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Use of Insulin and Insulin Analogs and Risk of Cancer — Systematic Review and Meta-Analysis of Observational Studies

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Abstract: *Background*: An association of insulin use and risk of cancer has been reported but evidence is conflicting and methodological issues have been identified.

Objective: To summarize results regarding insulin use and cancer risk by a systematic review and meta-analysis of cohort and case-control studies examining risk of cancer associated with insulin use in patients with diabetes.

Data *Sources*: Systematic literature search in 5 databases: PubMed, Embase, Web of Science, Scopus and Cochrane Library.

Study Eligibility Criteria (*PICOS*): Population: diabetes patients. Exposure: Users of any exogenous insulin. Comparison: Diabetes patients with or without use of antidiabetic drugs. Outcome: Any incident cancer. Study Design: Cohort and case-control studies.

Results: 42 eligible studies examined risk of any cancer and 27 site-specific cancers. Results of individual studies were heterogeneous. Meta-analyses were significant for: Insulin *vs* No Insulin: Increased risk for pancreas, liver, kidney, stomach and respiratory cancer, decreased risk for prostate cancer. Insulin *vs* Non-Insulin Antidiabetics: Increased risk for any, pancreatic and colorectal cancer. Glargine *vs* Non-Glargine Insulin: Increased risk for breast cancer, decreased risk for colon cancer.

Limitations: Few studies available for most cancer sites and exposure contrasts, and few assess effect of dose and duration of exposure. Methodological issues in several studies. Availability of confounders.

Conclusions: Insulin use was associated with risk of cancer at several sites. Cautious interpretation of results is warranted as methodological issues and limitations in several of the included studies have been identified. Choice of study design may have a profound effect on estimated cancer risk.

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

INTRODUCTION

Rationale

Associations between diabetes mellitus and increased risk of cancer at several sites have been established [1-3]. It remains unclear whether this relationship between diabetes and cancer is direct, e.g. because of hyperglycemia, or if it is mediated through underlying biologic factors like insulin resistance and hyperinsulinemia, or if it is indirectly linked through common risk factors such as obesity. Insulin is a growth factor, and it is biologically plausible that high levels of endogenous insulin or exposure to exogenous, administered insulin could stimulate neoplastic growth [4, 5]. In recent years, several studies have reported modification of cancer risk by use of specific antidiabetic drugs. A decreased risk associated with use of metformin has been reported in meta-analyses while results for thiazolidinedione are not conclusive [6-8]. Results from observational studies published in 2009 raised concerns of

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a link between insulin use and risk of cancer, but the results of these initial studies were inconclusive and conflicting [9-11]. Publication of many studies assessing risk of cancer at different sites from other data sources has ensued. Several of these observational studies have been hampered by methodological issues and did not take into account dose, duration and timing of insulin exposure or lacked information on important confounders [10, 12-14]. In addition, most studies have been too small for robust quantification of cancer risk, specially for examining cancer sites individually. The ability to study cancer at specific sites individually is important because cancer is not a homogenous disease and different pathways are involved in the aetiology for different subtypes of cancer [2].

Existing evidence from randomized controlled trials (RCT) is also limited. Two meta-analyses of RCT data published in the wake of the initial observational studies published in 2009 did not find an increased risk for insulin glargine and detemir [15, 16]. However, these studies were rather small for studying a rare event such as cancer and were of limited duration. A larger RCT study with 6 years duration that assessed insulin glargine exposure and had cancer incidence as a secondary outcome reported no increased risk of cancer overall and no significant results for site-specific cancers [17]. However, the general limitations of RCTs regarding representativeness of the study population apply [5], and this trial may have been too small to properly quantify risk of cancer at specific sites.

Clinical evidence suggests that there may be a link between use of exogenous insulin and risk of cancer at some sites but results are conflicting and inconclusive. The CAncer Risk and INsulin analogs (CARING) project aims to assess possible carcinogenic effects of insulin use combining data from health care databases in six European countries. As part of the CARING project, the present review and meta-analysis was undertaken to summarize published results on the topic.

