, and they presented an odds ratio of 1.09 (0.95-1.24) for head and neck cancer for diabetes patients compared to a non-diabetes reference. Thus it was not used in the included in the meta-analysis.

Synthesis of Results

Table 4 presents the pooled analysis of the studies and the pooled results are depicted in Fig. (2). All available cancer types were included. Diabetes patients have a significant increased risk of any cancer, biliary and gallbladder cancer, bladder cancer, bone cancer, breast cancer, colon cancer, colorectal cancer, rectal cancer, esophageus cancer, liver cancer, lung cancer, leukemia, lymphoma, non-Hodgkin lymphoma, pancreas cancer, kidney cancer, small intestine cancer, stomach cancer and thyroid cancer. Female diabetes patients were also at increased risk for breast, cervix, endometrial and ovary cancer. However; diabetes patients have a lower risk of prostate cancer and skin cancer than non-diabetic subjects. In these analyses, only bone and thyroid cancer did not display significant heterogeneity by chi square testing. For the remaining cancer types (testes cancer, myeloma, melanoma, lung, larynx, bone cancer and nervous system cancers) no significantly increased risk of any cancer, biliary and colon cancer types were included. Diabetes patients have a significantly increased risk of any cancer, biliary and colon cancer, and they presented an odds ratio of 1.09 (0.95-1.24) for head and neck cancer for diabetes patients compared to a non-diabetes reference. Thus it was not used in the included studies.

Subgroup analyses were performed on study design (cohort/case control) and gender (male/female). Figs. (3-6) illustrates the results of the analyses. Cohort studies found among diabetes patients an increased risk of any, biliary, breast, cervix, colon, colorectal, endometrial, kidney, liver, ovary, pancreas, rectum, small intestine, stomach, and thyroid cancer, as well as leukemia, all lymphomas, and non-Hodgkin lymphoma, while the risks of prostate, and skin cancer were decreased. Case control studies show similar results as cohort studies including an increased risk of larynx cancer; however; the pooled estimates for cervix-, kidney-, leukemia-, non Hodgkin lymphoma-, prostate-, stomach-, and thyroid cancer were without significance. Males with diabetes were at an increased risk of all cancers combined, biliary, colon, colorectal, kidney, liver, pancreas, rectum, small intestine, and thyroid cancer and leukemia, while the risk of prostate cancer was decreased. Females with diabetes were at an increased risk of any, breast, cervix, colon, colorectal, endometrial, kidney, leukemia, liver, ovary, and pancreas cancer.

Risk of Bias Across Studies

Egger’s regression test revealed significant publication bias for any cancer (p=0.048), colorectal cancer (p=0.024), esophageus cancer (p=0.022), larynx cancer (p=0.041), lymphoma (p=0.041) and lung cancer (p=0.015). The graphical depictions of the bias test for these cancer types are available in the electronic Supplementary Material 5. All these publication biases have a positive intercept value indicating higher effect size in smaller studies. None of the other cancer types displayed publication bias.

Meta-Regression

Table 5 presents results from the meta-analysis. These results reflect the effect modification of the variables on the measured cancer risk in the studies. A positive determinant increases the risk ratio for cancer among diabetes patients, whereas a negative determinant decreases the risk ratio for cancer among diabetes patients. The coefficient is the beta coefficient from the regression. Not all variables were available for all of the specific cancer analyses. In the following only specific parts will be highlighted. Male gender was a significant negative determinant of the risk of leukemia in (β = -1.52) and reduces the risk of leukemia among diabetes patients. Age difference may both be a significantly positive, negative and no determinant depending on cancer type. BMI differences was no determinant of breast-, colorectal-, endometrial-, kidney-, liver-, pancreas-, and prostate-cancer risk, however it was a negative determinant (β = -0.08) for lung cancer. Diabetes type was only a significantly negative determinant in colon
Table 1. Study Table of Included Cohort Studies Divided by Diabetes Type

