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

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[2-23], however it is not known whether the observed associations were due to diabetes per sé or caused by competing risks.

Associations between diabetes and cancer have been established by 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 results from #9 in the Embase search were used in this study.

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 study and between study variability. As all the measures are common effect estimates the pooled result can be interpreted as a risk ratio. Only estimates based on two or more populations were included in the meta-analysis. χ^2 tests were used to test for heterogeneity across studies. All analyses were performed in STATA 8 (StataCorp. 2003. *Stata Statistical Software: Release 8*. College Station, TX: StataCorp LP).

Risk of Bias Across Studies

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 ascertainments 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/m^2). 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

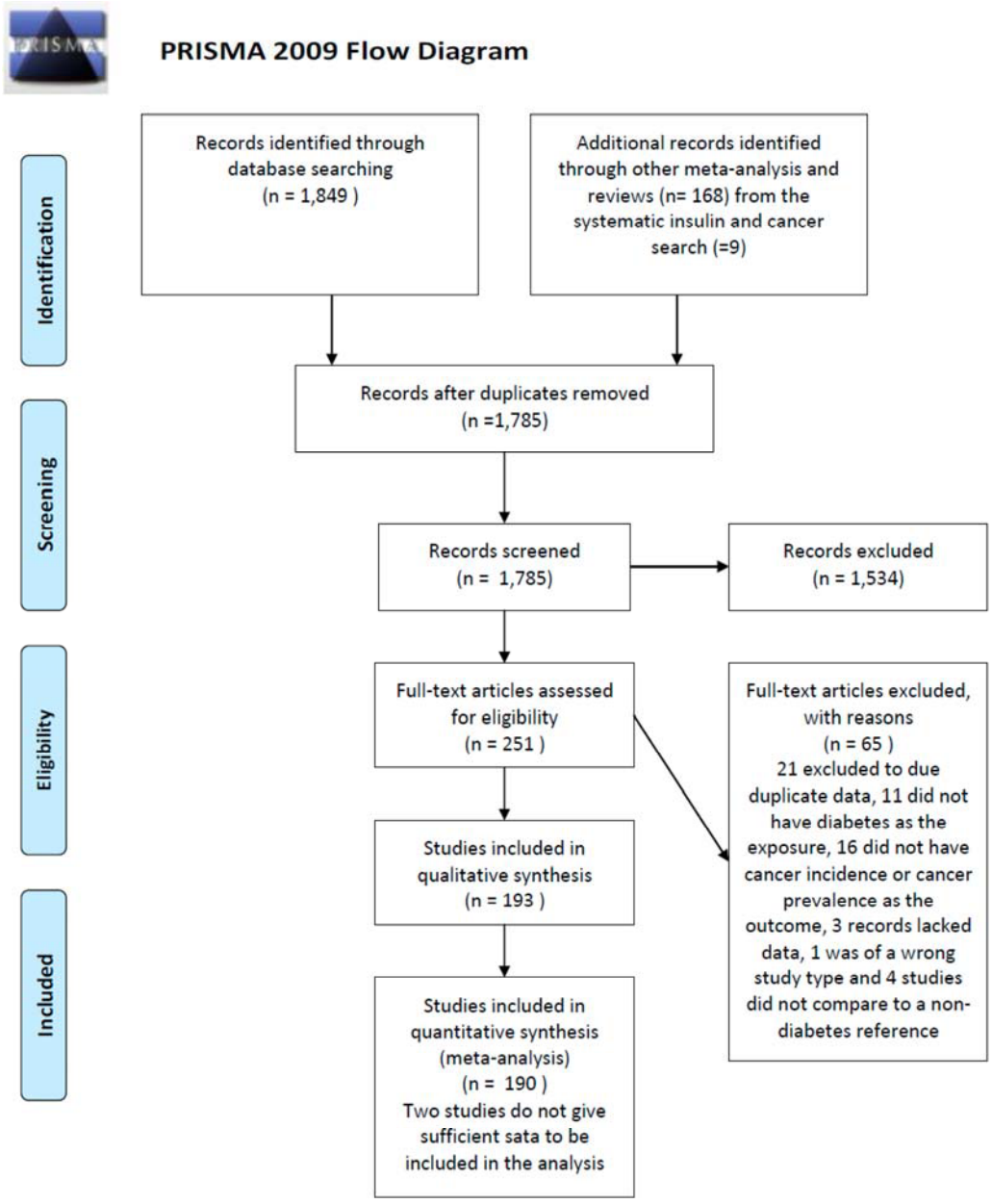


Fig. (1). PRISMA flow diagram.

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 interventional 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, esophagus 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 in- or decreased association between diabetes patients and non-diabetes was observed.