Objective

To perform a systematic review and meta-analysis of published cohort and case-control studies that examined the risk of any type of cancer associated with use of exogenous human insulin or insulin analogs in patients with type 1 or type 2 diabetes.

METHODS

Protocol and Registration

The present study was developed according to the PRISMA guidelines [18], and supplemented by guidance from the Cochrane Collaboration Handbook [19]. The protocol was registered on Prospero (registration number CRD42012002428) [20].

Eligibility Criteria

The following PICOS eligibility criteria were applied:

Population: diabetes patients.

Exposure: diabetes patients using any exogenous human insulin or insulin analogues.

Comparison: diabetes patients, with or without use of antidiabetic drugs (i.e. use other types of insulin, non-insulin antidiabetic drugs, not use any insulin, or not use any antidiabetic drugs). Studies that only had persons without diabetes as comparator group were excluded.

Outcome: incident cancer at specific sites or cancer at any site as a composite outcome. Studies that only report the risk of cancer-related mortality are not included.

Study design: cohort and case-control studies.

The studies had to report sufficient data for proper evaluation of the study population, exposure, comparator and outcome to be considered for inclusion in the present review.

Information Sources

We performed a systematic literature search in 5 databases: Medline at PubMed, Embase, Scopus, Web of Science and The Cochrane Library. The last search was performed on 27 November 2012. The CARING project group concurrently performed a systematic review on risk of cancer in persons with diabetes compared to persons without diabetes [21]. Records from that review were assessed for inclusion in the present review.

Search Strategy

The specific search strategy for each database is presented in Supplementary Material 1. Search terms for diabetes, insulin and cancer (or similar terms) were applied in all searches, while terms for risk or incidence were added in free text searches. For Scopus and Web of Science, free-text searches were used. For Medline, Embase and Cochrane, we used thesaurus (MESH and Emtree terms). In addition, we performed a free text search in Medline, Embase and Cochrane Library limited to references published during the last year in order to identify references not yet indexed with MESH and Emtree terms. Except for limiting the free text search to publications from the last year, no restrictions were used on publication date, language or publication status.

Study Selection and Collection Process

ØK and VH developed the search strategy for each database in collaboration with a research librarian. ØK performed the final search in the databases, compiled a mutual reference list for all searches and removed duplicate references. ØK and JSL independently screened title and abstract of records for eligibility, and records identified by either of the reviewers as eligible for inclusion were retrieved in full text. If a conference abstract was deemed eligible for inclusion, a full text article was searched for in databases and included for full text reading if found. ØK and JSL independently assessed the full text records for inclusion and records that ØK and JSL agreed on were included in the review. Disagreements were resolved by discussion and by conferring with a third reviewer (PV).

Data Items

From each study, information was retrieved on risk of cancer, cancer site, definitions of exposure and comparator group (reference), covariates, study design, source population, data sources, and patient characteristics including diabetes type, age group and geographical location

(country). Data was extracted by ØK and validated by JSL and disagreements were resolved by discussion.

Risk of Bias in Individual Studies

Risk of bias was assessed by the Newcastle Ottawa Scale (NOS) [22]. All studies were scored by two reviewers (ØK, JSL) and disagreement resolved by discussion and by conferring a third reviewer (PV). The user-defined items required in the NOS score were defined as follows (Supplementary Material 2): age was the most important adjustment factor, the exposed in cohorts should be representative of the average "diabetic population using insulin", minimum average exposure duration was 5 years, and loss to follow-up less than 10%. A conservative approach was chosen if information to score specific items were not available in the article, i.e. no points were given on an item if information was uncertain or missing.