| Authors             | Data Source          | Cancer Site | Follow Up Years | Source | DM (n) | Age | BMI | Non-DM (n) | Age | BMI | Co Morbidity | NOS-Score (0-9) |
|---------------------|----------------------|-------------|----------------|--------|--------|-----|-----|------------|-----|-----|--------------|-----------------|
| Zendehdel 2003 Sweden [39] | Swedish inpatient registry | Several | 14.4 | Population | 29,187 | 17.1 | - | External standard population | - | - | - | 8 |
| Type 1 diabetes     |                      |             |                |        |        |     |     |            |     |     |              |                 |
| Kao 2012 Taiwan [40] | NHIRD               | All         | 2001-2009      | Population | 22,910 | 56.5 | - | 91,636 | 56.5 | - | - | 8 |
| Bowker 2011 Canada [41] | BCLHD (1996-2006)   | Breast      | 4.4            | Population | 84,506 | 61.8 | - | 84,506 | 61.8 | - | - | 6 |
| Michels 2003 US [42] | Nurses health study (1976-1998) | Breast | 22 (total) | Nurses | 6,120 | 59.1 | 30.7 | 110,368 | 52.1 | 25.0 | - | 6 |
| Campbell 2010 [43]  | Cancer prevention study II Nutrition cohort | Colorectal | 1992-2007 | Population | 11,335 | 63 | - | 143,640 | 64 | - | - | 7 |
| Ren 2009 China [44] | Nan-Hu district      | Colorectal  | -              | Population | 7,938 | 61.1 | 23.6 | External standard population | - | - | - | 6 |
| Lai 2006 Taiwan [45] | KCIS (1999-2003)     | Liver       | 2.78           | Population | 5,732 | - | - | 49,184 | - | - | - | 5 |
| Wang 2009 Taiwan [46] | A-Lein Township      | Liver       | 8 (total) Viral hepatitis screened | 352 | - | - | 5,377 | 53.9 (total) | - | - | - | 9 |
| Joh 2011 US [47]    | Nurses Health study  | Kidney      | 1976-2008      | Nurses | 6,424 | 57.0 | 30.5 | 107,714 | 56.8 | 25.5 | - | 6 |
| Authors            | Data Source                              | Cancer Site | Follow Up Years | Source          | DM (n) | Age | BMI | Non-DM (n) | Age | BMI | Co Morbidity | NOS-Score (0-9) |
|--------------------|------------------------------------------|-------------|----------------|----------------|--------|-----|-----|------------|-----|-----|--------------|-----------------|
| Hemminiki 2010 Sweden [48] | Nationwide hospital discharge 1964-2007 | Several    | 13 median      | Population     | 125,126 | -   | -   | External standard population | -   | -   | -            | 9               |
| Hense 2011 Germany [49]     | SHI 2003-2008                            | Several    | 3.5 median     | Disease management programme | 26,742 | 64  | 29.7 | 31.0       | External standard population | -   | -   | -            | 6               |
| Lee 2012 Taiwan [50]        | NHI programme (1999-2009)                | Several    | 11 (total)     | Population     | 104,343 | -   | -   | 985,815 (Total) | -   | -   | -            | 9               |
| Ogunleye 2009 UK [51]       | Tayside                                  | Several    | 3.9            | Population (RISCH primary care) | 9,577 | -   | -   | 19,154     | 62 (total) | -   | -            | 6               |
| Diabetes type unspecified | Fillenbaum 2000 US [52]                  | EPESE       | 6 (total)      | Population     | 4034 total | 73.4 | 5               | -          | -   | -            | 5               |
| Larsson 2008 Sweden [53]    | COSM                                     | Bladder     | 9.3            | Population     | 2,835 | 64.5 | 27.4 | 43,071     | 60.1 | 25.7 | -            | 8               |
| Tripathi 2002 US [54]       | IWHS                                     | Bladder     | 13 (total)     | Population     | 6%   | -   | -   | 37,459 (total) | -   | -   | -            | 7               |
| Bosco 2012 US [55]          | Black women’s health study               | Breast      | 10.5           | Population     | 1,900 | 64.0 | -   | 49,172 (total) | -   | -   | -            | 6               |
| Chlebowski 2012 US [56]     | WHI                                      | Breast      | 11.8           | Postmenopausal Population based sample | 3,401 | 62.6 | -   | 64,618     | 64.0 | -   | -            | 7               |
| De Waard 1974 (36)          | GP Netherlands                           | Breast      | 5.4            | Population     | 7,259 women | 7,259 | -   | -            | 4               |
| Authors          | Data Source               | Cancer Site | Follow Up Years | Source                      | DM (n) | Age | BMI | Non-DM (n) | Age | BMI | Co Morbidity | NOS-Score (0-9) |
|------------------|---------------------------|-------------|----------------|----------------------------|--------|-----|-----|------------|-----|-----|--------------|-----------------|
| Goodman 1997 Japan | LSS Cohort               | Breast      | 8.31           | Population (atomic bomb survivors) | -      | -   | -   | 22,200 (total) | -   | -   |              | 6               |
| Lipscombe 2006 Canada | Ontario 1995-2002         | Breast      | 4.5 median     | Population                  | 73,796 | 66.2| -   | 391,714 | 64.9 | -   |              | 7               |
| Mink 2002 US     | ARIC                      | Breast      | 7.1            | Population                  | -      | -   | -   | 7,894 (total) | -   | -   |              | 8               |
| Reeves 2012 US   | SOF                       | Breast      | 14.4           | Population                  | 607    |     |     | 7,772   |      |     |              | 7               |
| Sellers 1994 US  | IWHS                      | Breast      | 5 (total)      | Population                  | -      | -   | -   | 36,603 (total) | -   | -   |              | 5               |
| Weiderpass 1997 Sweden | Swedish in patient registry | Breast, endometrial cancer | 6.7          | Population                  | 63,988♂ 70,110♀ | 59.2♂ 64.2♀ | - | External standard population | - | -   |              | 6               |
| Lambe 2011 Sweden | AMORIS                    | Breast, endometrial cancer | 11.7         | Population                  | 5,615    | 58.5 | 26.7 | 225,122 | 46.6 | 23.9 |              | 7               |
| Bowers 2006 Finland | Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study | Colorectal   | 14.1 median    | Population                  | 1,226 | -   | -   | 27,757 | -   | -   |              | 7               |
| Flood 2010 UK    | BCDDP                     | Colorectal   | 8.4            | Individuals with breast affection and matched healthy individuals (gives no statement on how these were determined.) | - | 64.3 | 28.0 | 43,078 | 61.8 | 24.5 |              | 6               |
| Authors            | Data Source   | Cancer Site | Follow Up Years | Source                          | DM (n) | Age | BMI | Non-DM (n) | Age | BMI | Co Morbidity | NOS-Score (0-9) |
|--------------------|---------------|-------------|----------------|--------------------------------|--------|-----|-----|------------|-----|-----|--------------|----------------|
| Hartz 2012 US [66] | WHI           | Colorectal  | 8 median       | Postmenopausal Population based sample | 4.5% of total | -   | -   | 150,912 (total) | 63.11 | -   | -            | 7              |
| He 2010 US [67]    | Multietnic cohort | Colorectal  | 1993-2006      | Population                     | $\leq 15,060$ | $\geq 16,271$ | -   | $\leq 74,418$ | $\geq 93,393$ | $\leq 60.2$ | $\geq 59.7$ | -            | 7              |
| Hu 1999 US [68]    | NHS           | Colorectal  | 18 (total)     | Nurses                          | 7,069 | 45  | 28  | 111,003 | 42  | 24  | -            | 5              |
| Khaw 2004 UK [69]  | Norfolk       | Colorectal  | 6              | Population                      | -     | -   | -   | 25,623 (total) | 45-79 | -   | -            | 7              |
| Larsson 2005 [70]  | COSM          | Colorectal  | 6.2            | Population                      | -     | -   | -   | 45,550 men (total) |      |     | 6            | 6              |
| Limburg 2005 US [71] | IWHS         | Colorectal  | 14 (total)     | Population                      | 1,900 | 62.3 | 30.6 | 33,072 | 61.5 | 26.8 | -            | 7              |
| Nilsen 2001, Norway [72] | Nord-trondelag | Colorectal  | 10.8 median    | Population                      | -     | -   | -   | 75,219 (total) | 48.5 | 49.8 | -            | 7              |
| Schoen 1999 US [73] | CHS 1989-1990 | Colorectal  | 6.6            | Population                      | -     | -   | -   | 5,201 | 72.8 (without cancer) |      |     | 6            | 6              |
| Seow 2006 Singapore [74] | Singapore Chinese health study | Colorectal  | 7.1            | Population                      | 5,469 | 60  | 24.1 | 55,851 | 56.0 | 23  | -            | 7              |
| Sturmer 2006 US [75] | The Physicians’ Health Study | Colorectal  | 19 median      | physicians                       | 9%    | -   | -   | 22,701 | 54   | -   | -            | 6              |
| Authors                  | Data Source       | Cancer Site                  | Follow Up Years | DM (n) | Age | BMI | Non-DM (n) | Age | BMI | Co Morbidity                  | NOS-Score (0-9) |
|-------------------------|-------------------|------------------------------|-----------------|--------|-----|-----|------------|-----|-----|-------------------------------|-----------------|
| Will 1998 US [76]       | Cancer prevention study | Colorectal                  | 1959-1972       | 25 states | 15,487 | 57.4 | 25.4 | 850,946 | 52.9 | 25.2 | -                            | 6               |
| Anderson 2001 US [77]   | IWHS              | Endometrial                  | 1986-1997       | Population | 1,325 | 62.6 | 30.5 | 23,150 | 61.8 | 26.8 | -                            | 7               |
| Friberg 2007 Sweden [78]| Uppsala           | Endometrial                  | 7               | Population | 1,628 | 66.5 | 27.5 | 35,145 | 61.7 | 24.9 | -                            | 8               |
| Lindemann 2008 Norway [79]| HUNT study      | Endometrial                  | 15.7            | Population | 1,010 | -    | -    | 35,751 | 49 (total) | -    | -                            | 7               |
| Lin 2011 US [80]        | NIH-AARP study    | Esophagus, gastric           | 7.96            | Population | 41,388 | 62.81 | 29.83 | 428,060 | 61.90 | 26.83 | -                            | 8               |
| Chuma 2008 Japan [81]   | Hokkaido University hospital | Liver                      | 10.2            | Hospital | 19 | -     | -     | 104 (total) | 50.5 (median) | -     | -                            | 7               |
| Di constanzo 2008 Italy [82]| Naples (1994-2004) | Liver                       | 7 median        | Hospital | 41 | -     | -     | 138 (total) | 63.3 | -    | Hepatitis C virus cirrhosis  | 4               |
| El-Serag 2004 US [83]   | PTF 1985-1990     | Liver                       | 8.6             | Hospital (Veteran Affairs (VA)) | 173,643 | 61.7 | - | 650,620 | 54.5 | -    | -                            | 6               |
| Hung 2011 Taiwan [84]   | Chang Gung Memorial Hospital | Liver                      | 4.4             | Hospital | 253 (T2D) | 56 median | 25 median | 1,217 | 52 median | 24 median | Interferon therapy for hepatitis c | 7               |
| Ionnau 2007 US [85]     | VA 1994-2005      | Liver                       | 3.6             | Veterans | 452 | -     | -     | 1,668 | -    | -                            | 6               |
(Table 1) contd.....