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), esophagus 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** present 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)
Cohort Studies												
Type 1 diabetes												
Zendehdel 2003 Sweden [39]	Swedish inpatient registry	Several	14.4	Population	29,187	17.1	-	External standard population	-	-	-	8
Type 2 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

(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)
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	Any	6 (total)	Population				4034 total	73.4			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			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				4

(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)
Goodman 1997 Japan [57]	LSS Cohort	Breast	8.31	Population (atomic bomb survivors)	-	-	-	22,200 (total)	-	-	-	6
Lipscombe 2006 [58] Canada	Ontario 1995-2002	Breast	4.5 median	Population	73,796	66.2	-	391,714	64.9	-	-	7
Mink 2002 US [59]	ARIC	Breast	7.1	Population	-	-	-	7,894 (total)	-	-	-	8
Reeves 2012 US [60]	SOF	Breast	14,4	Population	607			7,772				7
Sellers 1994 US [61]	IWHS	Breast	5 (total)	Population	-	-	-	36,603(total)	-	-	-	5
Weiderpass 1997 Sweden [62]	Swedish in patient registry	Breast, endometrial	6.7	Population	♂ 63,988 ♀ 70,110	♂ 59.2 ♀ 64.2	-	External standard population	-	-	-	6
Lambe 2011 Sweden [63]	AMORIS	Breast, endometrial, ovarian	11.7	Population	5,615	58.5	26.7	225,122	46.6	23.9	-	7
Bowers 2006 Finland [64]	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Colorectal	14.1 median	Population	1,226	-	-	27,757	-	-	-	7
Flood 2010 UK [65]	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

(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)
Hartz 2012 US [66]	WHI	Colorectal	8 median	Postmenopausal Population based sample	4.5% of total	-	-	150,912 (total)	63.11 (Total)	-	-	7
He 2010 US [67]	Multiethnic cohort	Colorectal	1993-2006	Population	♂15,060 ♀ 16,271	-	-	♂74,418 ♀93,393	♂60.2 ♀ 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] Sweden	COSM	Colorectal	6.2	Population				45,550 men (total)				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-trøndelag	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
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

(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)
Will 1998 US [76]	Cancer prevention study	Colorectal	1959-1972	25 states	15,487	♂57.4 ♀57.8	♂25.4 ♀26.2	850,946	♂52.9 ♀51.7	♂25.2 ♀24.2	-	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)		Chronic hepatitis or cirrhosis. Hepatitis C virus positive	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	Inteferon therapy for hepatitis c	7
Ionnau 2007 US [85]	VA 1994-2005	Liver	3.6	Veterans	452	-	-	1,668	-	-	Cirrhosis	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)	-	Inteferon 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

(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)
Lai 2012 Taiwan [96]	NHI Taiwan 1 million random sample cohort	Lung	2000-2008	Population	19624	56.4		78,496	56.5			8
Luo 2012 US [97]	WHI	Lung	11	Postmenopausal Population	8,154	64.3	32.1	137,611	63.0	27.7	-	7
Cerhan 1997 US [98]	IWHS	NHL	1986-1992	Population	-	-	-	37, 934 (total)	61.5 (total)	-	-	6
Erber 2009 US [99]	Multiethnic cohort (MEC) study	NHL	10 median	Population	13%	-	-	♂87,078 ♀105,972 (total)	-	-	-	6
Khan 2008 Europe [100]	EPIC	NHL and multiple myeloma	8.5	Population	♂5,111 ♀6,028	♂58% ♀56.8 %	-	♂134,320 ♀248,018	♂51.9 % ♀50.1 %	-	-	7
Gapstur 2012 US [101]	Cancer Prevention Study-II Nutrition Cohort	Ovary	1992-2007	Population	3,577	63.6	-	59,863	62.2	-	-	7
Chen 2011 Taiwan [102]	NHI	Pancreas	6.9 median	Population	615,532	60.1	-	614,871	60.0	-	-	9
Chow 1995 Sweden [103]	Swedish in patient register	Pancreas	6.8	Hospital	♂63,987 ♀70,109	-	-	External standard population	-	-	-	5
Gupta 2006 US [104]	Veterans Health Administration	Pancreas	1999-2004	Veterans (developed diabetes)	36,631	61.8	-	1,385,163	63.6	-	-	7
Larsson 2005 Sweden [105]	COSM and SMC	Pancreas	1997-2004	Population	-	-	-	♀37,147 ♂ 45,906 (total)	♀62 ♂ 60 (total)	♀25 ♂25.8 (total)	-	8

(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)
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
Giovannuci 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)	From a randomized controlled trial, where participants were randomized to cancer screening.	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