Summary Measures and Synthesis of Results (Meta-Analysis)

Initially, the types of exposure-comparator contrasts and cancer sites examined in records included in the systematic review were assessed by inspecting the summary tables (Supplementary Material 3). The contrasts can be categorized as: 1) insulin use versus no insulin use; 2) insulin use versus use of non-insulin antidiabetic drugs; 3) users of insulin A versus users of insulin B; and 4) users of insulin A versus users of insulin B or no insulin. Studies that examined contrast 1 and 2 were included in the pooled analyses while contrast 4 was omitted because of few populations. For contrast 3, glargine insulin users versus non-glargine insulin users was the most frequently used contrast and was included in pooled analyses.

Separate pooled analyses were performed for each combination of cancer site and exposure contrast (three selected) that had more than one study population available. One study could contribute more than one population to an analysis, e.g. if the presented risk estimate in the original study was stratified by gender. For studies that published several risk estimates for the same cancer site and exposure contrast (e.g. for different study designs), the following algorithm was applied for choosing which estimate to include (in order of importance): 1) estimates with prior cancer excluded was preferred over estimates adjusted for prior cancer: 2) intention-to-treat analysis preferred over other designs (e.g. as-treated analysis); 3) exposure categorized as exclusive use was preferred (monotherapy, e.g. "glargine only" preferred over "glargine and non-glargine"); 4) estimates without latency period preferred. If no decision could be made from this algorithm, reviewer 1 (ØK) made a final decision on which estimate to include. Estimates from statistical models adjusted for more covariates were preferred. Risk estimates stratified by dose or duration of insulin exposure were not included in pooled analyses.

Hazard ratio, incidence risk ratio, rate ratio and odds ratio as summary measures for the risk of incident cancer with 95% confidence intervals were retrieved from each study. These measures were weighted based on the inverse of the standard error of the risk estimator from the individual studies. Chi square test were used to measure heterogeneity across studies. DerSimonian and Laird random effects models [23] was used in the main analyses regardless of the result of the test for heterogeneity. Additional pooled analyses with a fixed effect model were performed if studies did not exhibit statistically significant heterogeneity. Data were prepared in Microsoft Excel 2010 and analyzed in Stata version 8.

Risk of Bias Across Studies in Meta-Analysis

Risk of publication bias across studies was assessed by Egger's regression analysis [24] in Stata version 8.

RESULTS

Study Selection

The selection process is shown in Fig. (**1**). Five databases were searched and 2,285 records were identified. After removal of duplicates and inclusion of 5 records from other sources, 1,578 records were screened. After screening of title and abstract by reviewer 1 (ØK) and reviewer 2 (JSL), 135 records were retrieved in full text. 42 records [25-66] were eligible for inclusion in the systematic review, while the remaining 93 records were excluded during full text reading for the following reasons: no insulin exposure group (25%), population includes non-diabetic patients (24%), only conference abstract available (16%), outcome was not incident cancer (12%), duplicate use of data from one source (10%), study type (9%), ambiguous or insufficient reporting of definitions (5%). For the category "duplicate use of data", records were excluded as they were likely to be using the same data as one of the records included in the review and study the same cancer site and exposure contrast. These excluded records [67-75] and the overlapping records that are included are listed in Supplementary Material 7. The records [76-80] that were excluded because of insufficient reporting of definitions are likely to fulfill the criteria for inclusion in the present review but cannot be properly classified. The definition of the comparator group was not clearly defined, or contradicting information regarding the comparator group was found in tables and text of these studies.

Study Characteristics and Risk of Bias Within Studies

Tables **1** and **2** present the characteristics of the studies included in the systematic review for cohort and case-control studies, respectively. 27 cohort studies [25-51] and 15 case-control studies (9 nested case-control studies) [52-66] were included in the systematic review.

Risk of Bias Within Studies

The NOS score for each study is presented in Tables **1** and **2**. The highest NOS score was 9 and the lowest score was 4 (attainable score was 0-9). Among 27 cohort studies, 1 had NOS 6 and the other 26 studies had NOS score 7-9, i.e. of fair quality according to NOS. Among the 15 case-control studies, 5 studies had NOS 4-6 and all of these were "traditional" case-control studies (i.e. not nested). The other case-control studies had NOS score 7-9.