| Authors       | Data Source                           | Cancer Site                  | Follow Up Years | Source | DM (n) | Age | BMI | Non- DM (n) | Age | BMI | Co Morbidity | NOS-Score (0-9) |
|---------------|---------------------------------------|------------------------------|-----------------|--------|--------|-----|-----|-------------|-----|-----|--------------|-----------------|
| Kavamura 2010 Japan [86] | Toronamon hospital, Tokyo            | Liver                        | 6.7 median      | Hospital | 104    | -   | -   | 1,954       | 50  | (total) | -             | Interferon therapy for hepatitis C | 7 |
| N’kontchou2 006 France [87] | -                                     | Liver                        | 4.2             | Screened for HCC | 231    | -   | -   | 540         | 61.4 | total 25.4 total | alcoholic or viral C cirrhosis | 6 |
| Ohata 2003 Japan [88] | Nagasaki university hospital         | Liver                        | 6.4             | Hospital | 26     | -   | -   | 161 (total) | 53  | 22.7 0.24 | Chronic HCV infection | 7 |
| Ohki 2008 Japan [89] | University of Tokyo Hospital 1994-2004 | Liver                        | 6.1             | Hospital | -      | -   | -   | 1,431       | 60.1 | - | Chronic HCV infection | 7 |
| Tazawa 2002 Japan [90] | Tsuchiura Kyodo General Hospital     | Liver                        | 5.4             | Hospital | 23     | -   | -   | 279 (all) | 49.4 | - | Hepatitis C infection | 5 |
| Veldt 2008 Europe and Canada [91] | Hepatology Units                   | Liver                        | 4.0             | Hospital | 85     | 51 (median) | 27 (median) | 456 | 49 median | 25 (median) | Hepatitis C and fibrosis or cirrhosis | 6 |
| Adami 1996 Sweden [92] | Swedish in patient register          | Liver and biliary tract     | 6.7             | Hospital | 153,852 | 60.5 | 65.2 | - | External standard population | - | - | - | 8 |
| Chen 2010 Taiwan [93] | NHI                                  | Liver and biliary tract     | 6.9 median      | Population | 615,532 | 60.1 | - | 614,871 | 60.0 | - | - | 9 |
| Ehrlich 2010 US [94] | Kaiser Permanente Medical Care Program Northern California | Lung                        | 1996-2005       | Medical Care Program | 70,645 | 60 median | 29.80 | 51,241 | 51 median | 26.06 | - | 7 |
| Hall 2005 UK [95] | GPRD                                 | Lung                        | 3.95            | Population (primary care) | 66,848 | 60.8 | - | 267,272 | 60.7 | - | - | 8 |
| Authors          | Data Source                  | Cancer Site | Follow Up Years | Source | DM (n) | Age | Non-DM (n) | Age | Co Morbidity | NOS-Score (0-9) |
|------------------|------------------------------|-------------|-----------------|--------|--------|-----|------------|-----|--------------|----------------|
| Lai 2012 Taiwan  | NHI Taiwan 1 million random | Lung        | 2000-2008       | Population | 19624 | 56.4  | 78,496     | 56.5 |              | 8              |
| Luo 2012 US      | WHI                          | Lung        | 11 Postmenopausal | Population | 8,154 | 64.3  | 32.1        | 137,611 | 63.0         | 27.7           |
| Cerhan 1997 US   | IWHS                         | NHL         | 1986-1992       | Population | -    | -    | 37,934 (total) | 61.5 (total) |              | 7              |
| Erber 2009 US    | Multiethnic cohort (MEC)     | NHL         | 10 median       | Population | 13%  | -    | -           | -    |              | 6              |
| Khan 2008 Europe | EPIC and multiple myeloma    | NHL         | 8.5 Population  | 5,111   | 58%   | 56.8% | 134,320    | 51.9% | -            | 7              |
| Gapstur 2012 US  | Cancer Prevention Study-II   | Ovary       | 1992-2007       | Population | 3,577 | 63.6  | 59,863     | 62.2  |              | 7              |
| Chen 2011 Taiwan | NHI                          | Pancreas    | 6.9 median      | Population | 615,532 | 60.1 | 614,871     | 60.0  |              | 9              |
| Chow 1995 Sweden | Hospital                     | Pancreas    | 6.8 Hospital    | 63,987  | -    | -    | External standard population | -    |              | 5              |
| Gupta 2006 US    | Veterans Health Administration | Pancreas | 1999-2004       | Veterans (developed diabetes) | 36,631 | 61.8  | 1,385,163 | 63.6  |              | 7              |
| Larsson 2005 Sweden | COSM and SMC                | Pancreas    | 1997-2004       | Population | -    | -    | 37,147 (total) | 62 (total) | 25 (total) | 8              |
| Authors                | Data Source     | Cancer Site        | Follow Up Years | Source      | DM (n) | Age  | BMI | Non-DM (n) | Age  | BMI | Co Morbidity | NOS-Score (0-9) |
|------------------------|-----------------|--------------------|-----------------|-------------|--------|------|-----|------------|------|-----|--------------|-----------------|
| Liao 2012 Taiwan [106] | NHI             | Pancreas           | 1998-2007       | Population  | 49,803 | 55.92| -   | 199,212    | 55.92| -   | -            | 8               |
| Shibata 1994 US [107]  | Laguna Hills    | Pancreas           | 9 (total)       | Retirement community | -     | -   | -   | 13,976 (total) | 74   | -   | -            | 6               |
| Stevens 2009 UK [108]  | Breast cancer screening | Pancreas | 7.2 | Population | 2.7\% | -  | -  | 1,290,000 | 55.9 | 26.2 | -            | 7               |
| Stolzenberg-Solomon 2002 Finland [109] | ATBC | Pancreas | 10.2 median | Population | -     | -   | -   | 29,048 | 57   | 26.0 | Smokers     | 8               |
| Yun 2006 Korea [110]   | NHIC            | Pancreas           | 10 (total)      | Population  | -     | -   | -   | 446407 | -    | -   | -            | 8               |
| Jamal 2009 US [111]    | VA              | Pancreas and gallbladder | 1990-2000 | Hospital | 278,761 (diabetes patients) | 65.8 | - | 836,283 (non diabetes patients) | 64.8 | - | -            | 7               |
| Giovannucci 1998 US [112] | Health professionals follow up study | Prostate | 1986-1994 | Health professionals | 2,551 | -   | -   | 45,230 | -    | -   | -            | 6               |
| Leitzmann 2008 US [113] | PLCO            | Prostate           | 8.9 (total)     | Population  | 3,024 | 64.0 | 28.7| 30,064 | 62.0 | 26.8 | -            | 7               |
| Li 2010 Japan [114]    | Ohsaki Cohort   | Prostate           | 1995-2003       | Population  | 1,645 | 62.41| 23.74| 20,813 | 59.07| 23.32| -            | 7               |
| Authors                  | Data Source                                      | Cancer Site | Follow Up Years | Source | DM (n) | Age | BMI | Non- DM (n) | Age | BMI | Co Morbidity | NOS-Score (0-9) |
|-------------------------|-------------------------------------------------|-------------|----------------|--------|--------|-----|-----|-------------|-----|-----|-------------|-----------------|
| Rodriguez 2005 US [115] | Cancer prevention study II nutrition cohort     | Prostate    | 1992-2001      | Population | 10,053 | 62,617 |     |             |     |     |             | 7               |
| Thompson 1989 US [116]  | Rancho bernardo                                 | Prostate    | 14 (total)     | Population | - | - | - | 1,776 (all) | 65.9 | 25.62 | - | 7               |
| Velicer 2007 US [117]   | VITAL                                           | Prostate    | 2000-2004      | Population | 2,878 | 64.3 | 30.5 | 32,361 | 61.5 | 27.4 | - | 6               |
| Waters 2009 US [118]    | The Multiethnic Cohort                          | Prostate    | 1993-2005      | Population | 10,825 | - | - | 86,303 total | 59.9 | - | - | 7               |
| Weiderpass 2002 Sweden [119] | Swedish In-Patient Register                    | Prostate    | 5.6            | Population | 135,950 | 61.7 | - | External standard population | - | - | - | 6               |
| Will 1999 US [120]      | 25 states 1959-1972                             | Prostate    | 13 (total)     | Population | 6,086 | - | - | 298,979 | - | - | - | 5               |
| Nicodemus 2004 US [121] | IWHS 1986-2000                                  | Kidney      | 15 total       | Population | - | - | - | 34,637 (total) | - | - | - | 6               |
| Adami 1991 Sweden [122] | Uppsala Inpatient registry                      | Several     | 1965-1984      | Hospital | 51,008 | - | - | Expected | - | - | - | 5               |
| Atchison 2010, US [123] | VA hospitals                                    | Several     | 10.5 (median)  | Veterans (male) | 594,815 | 57.5 | - | 3,906,763 | 51.5 | - | - | 7               |
| Carstensen 2012 Denmark [124] | Central personal register                     | Several     | 1995-2009      | The entire Danish Population | - | - | - | - | - | - | 7               |
(Table 1) contd.....