(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)
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 (mailing list)	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 (drivers license list)	-	-	-	34,637 (total)	-	-	-	6
Adami 1991 Sweden [122]	Uppsala In patient 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 born1949-1964 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♀ 1,571	♂54 ♀ 56	-	♂43,451 ♀ 49,652	♂51.2 ♀ 51.6	-	-	7
Jee 2005 Korea [130]	NHIC	Several	10 total	government employees, teachers and dependents (10.7% of total population)	♂5.1% ♀4.5%	-	-	♂829,770 ♀468,615 (total)	♂45.3 ♀49.6	♂23.2 ♀23.2	-	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 ♂ 499	♀ 58.5 ♂ 58.8	♀ 31.5 ♂ 30.0	11,667	-	-	-	6
Khan 2006 Japan [133]	JACC	Several	1988-1997	Population	3,307	40-79	-	53,574	40-79	-	-	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)
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	60 (cases) 48 (non-cases)	-	-	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 6 ♂21,207 (total)	♂43.3 ♀39.3	-	-	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. *Comobidity in the population examined. Body mass index (BMI), diabetes mellitus (DM), digital rectal examination (DRE), general practicioner (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 Germany [144]	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
Diabetes type unspecified												
Lawlor 2004 UK [145]	The British Women's Heart and Health Study	Breast	-	Randomly from GP	147 women with cancer	68.5	28.1	3,890 women without cancer	68.9	27.6	-	6
Sandhu 2001 UK [146]	Norfolk	Colorectal	-	Population (GP lists)	561	45-74	-	28,782	45-74	-	-	6
Tung 2010 Taiwan [35]	Tainan	Liver		Population	72	68.4	-	56,193	-	-	-	6
Moreira 2011 US [147]	Durham VA	Prostate	-	Hospital (performed prostate biopsy, high risk patient population (referred for biopsy because of elevated PSA or Abnomral DRE)))	284	64	30,4	714	63	27,7	-	5
Moses 2012 US [148]	Hospital (high risk population (referred to biopsy for elevated PSA or abnormal DRE))	Prostate		Hospital	1,045	-	-	1,265	-	-	-	5
Li 2011US [149]	BRFSS	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. *Comobidity in the population examined. Body mass index (BMI), diabetes mellitus (DM), digital rectal examination (DRE), general practicioner (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)
Case Control Studies											
Type 2 diabetes											
Khachatryan 2011 Armenia [150]	-	Breast	Population	150	55.79	29.03	152	51.11	27.67	-	6
Rollison 20078US [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	Biliary tract	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 129 ECC	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

(Table 3) contd…..

Authors	Data Source	Cancer Site	Source	Cases (n)	Age	BMI	Controls (n)	Age	BMI	Co Morbidity*	NOS-Score (0-9)
Kantor 1984 US [158]	SEER	Bladder	Population	2,982	-	-	5,782	-	-	-	6
Kravchick 2001, Israel [159]		Bladder	Hospital	252	♂71.5 ♀ 73	-	549	-	-	-	4
Mackenzie 2012 US [160]	New England	Bladder	Population	331	62	28.0	263	60	27,0	-	6
Ng 2003 UK [161]	Bedford General Hospital	Bladder	Hospital	125	-	-	80	-	-	-	5
Risch 1988 Canada [162]	Edmonton, Calgary, Toronto, and Kingston	Bladder	Population	835	35-79	-	792	-	-	-	6
Baron 2001 US [163]	Wisconsin and New Hampshire	Breast	Population	5,659	65.3	-	5,928	64.1	-	-	6
Beji 2007 Turkey [164]		Breast	Hospital	405	-	-	1050	-	-	-	3
Cleveland 2012 US [165]	Long Island Breast Cancer study project	Breast	Population	1,495	63.6	30.9	1,543	57.4	26.1		6
Garmendia 2007 Chile [166]		Breast	Hospital (mammography service)	170	56.5	28.59	170	55.18	29.23	-	5
Jordan 2009 Thailand [167]	Thai Cohort	Breast	University students	43	39 median	-	860	-	-	-	4

(Table 3) contd…..

Authors	Data Source	Cancer Site	Source	Cases (n)	Age	BMI	Controls (n)	Age	BMI	Co Morbidity*	NOS-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]		Colorectal	Population	1,192	♂67 ♀65 (median)	-	1,192	♂65 ♀65 (median)	-	-	7
Rinaldi 2008 European countries [172]	EPIC (8 countries)	Colorectal	Population	1,026	59.1 (CC) 58.2 (RC)	27.3 (CC) 27.0 (RC)	1,026	59.1 (Control CC) 58.2 (control RC)	26.9 (Control CC) 26.6 (control RC)		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 [177]	Osaka University Medical School	Endometrial	Hospital	143	53.6	-	143	53.2	-	-	5
Saltzman 2008 US [178]	Washington State	Endometrial	Population	1,303			1,779				7
Yamazawa 2003 Japan [179]	Chiba University Hospital	Endometrial	Hospital	41	-	-	123	-	-	-	5
Neale 2009 Australia [180]	Queensland 2001-2005	Esophagus	Population	1,102	-	-	1,580	-	-	-	6
Reavis 2004 US [181]	Portland VA Medical Center	Esophagus	Hospital (and dental clinic)	63	69.6	-	50 + 50 + 56	63.7 64.7 58.9	-	-	5
Rubenstein 2005 US [182]	Veterans database 1995-2003	Esophagus and gastric cardia	Veterans	311	71.2 median	-	10,154	66.3 median	-	GERD	7
Vineis 2000 Italy [183]	11 Italian areas	Haemapoietic	Population	2,669	56.1	-	1,718	54.9	-	-	6
Stott-Miller 2012 (38)	Pooled analysis	Head and neck	Mixed	6.448	-	-	13.747	-	-	-	4
Davila 2005 US [184]	Surveillance Epidemiology and End-Results Program (SEER)	Liver	Population	2,061	76.1	-	6,183	76.4	-	-	8
El-Serag 2001 US [185]	1997-1999 VA	Liver	Hospital (veterans)	823	62	-	3,459	60	-	-	4

(Table 3) contd…..