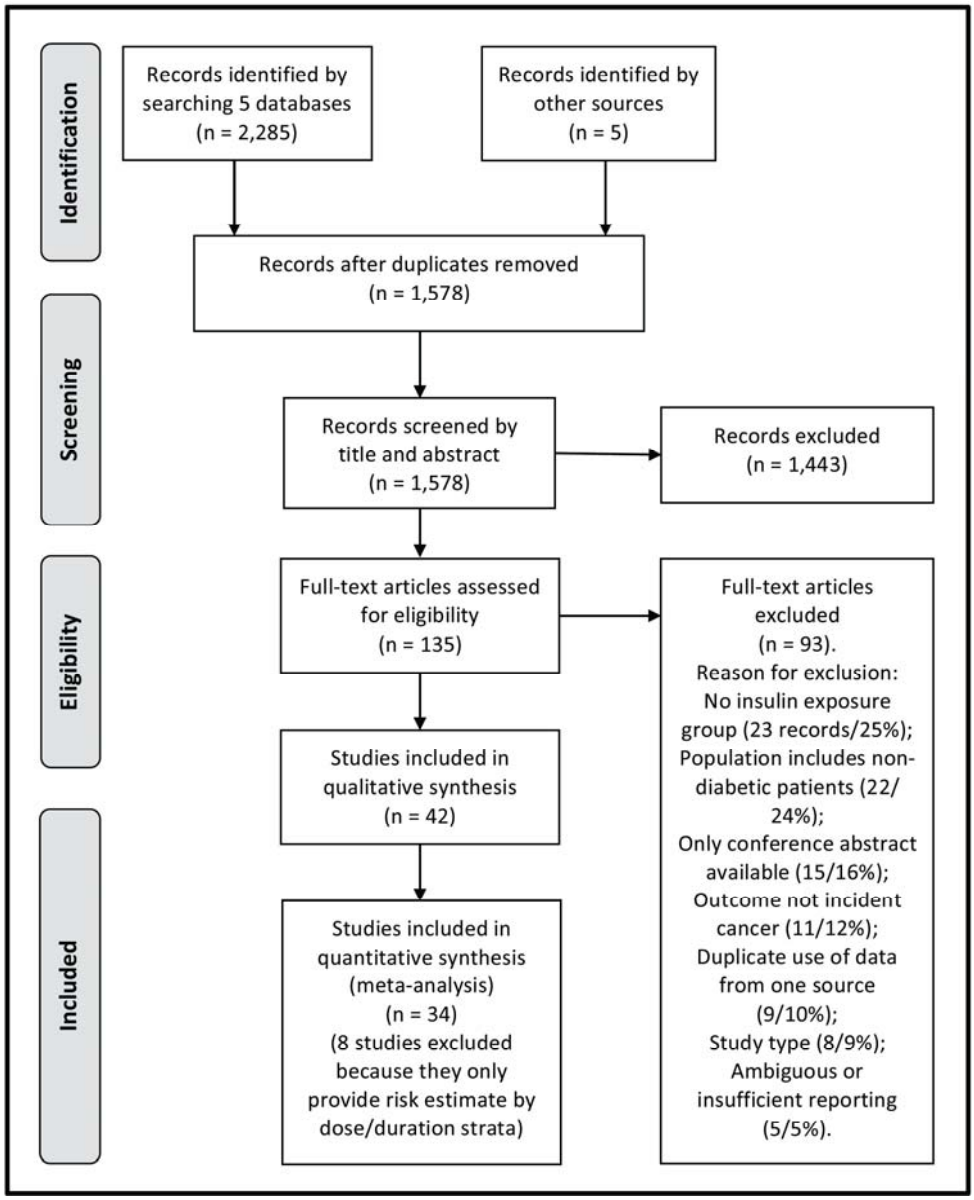

Fig. (1). Flow diagram for the study selection process (PRISMA).