| Authors                  | Data Source                  | Cancer Site                                      | Follow Up Years | Source                  | DM (n) | Age | BMI | Non-DM (n) | Age | BMI | Co Morbidity | NOS-Score (0-9) |
|--------------------------|------------------------------|--------------------------------------------------|-----------------|-------------------------|--------|-----|-----|------------|-----|-----|-------------|-----------------|
| Chodick 2010 Israel [125] | Maccabi Healthcare Services  | Several                                          | 8               | Population              | 16,721 | 61.6| -   | 83,874     | 61.6| -   | -           | 8               |
| Dankner 2007 Israel [126] | Population registry         | Several                                          | 20 (total)      | Population              | 437    | 57.6| -   | 1,740      | 51.9| -   | -           | 8               |
| Folsom 2008 [127]        | ARIC 1987-1989               | Several                                          | 1987-2000       | Population              | -      | -   | -   | 13,117 (total) | -   | -   | -           | 8               |
| Hjalgrim 1997 Denmark [128] | All men born 1949-1964 with DM before age 20 | Several                                          | 1968-1992       | Population              | 1,659  | -   | -   | External standard population | -   | -   | -           | 3               |
| Hjalgrim 1997 Denmark [128] | Funen county                 | Several                                          | 1973-1992       | Population              | 1,499  | -   | -   | External standard population | -   | -   | -           | 4               |
| Inoue 2006 Japan [129]   | Japan Public Health Center-Based Prospective Study | Several                                          | 10.7            | Population              | 3,097  | 54  | 54  | 1,571      | 56  | -   | -           | 7               |
| Jee 2005 Korea [130]     | NHIC                         | Several                                          | 10 total        | government employees, teachers and dependents (10.7% of total population) | 626  | 58.5| 58.8| 499        | 31.5| 30.0| -           | 7               |
| Johnson 2011 [131] Canada | BCLHD                       | Several                                          | 4.3             | Population              | 185,100 | 60.7| -   | 185,100    | 60.7| -   | -           | 8               |
| Joshu 2012 US [132]      | ARIC (1990-2006)             | Several                                          | 15 median       | Population              | 626    | 58.5| 58.8| 499        | 31.5| 30.0| -           | 6               |
| Khan 2006 Japan [133]    | JACC                         | Several                                          | 1988-1997       | Population              | 3,307  | 40.7| -   | 53,574     | 40-79| -   | -           | 7               |
| Authors | Data Source | Cancer Site | Follow Up Years | Source | DM (n) | Age | BMI | Non-DM (n) | Age | BMI | Co Morbidity | NOS-Score (0-9) |
|---------|-------------|-------------|----------------|--------|--------|-----|-----|------------|-----|-----|--------------|----------------|
| Ragozzino 1982 US [134] | Rochester, Minnesota | Several | - | Population | 1,135 | - | - | External standard population | - | - | - | 4 |
| Rapp 2006 Austria [135] | VHM&PP | Several | 8.4 | Population | 3.4% | - | - | 140,813 | 43 | - | - | 8 |
| Steenland 1995 US [136] | NHANES I | Several | 7.7 | Civilian population | - | - | - | 14,407 | - | - | - | 7 |
| Swerdlow 2005 UK [137] | The diabetes uk cohort | Several | 1972-2003 | Population | 29,701 | 0-49 | - | External standard population | - | - | - | 6 |
| Wideroff 1997 [138] Denmark | Danish Central Hospital Discharge Register | Several | 1977-1993 | Hospital | 109,581 | 64 | 69 | median | External standard population | - | - | - | 6 |
| Wotton 2011 UK [139] | ORLS 1 | Several | 1963-1998 | Hospital | 15,898 | - | - | 275,564 | - | - | - | 7 |
| Wotton 2011 UK [139] | ORLS 2 | Several | 1999-2008 | Hospital | 7,771 | - | - | 185,123 | - | - | - | 7 |
| Yeh 2012 US [140] | CLUE II | Several | 1989-2006 | Population | 599 | 61.8 | 29.5 | 17,681 | 51.5 | 26.3 | - | 7 |
| Aschebrook-kilfoy 2011 US [141] | NIH-AARP study | Thyroid | 10 | Population | 44,693 | 62.9 | 29.9 | 451,855 | 61.9 | 26.8 | - | 7 |
| Kitahara 2012 US [142] | Pooled analysis of 5 cohort studies | Thyroid | 10.5 median | Previous studies | 8% | - | - | 674,491 (total) | 59.8 | - | - | 7 |
| Meinhold 2010 US [143] | US Radiologic Technologists Study | Thyroid | 15.8 | Radiologic technologists | - | - | - | 69.50 | 43.3 | - | - | 6 |

Age and BMI are provided by means if nothing else is specified. Follow up years are provided by means, medians or follow up period. *Comorbidity in the population examined. Body mass index (BMI), diabetes mellitus (DM), digital rectal examination (DRE), general practitioner (GP), hepatitis C virus (HCV). Total: For the whole group or the complete study period.
### Table 2. Study Table of Cross-Sectional Studies by Diabetes Type

| Authors | Data Source | Cancer Site | Follow Up Years | Source | DM (n) | Age | BMI | Non-DM (n) | Age | BMI | Co Morbidity | NOS-Score (0-9) |
|---------|-------------|-------------|----------------|--------|--------|-----|-----|------------|-----|-----|--------------|----------------|
| **Cross-Sectional Studies** | | | | | | | | | | | | |
| **Type 2 diabetes** | | | | | | | | | | | | |
| Baur 2011 | DETECT study | Any | Population | 1,308 | 70.4 (with cancer) | 66.6 (without cancer) | 28.3 (with cancer) | 29.8 (without cancer) | 6,211 | 65.5 (with cancer) | 55.5 (without cancer) | 26.7 (with cancer) | 26.6 (without cancer) | 7 |
| Diabtes type unspecified | | | | | | | | | | | | | |
| Lawlor 2004 | UK [145] | Breast | Randomly from GP | 147 women with cancer | 68.5 | 28.1 | 3,890 women without cancer | 68.9 | 27.6 | | 6 |
| Sandhu 2001 | Norfolk | Colorectal | Population (GP lists) | 561 | 45-74 | - | 28,782 | 45-74 | - | - | 6 |
| Tung 2010 | Tainan | Liver | Population | 72 | 68.4 | - | 56,193 | - | - | - | 6 |
| Moreira 2011 | Durham VA | Prostate | Hospital (performed prostate biopsy, high risk patient population (referred for biopsy because of elevated PSA or abnormal DRE)) | 284 | 64 | 30.4 | 714 | 63 | 27.7 | | 5 |
| Moses 2012 | US [148] | Prostate | Hospital (high risk population (referred to biopsy for elevated PSA or abnormal DRE)) | 1,045 | - | - | 1,265 | - | - | - | 5 |
| Li 2011 | US [149] | Several | Population | - | - | - | 397,783 total | 46.8 | - | - | 4 |

Age and BMI are provided by means if nothing else is specified. Follow up years are provided by means, medians or follow up period. *Comorbidity in the population examined. Body mass index (BMI), diabetes mellitus (DM), digital rectal examination (DRE), general practitioner (GP), Total: For the whole group or the complete study period.
### Table 3. Study Table of Case Control Studies by Diabetes Type