Authors	Data Source	Cancer Site	Source	Cases (n)	Age	BMI	Controls (n)	Age	BMI	Co Morbidity*	NOS-Score (0-9)
Hassan 2002 US [186]	MD Anderson Cancer center 1994-1995	Liver	Hospital	115	59.5	-	230	59.1	-	-	7
Hassan 2010 US [187]	MD Anderson Cancer center 2000-2008	Liver	Hospital	420	63	-	1,104	60	-	-	7
Matsuo 2003 Japan [188]	Kyushu	Liver	Population	222	♂63.6. ♀ 64.3		222	♂ 63.5. ♀ 64.1			6
Tung 2010 Taiwan [35]	Tainan	Liver	Population	72	68.4	-	144	68.2	-	-	7
Tung 2010 Taiwan [35]	Tainan	Liver	Population	72	68.4	-	144	67.7	-	Hepatitis C infection	7
Yuan 2004 US [189]	Los Angeles county 1984-2001	Liver	Population	295	60.6	-	435	60.1	-	-	5
Fortuny 2005 Spain [190]		Lymphoma	Hospital	565	-	-	601	59 (total)	-	-	6
Cartwright 1988 UK [191]	1979-1984 Yorkshire	NHL	Hospital	437	-	-	724	-	-	-	4
Cerhan 2005 US [192]	Detroit, LA, Seattle 1998-2000	NHL	Population	759	56.6	27.7	589	56.9	27.7	-	6
Lin 2007 Taiwan [193]	CGMH	NHL	Population	242	59 median at diagnosis	-	71,379	-	-	-	6

(Table 3) contd…..

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	Pancreas	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)	Pancreas	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 Zeeland [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

(Table 3) contd…..

Authors	Data Source	Cancer Site	Source	Cases (n)	Age	BMI	Controls (n)	Age	BMI	Co Morbidity*	NOS-Score (0-9)
Hiatt 1988 US [204]	KPMPC (1960-1984)	Pancreas	Member of medical care program	49	67.6	-	12,104	-	-	-	6
Jain 1991 Canada [205]	Toronto 1983-1986	Pancreas	Population	249	64.6	-	505	64.8	-	-	6
Kalapothaki 1993 Greece [206]	Athens 1991-1992	Pancreas	Population	181	-	-	181; 818 (2 control groups)	-	-	-	5
Li 2011 US [207]	Three previous studies-pooled analysis	Pancreas	Population	2,192	63		5,113	63			7
Maisonnueve 2010 Australia, Canada, Poland [208] Netherlands	Multicenter (pooled analysis)	Pancreas	Population	823	-	-	1,679	-	-	-	5
Matsubayashi 2011 Japan [209]	Shizuoka Cancer center	Pancreas	Hospital	577	64.9		577	64.9			5
Mizuno 1992 Japan [210]	Japanese university hospitals	Pancreas	Hospital	124	-	-	124	-	-	-	6
Baradaran 2009 Iran [211]	Multicenter	Prostate	Hospital	194	71.06	26.3	317	66.5	26.8	-	4
Coker 2004 US [212]	South Carolina Central Cancer Registry (SCCCR) (1999-2001)	Prostate	Population	407	65-79	-	393	65-79	-	-	6
Gong 2006 [213]	PCPT	Prostate	Previous study	1,936	63.7	27.6	8,322	62.6	27.7		7

(Table 3) contd…..