Results of Individual Studies

In the summary tables all cancer sites are presented together (Supplementary Material 3). Several studies have more than one risk estimate presented for each cancer site and exposure contrast because the study reported results for several study designs (e.g. with or without latency period, intention-to-treat and as-treated analyses), or reported both an overall risk estimate as well as risk by strata of dose/duration of insulin exposure. Results of individual studies are presented in Supplementary Material 4 separately for the site-specific cancers examined and for any cancer as a composite outcome. Only the preferred risk estimate for each combination of cancer site and exposure contrast according to the algorithm given in Methods is presented.

Cancer at any site and at the following 13 specific sites was examined in more than one study per exposure contrast and was eligible for inclusion in pooled analyses: breast, prostate, stomach, pancreatic, liver, colorectal, colon, rectal, respiratory, bladder, kidney, melanoma, and non-Hodgkin's lymphoma (NHL). The results for these cancer sites (Supplementary Material 4) reveals substantial heterogeneity of results, as point estimates for risk were spread both above and below unity (RR=1) for most cancer sites and exposure contrasts. More consistent results (point estimates) may be present for the exposure contrast insulin versus no insulin for any cancer (3 of 4 populations had point estimate above unity, and with statistical significance), pancreas (7 of 8 populations above unity, 6 significant), liver (5 of 6 populations above unity, 4 significant), stomach (3 of 3 populations above unity, 3 significant), respiratory (5 of 6 populations above unity, 4 significant), bladder (4 of 5 populations above unity, 1 significant), kidney (4 of 4 populations above unity, 2 significant), and prostate cancer

Table 1. Characteristics of Cohort Studies Included in the Systematic Review (27 Records)

Author (Country)	Study Design	Study Period	Data Source Population	Source Population	Diabetes Type	Data Source Exposure	New/ Prevalent Drug User	Data Source Outcome	Covariates	NOS
Blin 2012 (France) [25]	cohort	2003-2010	insurance database	nationwide	DM2	insurance database (claims)	new	insurance database	Medication possession ratio of insulin; age; sex; DM duration; DM type; ad drugs; comorbidities; all ATC codes (1st level);	8
Campbell 2010 (USA) [26]	cohort	1992-2007	Self-reported questionnaire	21 states	DM2	Self-reported questionnaire	prevalent	Self-reported questionnaire	sex (separate models); age; bmi; physical activity; NSAIDs; alcohol; family history colorectal cancer; endoscopy history; education;	6
Carstensen 2012 (Denmark) [27]	cohort	1995-2009	Diabetes register	nationwide	Unspecified	Diabetes register or prescription database	new	Cancer register	age; sex (separate models);calendar time; date of birth;	9
Chang 2011 (Taiwan) [28]	cohort	2004-2007	insurance database	nationwide	DM2	insurance database (claims)	new	Cancer register	age; sex; dose of fast-acting insulin; metformin; sulfonylurea; alpha-glucosidase inhibitors; tzd; glinides; fast-acting insulin; premixed insulin; detemir; diabetes-related complications; comorbidities inpatients/outpatient; statins; aspirin; health service utilization; outpatient visits diabetes; outpatient visits non-diabetes; examinations various; physician characteristics; initiation year insulin;	8
Colhoun 2009 (Scotland) [29]	cohort	2002/3-2005	Diabetes register	nationwide	unspecified/ DM2/DM1 (varies by analysis)	Diabetes register	new/ prevalent (varies by analysis)	cancer register and causes of death register	varies by cancer site, design and model: prior cancer; age; sex; DM type; calendar year; bmi; hba1c; DM duration; smoking; diastolic bp; systolic bp; deprivation; metformin; sulfonlyurea; other oad;	7/8*
Currie 2009 (UK) [30]	cohort	2000-?	Physician database	nationwide	DM2	Physician database (prescribed)	new	Physician database	age; sex; prior cancer; smoking;	7/8*
Fagot 2012 (France) [31]	cohort	2007-2010	insurance database	nationwide	DM2	insurance database (claims)	new	Hospital records database	age; sex; DM duration; metformin; pioglitazone; rosiglitazone; sulfonylurea; other niad;	8

(Table 1) contd…..