| Authors                  | Data Source                  | Cancer Site                     | Source | Cases (n) | Age | BMI | Controls (n) | Age | BMI | Co-Morbidity* | NOS-Score (0-9) |
|--------------------------|------------------------------|---------------------------------|--------|-----------|-----|-----|-------------|-----|-----|--------------|-----------------|
| **Type 2 diabetes**      |                              |                                 |        |           |     |     |              |     |     |              |                 |
| Khachatryan 2011 Armenia | [150]                        | Breast                          | Population | 150   | 55.79 | 29.03 | 152 | 51.11 | 27.67 | -               | 6               |
| Rollison 2007 US [151]   | 4 corners breast cancer study| Breast                          | Population | 2,324 | -     | -     | 2,523 | 56    | -     | -               | 6               |
| Li 2012 China [152]      | -                            | Liver                           | Hospital | 1,105 | 53.8  | -     | 5,170 | 44.9  | -     | Chronic hepatitis B | 6               |
| **Diabetes type unspecified** |                              |                                 |        |           |     |     |              |     |     |              |                 |
| Grainge 2009 UK [153]    | GPRD 1987-2002               | Biliary tract                   | Population | 611   | 71.3  | (at diagnosis) | - | 5,760 | -    | -               | 8               |
| Khan 1999 US [154]       | CPMC 1980-1994               | Hospital                        | Hospital | 69     | -     | -     | 138  | -     | -    | -               | 6               |
| Shaib 2007 US [155]      | M.D. Anderson Cancer Center  | Biliary tract                   | Hospital | 83 ICC | 163 ECC | ICC 59.8 | ECC 61.1 | - | 236 | 58.1 | -               | 5               |
| Shebl 2010 China         | Shanghai, China              | Biliary tract                   | Population | 627   | -     | -     | 959  | -     | -    | -               | 7               |
| Tao 2010 China [156]     | PUMCH                        | Biliary tract                   | Hospital | 190(total) | 61 ICC | 58.6 ECC | 58.7 ICC | 380 | 59.7 | -    | -               | 5               |
| Welzel 2007 US [157]     | SEER                         | Biliary tract                   | Population | ECC 549 | ICC 535 | ECC 78.7 ICC 79 | - | 102,782 | 77.1 | -               | 7               |
| Authors          | Data Source      | Cancer Site     | Source          | Cases (n) | Age | BMI | Controls (n) | Age | BMI | Co Morbidity | NOS-Score (0-9) |
|------------------|------------------|-----------------|-----------------|-----------|-----|-----|--------------|-----|-----|--------------|-----------------|
| Kantor 1984 US  | SEER             | Bladder         | Population      | 2,982     | -   | -   | 5,782        | -   | -   | -            | 6               |
| Kravchick        | Israel Hospital  | Bladder         | Hospital        | 252       | ♂71.5 | 73  | 549          | -   | -   | -            | 4               |
| Mackenzie        | New England      | Bladder         | Population      | 331       | 62  | 28.0| 263          | 60  | 27.0| -            | 6               |
| Ng 2003 UK       | Bedford General  | Bladder         | Hospital        | 125       | -   | -   | 80           | -   | -   | -            | 5               |
| Risch 1988       | Canada           | Bladder         | Population      | 835       | 35-79| -   | 792          | -   | -   | -            | 6               |
| Baron 2001       | Wisconsin        | Breast          | Population      | 5,659     | 65.3| -   | 5,928        | 64.1| -   | -            | 6               |
| Beji 2007        | Turkey           | Breast          | Hospital        | 405       | -   | -   | 1,050        | -   | -   | -            | 3               |
| Cleveland        | Long Island      | Breast          | Population      | 1,495     | 63.6| 30.9| 1,543        | 57.4| 26.1| -            | 6               |
| Garmendia        | Chile            | Breast          | Hospital        | 170       | 56.5| 28.59| 170          | 55.18| 29.23| -            | 5               |
| Jordan 2009      | Thailand         | Breast          | University      | 43        | 39   | median | 860         | -   | -   | -            | 4               |
| Authors            | Data Source                  | Cancer Site | Source                      | Cases (n) | Age  | BMI  | Controls (n) | Age  | BMI  | Co Morbidity | Now-Score (0-9) |
|--------------------|------------------------------|-------------|-----------------------------|-----------|------|------|--------------|------|------|--------------|-----------------|
| Weiss 1999 US [168]| New Jersey, Atlanta, Seattle| Breast      | Population                  | 2,173     | -    | -    | 1,990        | -    | -    |              | 5               |
| Wu 2007 US [169]   | Los Angeles County Cancer Surveillance Program | Breast      | Population                  | 1,248     | -    | -    | 1,148        | -    | -    |              | 6               |
| Kune 1988 Australia [170] | Melbourne 1980-1981 | Colorectal | Population                  | 715       | 65   | -    | 727          | 65   | -    |              | 6               |
| Le Marchand 1997 US [171] | Australia               | Colorectal | Population                  | 1,192     | ≥67  | ≥65  | 1,192        | ≥65  | ≥65  |              | 7               |
| Rinaldi 2008 European countries [172] | EPIC (8 countries) | Colorectal | Population                  | 1,026     | 59.1 (CC) | 27.3 (CC) | 1,026    | 59.1 (Control CC) | 26.9 (Control CC) | 8               |
| Safaee 2009 Iran [173] | Shahid Beheshti University of Medical Sciences, Tehran, Iran | Colorectal | Population (cases: cancer registry. Controls: health survey) | 862  | -    | -    | 862          | -    | -    |              | 4               |
| Vinikoor 2009 US [174] | NCCCS1                    | Colorectal | Population                  | 637       | 63.69 |      | 1,044        | 66.06 |      |              | 6               |
| Vinikoor 2009 US [174] | NCCCS2                    | Colorectal | Population                  | 1,007     | 61.88 |      | 988          | 63.86 |      |              | 6               |
| Yang 2005 UK [175] | GPRD                        | Colorectal | Population                  | 10,447    | -    | -    | 104,429      | -    | -    |              | 8               |
| Fortuny 2009 US [176] | EDGE study                | Endometrial | Population                  | 469       | 61.7 | -    | 467          | 63.6 (all) | -    |              | 6               |
(Table 3) contd……