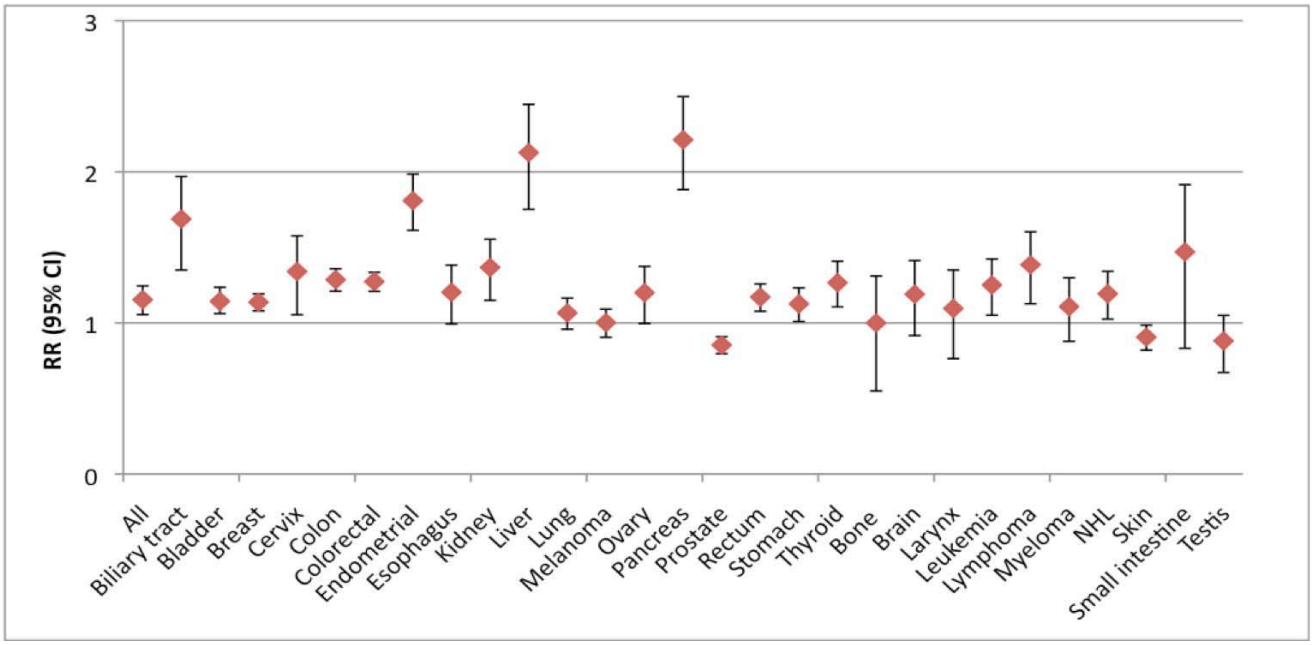
Authors	Data Source	Cancer Site	Source	Cases (n)	Age	BMI	Controls (n)	Age	BMI	Co Morbidity*	NOS-Score (0-9)
Gonzales-Perez 2005 UK [214]	GPRD 1995-2001	Prostate	Population	2,183	72 median	-	10,000	72 median	-	-	8
Lightfoot 2004 Canada [215]	Ontario 1995-1999	Prostate	Population	760	-	-	1,632	-	-	-	5
Rosenberg 2002 US [216]	University Medical Center in New York City	Prostate	Hospital	320	69.6	-	189	68.1	-	-	6
Tavani 2002 Italy and Greece [217]	Milan Pordenone and Athens, Greece	Prostate	hospital	608	-	-	1,008	-	-	-	6
Turner 2011 UK [218]	Protect study	Prostate	Population	1,291	62.2	26.7	6,479	62.0	26.9	-	7
Zhu 2004 US [219]	US Physicians' Health Study	Prostate	Physicians	1,110	-	24.9	1,110	-	24.9	-	6
Attner 2012 Sweden [220]	Swedish cancer registry (2003-2007)	Several	Population	19,756	45-84	-	147,324	45-84	-	-	7
Bosetti 2011 Italy and Switzerland [221]	1991-2009	Several	Hospital	230-2390 depending on cancer type	56-66 depending on cancer type		12,060	56-65 depending on cancer type			7
Jorgensen 2012 Denmark [222]	Funen county	Several	Population	6,325	78 median	-	25,299	78 Median	-	-	7
Kuriki 2007 Japan [223]	HERPACC 1989-2000	Several	Hospital	♂5,341 ♀6,331	♂65.3 ♀60.6	♂22.7 ♀22.4	♂14,199 ♀ 33,569	♂60.6 ♀57.0	♂23.0 ♀22.1	-	6

(Table 3) contd…..

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) (1957-1965)	Several	Hospital	14,910	-	-	4,838	-	-	-	3
Rousseau 2006 Canada [225]	Montreal 1979-1985	Several	Population	3,107	-	-	509	59.6	58.2 % BMI>25	-	6

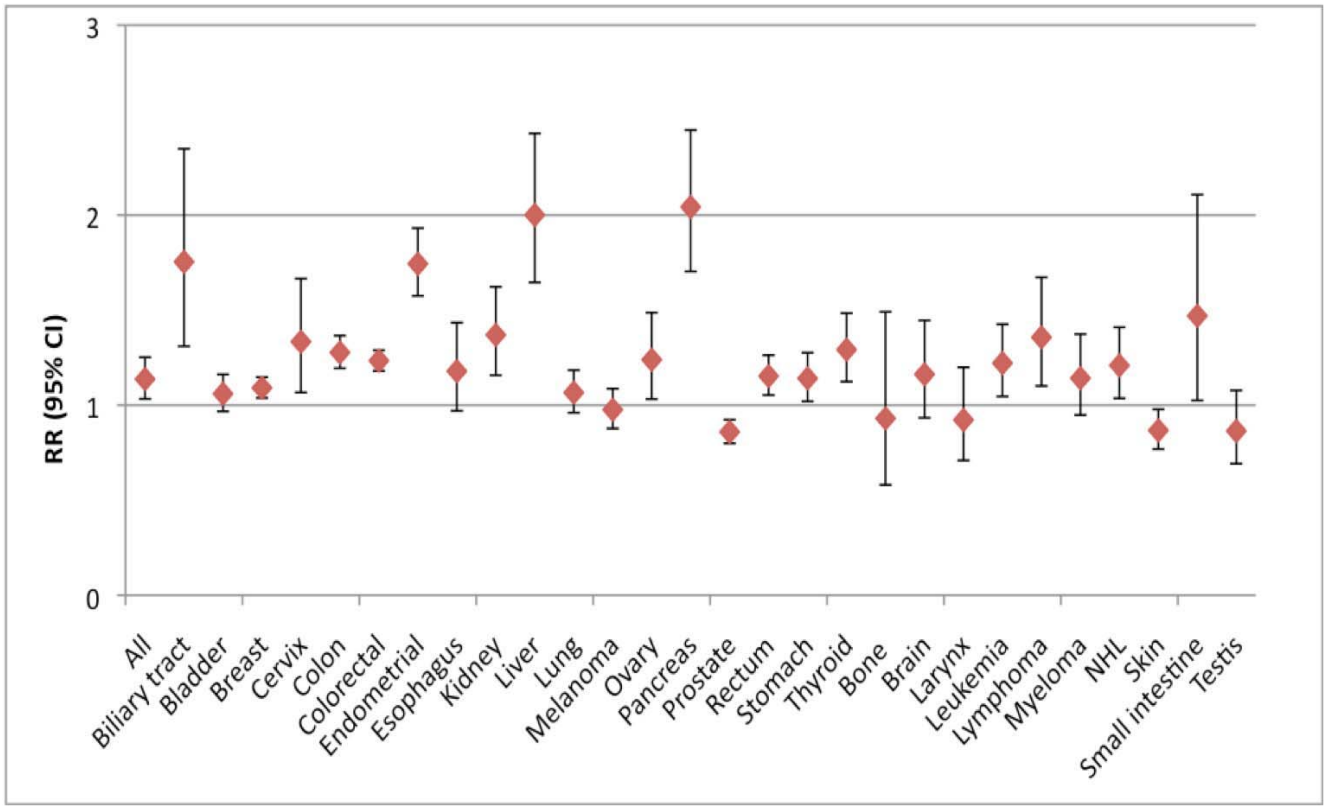
Age and BMI are provided by means if nothing else is specified. Follow up years are provided by means, medians or follow up period. *Comobidity in the population examined. Body mass index (BMI), diabetes mellitus (DM), digital rectal examination (DRE), general practicioner (GP), hepatitis C virus (HCV),. Total: For the whole group or the complete study period.