Author (Country)	Study Design	Study Period	Data Source Population	Source Population	Diabetes Type	Data Source Exposure	New/ Prevalent Drug User	Data Source Outcome	Covariates	NOS
Ferrara 2011 (USA) [32]	cohort	1997-2005	Diabetes register	Northern California	Unspecified	pharmacy database (dispensed)	prevalent	Cancer register	age; sex; HbA1c (baseline); DM duration; oad (pioglitazone, other tzd (almost exclusively troglitazone), metformin, insulin, sulfonylurea, and other oral agents (e.g. miglitol, acarbose, nataglinide, repaglinide)); year cohort entry; ethnicity; income; smoking; creatinine; congestive heart failure; new DM diagnosis;	8
Hemkens 2009 (Germany) [33]	cohort	2001-2005	insurance database	nationwide	Unspecified	insurance database (claims)	new	insurance database	age; sex; dose; oad; federal state; year first insulin; drug use (gastrointestinal agents, ACE, antiarrhythmic, corticosteroids, parathyroid gland drugs, cytostatics for non-malignant disease);	8
Hense 2011 (Germany) [34]	cohort	2003-2008	insurance database	Munster district	DM2	insurance database (claims)	prevalent	Cancer register	age; sex; DM duration; bmi;	8
Hsieh 2012 (Taiwan) [35]	cohort	2000-2008	insurance database	random sample of nationwide database	DM2	insurance database (claims)	prevalent	insurance database	age; sex;	9
Kostev 2012 (Germany) [36]	cohort	2000-2011	Physician database	ns (IMS Disease Analyzer, covers 20 mill patients)	DM2	Physician database (prescribed)	prevalent?	Physician database	age; sex; hba1c; cumulative duration exposure; private insurance status; urban location of practice; region; Charlson Comorbidity Index;	7
Lai 2012 (Taiwan) [37]	cohort	2000-2008	insurance database	random sample of nationwide database	Unspecified	insurance database (claims)	prevalent	insurance database	age; sex;	8
Lai 2012 (Taiwan) [38]	cohort	2000-2008	insurance database	random sample of nationwide database	Unspecified	insurance database (claims)	prevalent	insurance database	age; sex; obesity; pulmonary tuberculosis; copd; obesity; pneumoconiosis; asbestosis; tobacco use;	8
Lai 2012 (Taiwan) [39]	cohort	2000-2008	insurance database	random sample of nationwide database	Unspecified	insurance database (claims)	prevalent	insurance database	age; sex; comorbidities (cirrhosis, alcoholic liver damage, hepatitis B, hepatitis C);	8
Lind 2012 (Sweden) [40]	cohort	1985-2007	Hospital records database	ns (17 hospitals)	Unspecified	Hospital records database	prevalent?	Cancer register	age; bmi; time since start glargine; last insulin dose used; smoking	9
Ljung 2011 (Sweden) [41]	cohort	2006/7-2008	prescription database	nationwide	Unspecified/ DM2	pharmacy database (dispensed)	prevalent	Cancer register	age; sex. breast cancer: age at onset DM; bmi; smoking; cvd; age at first child; oestrogen;	8

(Table 1) contd…..