| Authors              | Data Source                          | Cancer Site   | Source               | Cases (n) | Age  | BMI     | Controls (n) | Age  | BMI     | Co Morbidity* | NOS-Score (0-9) |
|----------------------|--------------------------------------|---------------|----------------------|-----------|------|---------|--------------|------|---------|---------------|-----------------|
| Inoue 1994 Japan     | Osaka University Medical School      | Endometrial   | Hospital             | 143       | 53.6 | -       | 143          | 53.2 | -       | 5             |                 |
| Saltzman 2008 US     | Washington State                     | Endometrial   | Population           | 1,303     |      |         | 1,779        |      |         | 7             |                 |
| Yamazawa 2003 Japan  | Chiba University Hospital            | Endometrial   | Hospital             | 41        |      |         | 123          |      |         | 5             |                 |
| Neale 2009 Australia | Queensland 2001-2005                 | Esophagus     | Population           | 1,102     |      |         | 1,580        |      |         | 6             |                 |
| Reavis 2004 US       | Portland VA Medical Center           | Esophagus     | Hospital (and dental clinic) | 63 | 69.6 | - | 50 + | 63.7 | 50 + | 64.7 | 58.9 | 5 |
| Rubenstein 2005 US    | Veterans database 1995-2003          | Esophagus and gastric cardia | Veterans | 311 | 71.2 | median | 10154 | 66.3 | median | GERD | 7 |
| Vincis 2000 Italy    | 11 Italian areas                    | Haemopoietic  | Population           | 2,669     | 56.1 | -       | 1,718        | 54.9 | -       | 6             |                 |
| Stott-Miller 2012    | Pooled analysis                     | Head and neck | Mixed                | 6,448     |      |         | 13,747       |      |         | 4             |                 |
| Davila 2005 US       | Surveillance Epidemiology and End-Results Program (SEER) | Liver | Population | 2,061 | 76.1 | - | 6,183 | 76.4 | - | 8 |
| El-Serag 2001 US     | 1997-1999 VA                         | Liver         | Hospital (veterans)  | 823       | 62   | -       | 3,459        | 60   | -       | 4             |                 |
| Authors          | Data Source                  | Cancer Site            | Source     | Cases (n) | Age | BMI | Controls (n) | Age | BMI | Co-Morbidity* | NOS-Score (0-9) |
|-----------------|------------------------------|------------------------|------------|-----------|-----|-----|--------------|-----|-----|---------------|-----------------|
| Hassann 2002    | MD Anderson Cancer center 1994-1995 | Liver                  | Hospital   | 115       | 59.5| -   | 230          | 59.1| -   |               | 7               |
| Hassann 2010    | MD Anderson Cancer center 2000-2008 | Liver                  | Hospital   | 420       | 63  | -   | 1,104        | 60  | -   |               | 7               |
| Matsuo 2003     | Japan                        | Kyushu                 | Population | 222       | ♂ 63.|♀ 64.3| 222 ♂ 63.5 |♀ 64.1|       |               | 6               |
| Tung 2010       | Taiwan                       | Tainan                 | Population | 72        | 68.4| -   | 144          | 68.2| -   |               | 7               |
| Tung 2010       | Taiwan                       | Tainan                 | Population | 72        | 68.4| -   | 144          | 67.7| -   | Hepatitis C infection | 7               |
| Yuan 2004       | US                           | Los Angeles county 1984-2001 | Population | 295       | 60.6| -   | 435          | 60.1| -   |               | 5               |
| Fortuny 2005    | Spain                        | Lymphoma               | Hospital   | 565       | -   | -   | 601          | 59 (total)| -   |               | 6               |
| Cartwright 1988| UK                           | NHL                    | Hospital   | 437       | -   | -   | 724          | -   | -   |               | 4               |
| Cerhan 2005     | NHL                          | Population             | 759        | 56.6      | 27.7| 589 | 56.9         | 27.7| -   |               | 6               |
| Lin 2007        | CGMH                         | NHL                    | Population | 242       | 59 | median at diagnosis | - | 71,379 | - | - |               | 6               |
| Authors                          | Data Source | Cancer Site | Source           | Cases (n) | Age | BMI | Controls (n) | Age | BMI | Co Morbidity* | NOS-Score (0-9) |
|---------------------------------|-------------|-------------|------------------|-----------|-----|-----|--------------|-----|-----|---------------|----------------|
| Smedby 2006 Denmark, Sweden [194] | SCALE       | NHL         | Population       | 3,055     | 60 median | -   | 3,187        | 59 median | -   | -             | 6              |
| Bonelli 2003 Italy [195]         | Northern Italy 1992-1996 | Hospital | 202             | -         | -   | 404 | -            | -   | -   | -             | 6              |
| Bueno de mesquita 1992 Netherlands [196] | 1984-1987 | Pancreas | Population | 174 | 35-79 | 487 | 35-79 | 6 |
| Cuzick 1989 UK [197]              | Leeds, London, Oxford (1983-1986) | Hospital | 216             | -         | -   | 279 | -            | -   | -   | -             | 7              |
| Ekoe 1992 Canada [198]            | Quebec      | Pancreas | Population       | 179       | 63,9 | 239 | 62,1          | -   | -   | -             | 7              |
| Friedman 1993 US [199]           | Kaiser Permanente Medical Care Program | Pancreas | Kaiser Permanente Medical Care Program (inpatient and outpatient) | 450 | 54,6 | - | 2,687 | 54,4 | - | - | 6 |
| Frye 2000 New Zealand [200]      | Canterbury Health case mix database | Pancreas | Hospital        | 116       | 70,1 | - | 116 | 70,2 | - | Controls: Fracture of femur neck | 6 |
| Grote 2011 [201]                 | EPIC (10 countries) | Pancreas | Population       | 466       | 58   | 26,6 | 466 | 58   | 25,9 | - | 5 |
| Gullo 1994 Italy [202]            | 14 Italian university and community hospitals (1987-1989) | Pancreas | Hospital        | 720       | 62,6 | - | 720 | - | - | - | 6 |
| Hassan 2007 US [203]              | Pancreas    | Hospital | 808             | 61,9      | -   | 808 | 60,2          | -   | -   | -             | 7              |
| Authors                  | Data Source                      | Cancer Site | Source                                      | Cases (n) | Age | BMI | Controls (n) | Age | BMI | Co Morbidity* | NOS-Score (0-9) |
|--------------------------|----------------------------------|-------------|---------------------------------------------|-----------|-----|-----|---------------|-----|-----|---------------|-----------------|
| Hiatt 1988               | US [204]                         | Pancreas    | Member of medical care program              | 49        | 67.6| -   | 12,104        | -   | -   | -             | 6               |
| Jain 1991                | Canada [205]                     | Pancreas    | Population                                  | 249       | 64.6| -   | 505           | 64.8 | -   | -             | 6               |
| Kalapothaki 1993         | Greece [206]                     | Pancreas    | Population                                  | 181       | -   | -   | 181; 818 (2 control groups) | -   | -   | -             | 5               |
| Li 2011                  | US [207]                         | Pancreas    | Population                                  | 2,192     | 63  | -   | 5,113         | 63   | -   | -             | 7               |
| Maisonnueve 2010         | Australia, Canada, Poland [208]  | Pancreas    | Population                                  | 823       | -   | -   | 1,679         | -   | -   | -             | 5               |
| Matsubayashi 2011        | Japan [209]                      | Pancreas    | Hospital                                    | 577       | 64.9| -   | 577           | 64.9 | -   | -             | 5               |
| Mizuno 1992              | Japan [210]                      | Pancreas    | Hospital                                    | 124       | -   | -   | 124           | -   | -   | -             | 6               |
| Baradaran 2009           | Iran [211]                       | Prostate    | Hospital                                    | 194       | 71.06| 26.3| 317           | 66.5 | 26.8| -             | 4               |
| Coker 2004               | US [212]                         | Prostate    | Population                                  | 407       | 65-79| -   | 393           | 65-79| -   | -             | 6               |
| Gong 2006                | [213]                            | Prostate    | Previous study                              | 1,936     | 63.7| 27.6| 8,322         | 62.6 | 27.7| -             | 7               |
| Authors                     | Data Source                  | Cancer Site                | Data Source   | Data Source   | Data Source   | BMI | BMI | Co Morbidity* | BMI | BMI | Co Morbidity* |
|-----------------------------|------------------------------|----------------------------|---------------|---------------|---------------|-----|-----|---------------|-----|-----|---------------|
| Gonzales-Perez 2005         | GPRD 1995-2001               | Population                 |                |               |               | 2,183 | 72 median | 10,000 | 72 median | - | - | 8 |
| Lightfoot 2004              | Ontario 1995-1999            | Population                 |                |               |               | 760 | - | - | 1,632 | - | - | 5 |
| Rosenberg 2002              | University Medical Center in | Population                 |                |               |               | 320 | 69.6 | - | 189 | 68.1 | - | - | 6 |
| Tavani 2002                 | Milan Pordenone and Athens, | hospital                   |                |               |               | 608 | - | - | 1,008 | - | - | 6 |
| Turner 2011                 | Protect study                | Population                 |                |               |               | 1,291 | 62.2 | 26.7 | 6,479 | 62.0 | 26.9 | - | 7 |
| Zhu 2004                    | US Physicians' Health Study | Physicians                 |                |               |               | 1,110 | - | 24.9 | 1,110 | - | 24.9 | - | 6 |
| Atmer 2012                  | Swedish cancer registry      | Population                 |                |               |               | 19,756 | 45-84 | - | 147,324 | 45-84 | - | - | 7 |
| Bosetti 2011                 | 1991-2009                    | Hospital                   | 230-2390      | 56-66 depending on cancer type | 12,060 | 56-65 depending on cancer type | 7 |
| Jorgensen 2012              | Funen county                 | Population                 | 78 median | - | 25,299 | 78 Median | - | - | 7 |
| Kuriki 2007                 | HERPACC 1989-2000            | Hospital                   | 5,341 | 65.3 | 6,331 | 60.6 | 22.7 | 14,199 | 60.6 | 23.0 | - | 6 |
(β =-0.23) and colorectal (β =-0.23) cancer and otherwise not a determinant like follow up years was not a determinant. Compared to adjustment of age, adjustment of both age and BMI was a significantly positive determinant in the risk of biliary tract and gallbladder cancer (β =0.79), cervix cancer (β =0.37), myeloma (β =0.49), non Hodgkin lymphoma (β =0.39), ovary-(β =0.52), prostate cancer (β =0.11), rectum cancer (β =0.40) and thyroid cancer (β =0.47), while it was a significantly negative determinant of larynx cancer (β =-0.23). In addition adjustment of age, diabetes and smoking was a positive determinant of risk ratio in colorectal- (β =0.11), ovary-(β =0.51), and skin cancer (β =0.69) compared to adjustment by age. Furthermore some specific cancer risks may be determined by diabetes ascertainment, cancer ascertainment, and data source. In the electronic Supplementary Material 4 the results of the meta-regression are available.

| Authors          | Data Source | Cancer Site Source | Cases (n) | Age | BMI | Controls (n) | Age | BMI | Co Morbidity* | NOS-Score (0-9) |
|------------------|-------------|--------------------|-----------|-----|-----|--------------|-----|-----|--------------|----------------|
| La Vecchia 1994 Italy [224] | Milan 1983-1992 | Several Hospital | 9,991 | -   | -   | 7,834 | -   | -   | -            | 5              |
| O Mara 1985 US(37) | Roswell Park Memorial Institute (RPMI) (1957-1985) | Several Hospital | 14,910 | -   | -   | 4,838 | -   | -   | -            | 3              |
| Rousseau 2006 Canada [225] | Montreal 1979-1985 | Population | 3,107 | -   | -   | 509   | 59.6 | BMI>25 | 58.2 % BMI>25 | 6              |

Age and BMI are provided by means if nothing else is specified. Follow up years are provided by means, medians or follow up period. *Comorbidity in the population examined.

Body mass index (BMI), diabetes mellitus (DM), digital rectal examination (DRE), general practitioner (GP), hepatitis C virus (HCV), Total: For the whole group or the complete study period.

Non Hodgkin lymphoma (NHL), Nervous system (Brain), RR (risk ratio)

Fig. (2). Plot of the pooled analysis of all populations of the risk of cancer among diabetes patients compared to a non-diabetes population.
Non Hodgkin lymphoma (NHL), Nervous system (Brain), RR (Risk ratio)

Fig. (3). Plot of the pooled analysis of all cohort populations of the risk of cancer among diabetes patients compared to a non-diabetes population.

Non Hodgkin lymphoma (NHL), RR (Risk ratio)

Fig. (4). Plot of the pooled analysis of all case control populations of the risk of cancer among diabetes patients compared to a non-diabetes population.
Non Hodgkin lymphoma (NHL), RR (Risk ratio)

Fig. (5). Plot of the pooled analysis of all populations only consisting of males of the risk of cancer among diabetes patients compared to a non-diabetes population.