(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.



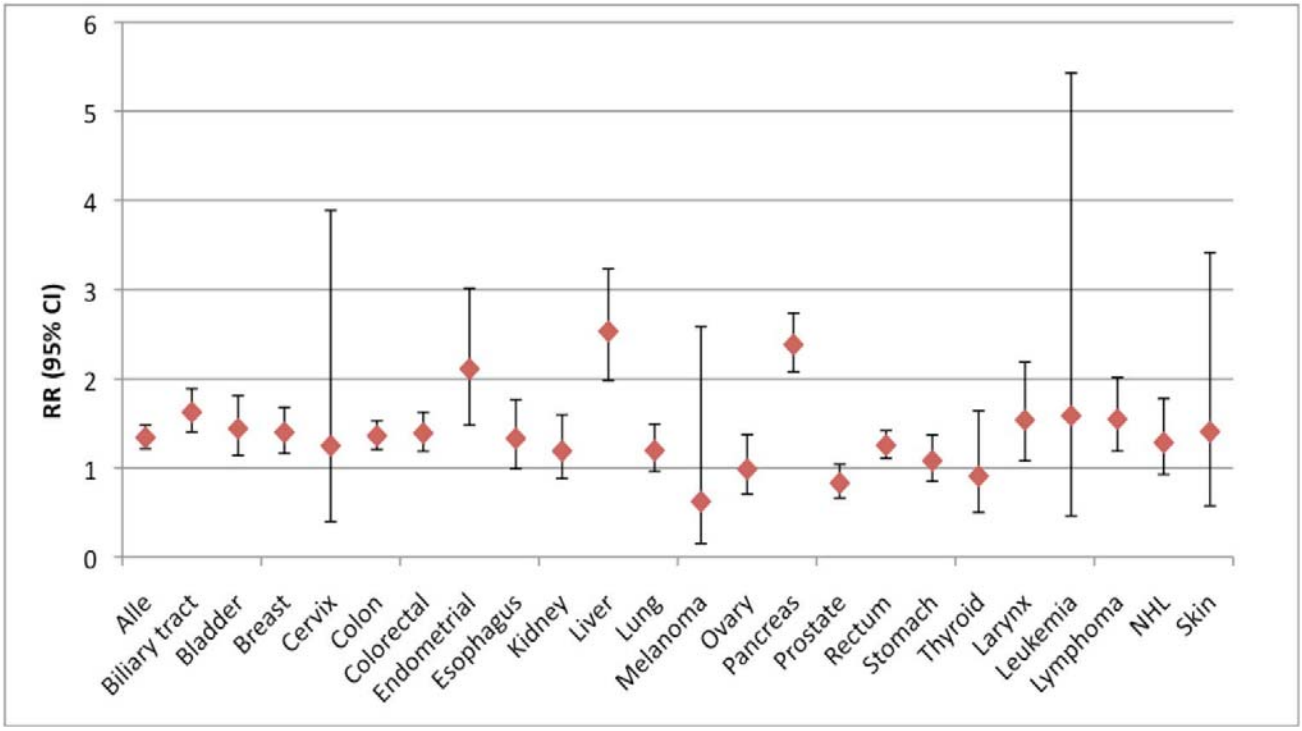
Non Hodgkin lymphoma (NHL), Nervous system (Brain), RR (risk ratio)

Fig. (2). Plot of the pooled analysis of all populations of the risk of cancer among diabetes patients compared to a non-diabetes population.