Non Hodgkin lymphoma (NHL), Nervous system (Brain), RR (Risk ratio)

Fig. (6). Plot of the pooled analysis of all populations only consisting of females of the risk of cancer among diabetes patients compared to a non-diabetes population.
**DISCUSSION**

**Summary of Evidence**

This systematic review and meta-analysis confirms the previous findings of an increased cancer risk among diabetes patients. The addition of several databases to the literature search compared to previous meta-analyses did not change the associations previously found. Diabetes patients were especially susceptible to liver cancer (RR= 2.13; 95% CI 1.81-2.50), pancreas cancer (RR= 2.21; 95% CI 1.93-2.54), and endometrial cancer (RR= 1.81; 95% CI 1.63-2.01). In addition, new cancer sites have been investigated: risks of cervix (RR=1.34; 95% CI 1.10-1.63), ovary cancer (RR= 1.20; 95% CI 1.03-1.40), and small intestinal cancer was reported (RR=1.47; 95% CI 1.03-2.11) were also slightly increased in diabetes patients. In addition female diabetes patients were at increased risk of breast (RR= 1.13 95% CI 1.07-1.18). Thus females with diabetes were at increased risk of gender specific and hormone related cancers compared to their non-diabetic counterparts. However, male diabetes patients seem to be have a reduced risk of prostate cancer (RR= 0.85; 95% CI 0.80-0.91), which support the previous findings [9,10]. Furthermore, our findings support an increased risk of gastric and stomach cancer (RR=1.13; 95% CI 1.02-1.24), whereas former reports have been conflicting [15,16]. An elevation in thyroid cancer (RR=1.27; 95% CI 1.12-1.43) was also present among diabetes patients. A single study reported on head and neck cancer, which found

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### Table 4. Results of the Pooled Analysis by Random Effects Model for All Included Studies on Any Cancer and Specific Cancer Sites

| Cancer Site                  | RR (95% Confidence Interval) | Number of Populations | Test for Heterogeneity |
|------------------------------|-----------------------------|-----------------------|------------------------|
| Any                          | 1.15 (1.06-1.25)            | 42                    | P < 0.001              |
| Biliary tract and gall bladder* | 1.69 (1.41-2.03)            | 26                    | P < 0.001              |
| Bladder                      | 1.14 (1.05-1.22)            | 35                    | P < 0.001              |
| Bone                         | 1.00 (0.69-1.45)            | 7                     | P = 0.895              |
| Breast                       | 1.14 (1.08-1.19)            | 62                    | P < 0.001              |
| Cervix                       | 1.34 (1.10-1.63)            | 19                    | P < 0.001              |
| Colon                        | 1.29 (1.21-1.36)            | 41                    | P < 0.001              |
| Colorectal                   | 1.27 (1.21-1.34)            | 51                    | P < 0.001              |
| Endometrial                  | 1.81 (1.63-2.01)            | 29                    | P < 0.001              |
| Esophagus                    | 1.20 (1.02-1.41)            | 29                    | P < 0.001              |
| Kidney                       | 1.37 (1.18-1.59)            | 33                    | P < 0.001              |
| Larynx                       | 1.10 (0.84-1.43)            | 11                    | P < 0.001              |
| Leukemia                     | 1.25 (1.08-1.45)            | 20                    | P < 0.001              |
| Liver                        | 2.13 (1.81-2.50)            | 61                    | P < 0.001              |
| Lung                         | 1.07 (0.97-1.17)            | 44                    | P < 0.001              |
| Lymphoma**                   | 1.39 (1.17-1.64)            | 18                    | P < 0.001              |
| Melanoma                     | 1.00 (0.91-1.10)            | 18                    | P = 0.002              |
| Myeloma                      | 1.11 (0.92-1.34)            | 11                    | P < 0.001              |
| Nervous system               | 1.19 (0.97-1.46)            | 19                    | P < 0.001              |
| Non-Hodgkin lymphoma         | 1.19 (1.05-1.36)            | 28                    | P < 0.001              |
| Ovary                        | 1.20 (1.03-1.40)            | 21                    | P < 0.001              |
| Pancreas                     | 2.21 (1.93-2.54)            | 65                    | P < 0.001              |
| Prostate                     | 0.85 (0.80-0.91)            | 27                    | P < 0.001              |
| Rectum                       | 1.17 (1.08-1.27)            | 37                    | P < 0.001              |
| Skin***                      | 0.91 (0.83-0.99)            | 18                    | P < 0.001              |
| Small intestine              | 1.47 (1.03-2.11)            | 6                     | P = 0.005              |
| Stomach                      | 1.13 (1.02-1.24)            | 37                    | P < 0.001              |
| Testes                       | 0.88 (0.71-1.09)            | 6                     | P = 0.924              |
| Thyroid                      | 1.27 (1.12-1.43)            | 21                    | P = 0.076              |

Significance is indicated by **bold**. Number of populations covers the number of populations used in the pooled analysis, this may not be the same as the number of records used in the analysis, thus some records have multiple populations. RR: Risk ratio; CI: Confidence interval. * In this category studies estimating the risk of biliary tract extra- and intra hepatic, gallbladder cancer and cholangiocarcinoma were pooled ** In this category estimates of lymphoma, Hodgkin lymphoma and combined estimates of lymphoma including Non-Hodgkin lymphoma were pooled. *** Some estimates used in skin cancer cover both non-melanoma skin cancer and melanoma.
that cancer risk, was not significantly increased among diabetes patients [38].

Neither study design nor gender appears to modulate the overall increase in cancer risk among diabetes patients. Duration of diabetes was not available for analyses, which may influence results. The increased risk of pancreas cancer in diabetes may be due to cancer diagnosis in the following years after diabetes diagnosis, where the risk especially was

Table 5. Results of the Meta-Regression on the Specific Cancer Types

| Cancer Site            | Gender* | Age (Years)* | BMI (kg/m²)* | Diabetes Type* | Follow Up (Years)* | Source* | Adjustment for Age | Adjustments for Age and BMI | Diabetes Ascertainment | Cancer Ascertainment | NOS* |
|------------------------|---------|--------------|--------------|----------------|-------------------|---------|-------------------|--------------------------|------------------------|----------------------|------|
| Any                    | 0 (5)   | - (5)        |              |                | 0 (42)            | 0 (42)  |                  |                          |                        |                      |      |
| Biliary tract and gall bladder | 0 (7)   | 0 (7)        |              |                | - (25)            | + (25)  | 0 (25)            | 0 (25)                    |                        |                      |      |
| Bladder                | 0 (5)   | - (5)        |              |                | 0 (33)            | 0 (33)  | 0 (33)            | 0 (33)                    |                        |                      |      |
| Bone                   | 0 (4)   |              |              |                | 0 (7)             | 0 (7)   |                  |                          |                        |                      |      |
| Breast                 | 0 (7)   | 0 (7)        | 0 (7)        |                | 0 (60)            | 0 (60)  | 0 (60)            | 0 (60)                    |                        |                      |      |
| Cervix                 | 0 (6)   |              |              |                | 0 (17)            | + (17)  | 0 (17)            | 0 (17)                    |                        |                      |      |
| Colon                  | 0 (13)  | 0 (13)       | - (13)       |                | 0 (40)            | 0 (40)  | 0 (40)            | 0 (40)                    |                        |                      |      |
| Colorectal             | 0 (7)   | 0 (7)        | 0 (7)        | - (9)**         | 0 (47)            | 0 (47)  | 0 (47)            | 0 (47)                    |                        |                      |      |
| Endometrial            | 0 (5)** | 0 (4)        |              |                | 0 (26)            | 0 (26)  | 0 (26)            | 0 (26)                    |                        |                      |      |
| Esophagus              | 0 (5)   | - (5) C      |              |                | 0 (27)            | 0 (27)  | 0 (27)            | 0 (27)                    |                        |                      |      |
| Kidney                 | 0 (5)   | 0 (5)        | 0 (4)        |                | 0 (31)            | 0 (31)  | + (31)            | 0 (31)                    |                        |                      |      |
| Larynx                 | 0 (6)   |              |              |                | 0 (10)            | - (10)  | + (10)            | 0 (10)                    |                        |                      |      |
| Leukemia               | - (5)   | 0 (5)        |              |                | 0 (18)            | 0 (18)  | 0 (18)            | 0 (18)                    |                        |                      |      |
| Liver                  | 0 (7)** | (10)** C     | 0 (4)        |                | 0 (58)            | 0 (58)  | 0 (58)            | 0 (58)                    |                        |                      |      |
| Lung                   | 0 (6)** | 0 (6)**      | - (5)        |                | 0 (42)            | 0 (42)  | 0 (42)            | 0 (42)                    |                        |                      |      |
| Lymphoma               | 0 (9)   |              |              |                | - (18)            | 0 (18)  | 0 (18)            | 0 (18)                    |                        |                      |      |
| Melanoma               | 0 (12)  |              |              |                | 0 (16)            | 0 (16)  | 0 (16)            | 0 (16)                    |                        |                      |      |
| Myeloma                | 0 (6)   |              |              |                | - (11)            | + (11)  | 0 (11)            | 0 (11)                    |                        |                      |      |
| Nervous system         | 0 (12)  |              |              |                | 0 (17)            | 0 (17)  | 0 (17)            | 0 (17)                    |                        |                      |      |
| NHL                    | 0 (13)  |              |              |                | - (26)            | + (26)  | 0 (26)            | 0 (26)                    |                        |                      |      |
| Ovary                  | 0 (7)   |              |              |                | 0 (19)            | + (19)  | 0 (19)            | - (19)                    |                        |                      |      |
| Pancreas               | 0 (7)** | 0 (7)**      | 0 (4)        |                | 0 (63)            | 0 (63)  | 0 (63)            | 0 (63)                    |                        |                      |      |
| Prostate               | + (5)** 0 (5)** | 0 (12) |              |                | 0 (26)            | + (26)  | 0 (26)            | + (26)                    |                        |                      |      |
| Rectum                 | 0 (11)**| 0 (11)**     | 0 (3)        | 0 (11)**        | 0 (35)            | + (35)  | 0 (35)            | 0 (35)                    |                        |                      |      |
| Skin                   | 0 (10)  |              |              |                | 0 (18)            | 0 (18)  | 0 (18)            | 0 (18)                    |                        |                      |      |
| Small intestine        | 0 (5)   |              |              |                | - (6)             | 0 (6)   |                  |                          |                        |                      |      |
| Stomach                | 0 (7)   | - (7) C      |              |                | 0 (35)            | 0 (35)  | 0 (35)            | 0 (35)                    |                        |                      |      |
| Testes                 | 0 (6)   |              |              |                | 0 (6)             |        |                  |                          |                        |                      |      |
| Thyroid                | 0 (6)   | 0 (6)        |              |                | 0 (5)             | 0 (20)  | + (20)            | 0 (20)                    |                        |                      |      |