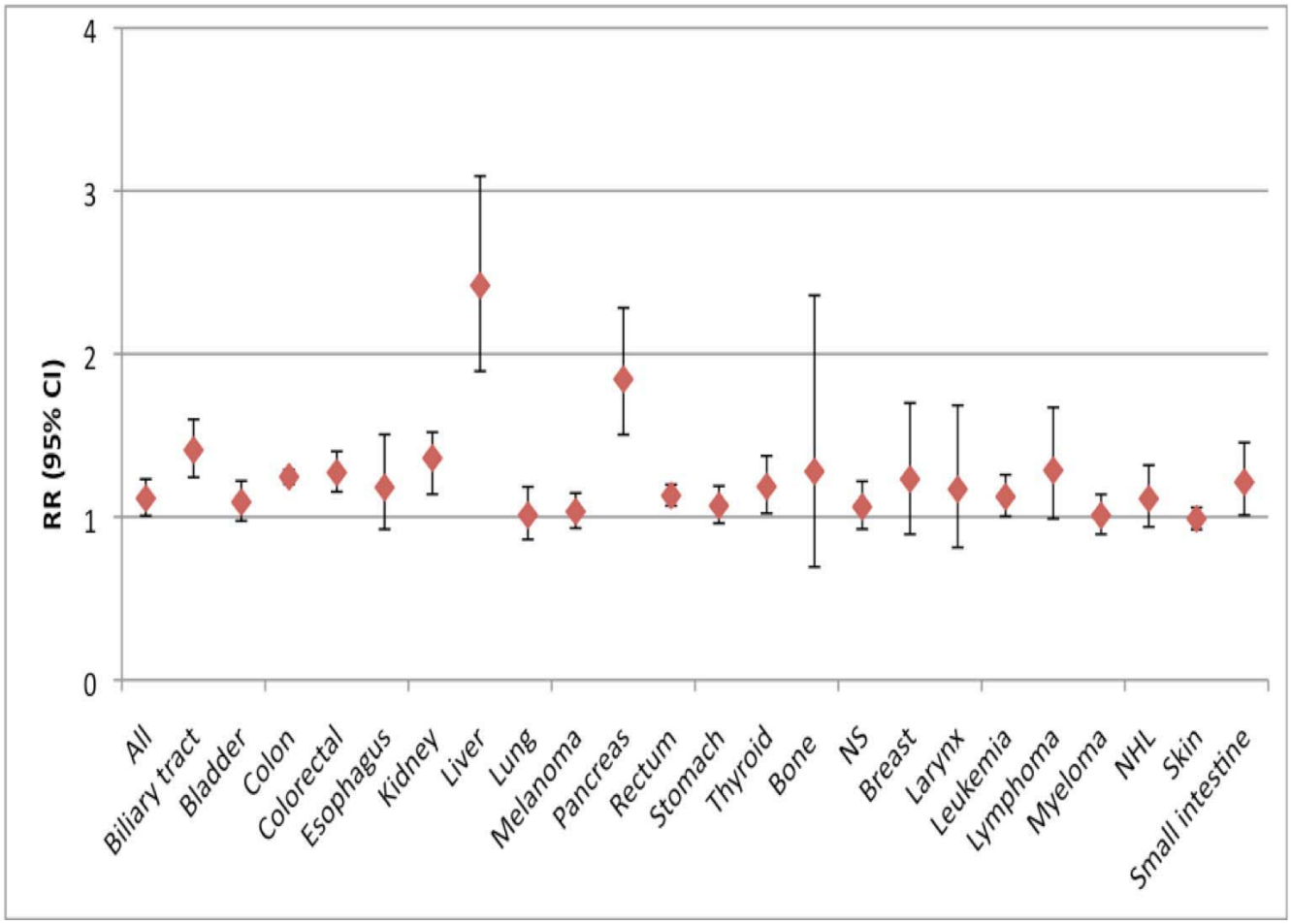
Non Hodgkin lymphoma (NHL), Nervous system (Brain), RR (Risk ratio)

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.



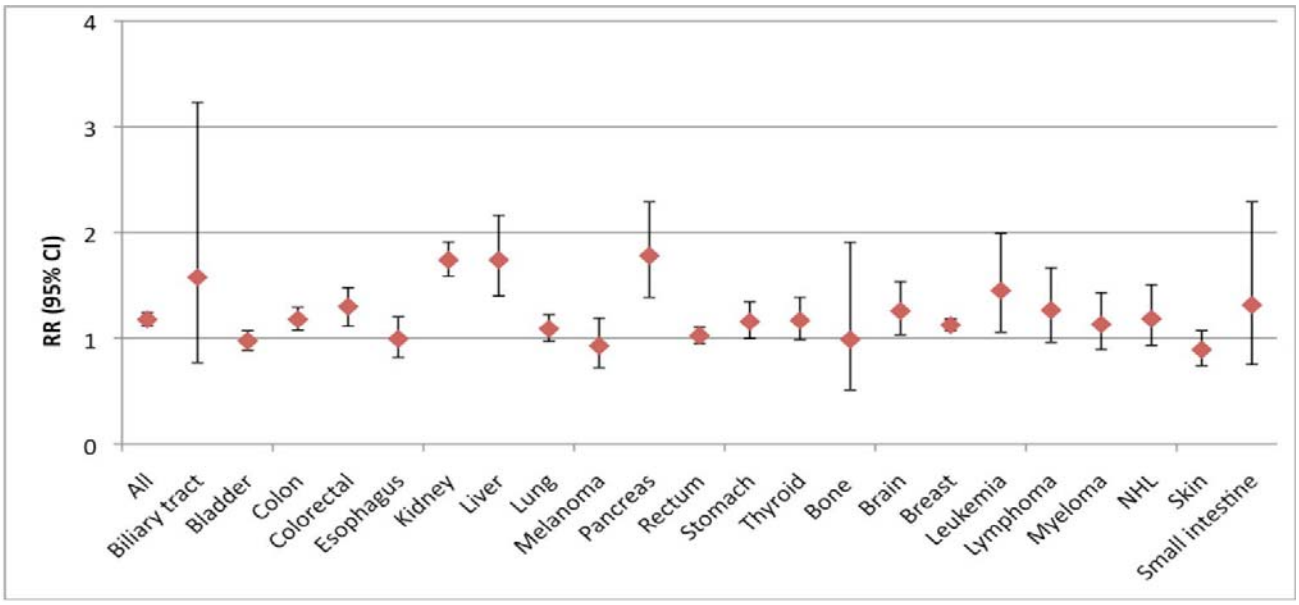
Non Hodgkin lymphoma (NHL), RR (Risk ratio)

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.

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 lymfoma	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.

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

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

Cancer Site	Gender*	Age (Years)*	BMI (kg/m^2)*	Diabetes Type*	Follow Up (Years) *	Source£	Adjustment (Adjustment for Age *vs* Adjustment for Age and BMI)£	Diabetes Ascertainment£	Cancer Ascertainment£	NOS*
Any	0 (5)	- (5)				0 (42)	0 (42)	0 (42)	0 (42)	- (5)
Biliary tract and gall bladder	0 (7)	0 (7)				- (25)	+ (25)	0 (25)	0 (25)	0 (7)
Bladder	0 (5)	- (5)				0 (33)	0 (33)	0 (33)	0 (33)	0 (5)
Bone	0 (4)					0 (7)	0 (7)			0 (4)
Breast		0 (7)	0 (7)	0 (7)		0 (60)	0 (60)	0 (60)	0 (60)	0 (7)
Cervix		0 (6)		0 (6)		0 (17)	+ (17)	0 (17)	0 (17)	0 (6)
Colon	0 (13)	0 (13)		- (13)		0 (40)	0 (40)	0 (40)	0 (40)	0 (13)
Colorectal	0 (7)	0 (7)	0 (7)	- (9)**		0 (47)	0 (47)	0 (47)	0 (47)	0 (7)
Endometrial		0 (5)**	0 (4)		0 (5)**	0 (26)	0 (26)	0 (26)	0 (26)	0 (5)**
Esophagus	0 (5)	- (5) C				0 (27)	0 (27)	0 (27)	0 (27)	- (5)
Kidney	0 (5)	0 (5)	0 (4)			0 (31)	0 (31)	+ (31)	0 (31)	0 (5)
Larynx	0 (6)					0 (10)	- (10)	+ (10)	0 (10)	0 (6)
Leukemia	- (5)	0 (5)				0 (18)	0 (18)	0 (18)	0 (18)	0 (5)
Liver	0 (7)**	- (10)**CC	0 (4)			0 (58)	0 (58)	0 (58)	0 (58)	0 (7)**
Lung	0 (6)**	0 (6)**	- (5)			0 (42)	0 (42)	0 (42)	0 (42)	- (6)**
Lymphoma	0 (9)					- (18)	0 (18)	0 (18)	0 (18)	0 (9)
Melanoma	0 (12)					0 (16)	0 (16)		0 (16)	0 (12)
Myeloma	0 (6)					- (11)	+ (11)	0(11)	0 (11)	0 (6)
Nervous system	0 (12)					0 (17)	0 (17)	0 (17)	0 (17)	0 (12)
NHL	0 (13)					- (26)	+ (26)	0 (26)	0 (26)	0 (13)
Ovary		0 (7)				0 (19)	+ (19)	0 (19)	- (19)	0 (7)
Pancreas	0 (7)**	0 (7)**	0 (4)			0 (63)	0 (63)	0 (63)	0 (63)	0 (7)**
Prostate		+ (5)***0	0 (5)***	0 (12)		0 (26)	+ (26)	0 (26)	- (26)	+ (5)***
Rectum	0 (11)**	0 (11)**	0 (3)	0 (11)**		0 (35)	+ (35)	0 (35)	0 (35)	0 (11)**
Skin	0 (10)					0 (18)	0 (18)	0 (18)	0 (18)	- (10)
Small intestine	0 (5)					- (6)		0 (6)		0 (5)
Stomach	0 (7)	- (7) C			0 (6)	0 (35)	0 (35)	0 (35)	0 (35)	0 (7)
Testes										0 (6)
Thyroid	0 (6)	0 (6)			0 (5)	0 (20)	+ (20)	0 (20)	0 (20)	0 (6)

+: 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.

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

increased [207]. Normalization of the cancer risk occurs10 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 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 (Table **5**), however study quality based on NOS score was a significantly negative determinant risk of lung cancer and a significantly positive determinant of prostate cancer; meaning that the risk ratios drew closer towards 1 for both cancers. 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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