*: statistically significant positive determinant, -: statistically significant negative determinant, 0: no statistical significance, blank: could not be performed and not included in the meta-regression. The () marks how many populations were available for the regression results. Number of populations covers the number of populations used in the pooled analysis, this may not be the same as the number of records used in the analysis, thus some records have multiple populations. Some estimates used in skin cancer cover both non melanoma skin cancer and melanoma. Gender, diabetes type, source, diabetes ascertainment, cancer ascertainment, adjustment and NOS were all coded as categorical values, * regression analysis included age, gender, NOS and BMI if available. £ regression analyses included study design, source, diabetes ascertainment, adjustment factors and cancer ascertainment.

** Regression performed without BMI. *** Regression performed without diabetes type. BMI: Body Mass Index, NHL: Non Hodgkin lymphoma, NOS: Newcastle Ottawa Scale score. C: significance only applies to cohort studies not case control studies. CC: significance only apply to case control studies. Variables were entered in the categories as described in the methods section.
increased [207]. Normalization of the cancer risk occurs 10 years after diabetes diagnosis [207], and may be a result of detection bias or indicate that diabetes diagnosis was a symptom of pancreatic cancer. Johnson et al. [131] investigated time dependent factors in cancer risk and diabetes and conclude that the increased cancer risk may be due to increased ascertainment after diabetes diagnosis.

Obesity may be a confounder when assessing cancer risk in diabetes patients [30]. This was not supported by the meta-regression conducted. BMI was a negative determinant for risk of lung cancer, while no other cancer risk was determined by BMI; hence effect modification was only apparent when looking at lung cancer. When looking at the adjustment performed by the studies in the meta-analysis; adjustment by BMI and age were positive determinants of cancer risk in comparison to adjustment for age alone. These results indicate that obesity among diabetes patients was not an effect modifier on the risk of cancer in diabetes, and obesity may not be the explanation for the increased cancer risk for the types rectum, thyroid, biliary tract and obesity may not be the explanation for the increased cancer risk in comparison to adjustment for age alone. These results indicate that obesity among diabetes patients was not an effect modifier on the risk of cancer in diabetes, and obesity may not be the explanation for the increased cancer risk for the types rectum, thyroid, biliary tract and gallbladder, ovary, non-Hodgkin lymphoma, myeloma and cervix cancer (adjustment by BMI and age was a positive determinant for these cancer types). Unsurprisingly, age differences may also affect the outcome (Table 5). The limited analyses on follow up time were inconclusive. Male gender was a significantly negative determinant of risk of leukemia, which was in accordance with the fact that risk of leukemia was increased in female diabetes patients (RR= 1.45, 95% CI 1.06-1.99) and only slightly increased in male diabetes patients (RR= 1.12, 95% CI 1.00-1.26).

From the present literature, it was impossible to distinguish the cancer risk between T1D and T2D. Only a single study report of T1D [39], whereas some studies report of T2D. Some of the studies classified as diabetes unspecified in Table 1-3 claim to report only of T2D, however exclude T1D by age at diagnosis: excluding diabetes diagnosed at younger age than 18 [45], 20 [97], 21 [56], 25 [65] or 30 [68,71,115,139]. Nevertheless, the investigated population may consist of both T1D and T2D.

Diabetes ascertainment and cancer ascertainment (available in the electronic Supplementary Material 2) varied between studies and may, based on the meta-regression, be a determinant of the study outcome. Whether the study was hospital or population based may also affect the outcome (Table 5). These methodological differences, which may bias the results, raise the question of the necessity of uniform standards to reduce bias. In general the study quality did not determine the outcome of the pooled analysis; male gender was a significantly negative determinant of risk of leukemia, which was in accordance with the fact that risk of leukemia was increased in female diabetes patients (RR= 1.45, 95% CI 1.06-1.99) and only slightly increased in male diabetes patients (RR= 1.12, 95% CI 1.00-1.26). Adjustment for the NOS score only changed the outcome little. Some publication bias was present, with an underreporting of non-significant results from small studies. This may also affect the outcomes. Also only published data as age and BMI were collected, whereas not all studies reported these factors. This may affect the results of the meta-regression. These restrictions and limitations may affect the results, but it is implausible to be the explanation of the increased risk of cancer among diabetes patients.

CONCLUSION

The present systematic review and meta-analysis confirms the previous findings of an increased cancer risk in diabetes and extends these findings to additional cancer types. The results indicate that the risk was not modified by obesity and was thus either due to diabetes per se or other confounders. Unfortunately, important covariates as HbA1c and duration of diabetes were not available in a sufficient number of studies. It is thus difficult to determine whether the increased cancer risk was due to diabetes per se or other prognostic factors like anti-diabetic treatment.

Nevertheless, the clinical implications of this and previous studies are of importance. It is recommendable that physicians in contact with patients with diabetes are attentive to the increased cancer risk associated with diabetes. Whether the awareness should be aimed at a diabetes group receiving a specific treatment is unknown and the future results of the CARING project are awaited.

CONFLICT OF INTEREST

Frank de Vries and Anthonius de Boer are employed by Utrecht University and are conducting research under the umbrella of the Centre for Research Methods. This Centre has received unrestricted funding from the Netherlands Organisation for Health Research and Development (ZonMW), the Dutch Health Care Insurance Board (CVZ), the Royal Dutch Pharmacists Association (KNMP), the private-public funded Top Institute Pharma (www.tipharma.nl, includes co-funding from universities, government, and industry), the EU Innovative Medicines Initiative (IMI), the EU 7th Framework Program (FP7), the Dutch Ministry of Health and industry (including GlaxoSmithKline, Pfizer, and others). ML De Bruin is employed by Utrecht University and is conducting research under the umbrella of the WHO Collaborating Centre for pharmaceutical policy and regulation. This Centre receives no direct funding or donations from private parties, including pharma industry. Research funding from public-private partnerships, e.g. IMI, TI Pharma (www.tipharma.nl) is accepted under the condition that no company-specific product or company related study is conducted. The Centre has received unrestricted research funding from public sources, e.g. Netherlands Organisation for Health Research and Development (ZonMW), the Dutch Health Care Insurance Board (CVZ), EU 7th Framework Program (FP7), Dutch Medicines Evaluation Board (MEB), and Dutch Ministry of Health. None of the abovementioned companies was involved in the preparation of this manuscript. Other authors had no conflicts of interest

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PATIENT CONSENT

Declared none.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher’s web site along with the published article.

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