Author (Country)	Study Design	Study Period	Data Source Population	Source Population	Diabetes Type	Data Source Exposure	New/ Prevalent Drug User	Data Source Outcome	Covariates	NOS
Morden 2011 (USA) [42]	cohort	2006-2008	insurance database	nationwide	DM2	insurance database (claims)	prevalent	insurance database	age; sex; obesity; insulin dose; metformin; ethnicity; diabetes complications; oestrogen; poverty; 14 Charlson comorbidities; tobacco;	8
Neumann 2012 (France) [43]	cohort	2006-2009	insurance database	nationwide	Unspecified	insurance database (claims)	prevalent	Hospital records database	age; sex; oad;	8
Newton 2012 (USA) [44]	cohort	1992-2007	Self-reported questionnaire	ns (CPS-II Nutrition Cohort participants, 1.2 million participants)	DM2	Self-reported questionnaire	prevalent	questionnaire verified by medical records/ cancer register/ death index	age; sex; bmi; race; smoking; education; alcohol;	7
Oliveria 2008 (USA) [45]	cohort	2000-2004	insurance database	insured population (covers 42 million individuals)	Unspecified	insurance database (claims)	prevalent	insurance database (ICD-9) verified by pathology/medical records	age; sex. Colorectal cancer: history polyps; ulcerative colitis; Crohn's disease. Bladder cancer: schistosomiasis; pelvic radiation. Liver cancer: hepatitis B/C; cirrhosis; alcoholism. Pancreas cancer: partial gastrectomy; chronic pancreatitis; dvt; dermatomyositis/polymyositis; alcoholism; hepatitis B/C; history polyps;	8
Redaniel 2012 (UK) [46]	cohort	1987-2007	Physician database	nationwide	DM2	Physician database (prescribed)	new	ns	cohort entry year; geography;	9
Ruiter 2012 (Netherlands) [47]	cohort	2000-2008	prescription database	Pharmo database from community pharmacies (covers 2.5 million individuals)	DM2	pharmacy database (dispensed)	new	Hospital records database	age; sex; other insulin; calendar time; number hospitalisations; number of non- DM drugs used;	8
Suissa 2011 (UK) [48]	cohort matched	2002-2009	Physician database	nationwide	DM2	Physician database (prescribed)	new/prevalent (varies by analysis)	Physician database	Matching on: birth year; calendar time; duration prior insulin use. Adjust for: age; bmi; HbA1c; DM duration; duration insulin use; history of cancer other than breast and nmsc cancer; metformin; sulfonylurea; tzd; smoking; alcohol; oophorectomy; hrt; statin;	8
Tseng 2012 (Taiwan) [49]	cohort	2005	insurance database	random sample of nationwide register	DM2	insurance database (claims)	prevalent	insurance database	age; sex; occupation; geography;	8

(Table 1) contd…..

Author (Country)	Study Design	Study Period	Data Source Population	Source Population	Diabetes Type	Data Source Exposure	New/ Prevalent Drug User	Data Source Outcome	Covariates	NOS
Van Staa 2012 (UK) [50]	cohort matched	1997-2006	Physician database	nationwide (GPRD)	DM2	Physician database (prescribed)	new	Physician database	Matching on: age; sex; calendar year. Adjust for: age; sex; bmi; HbA1c; oad; ses; smoking; alcohol; coronary heart disease; coronary revascularization; hyperlipidaemia; hypertension; peripheral vascular disease; renal impairment; angina; ARB; antiplatelet; beta-blockers; calcium-channel blockers; diuretics; nitrates; NSAIDs; aspirin; statins; calendar year; (some variables only for subset of patients)	8
Yang 2010 (Hong Kong) [51]	cohort matched	1996-2005	Diabetes register	nationwide (all public hospitals)	DM2	hospital inpatient and outpatient database	new	Hospital records database	Matching on: age; smoking; propensity score. Adjust for: Specific cancer sites: only adjust for hba1c? Any cancer: age; DM duration; HbA1c; spot urinary albumin-to-creatinine ratio (Ln ACR 1); retinopathy; metformin; smoking; hdl; triglycerides; estimated glomerular filtration rate (eGFR);	9

Abbreviations: ACE, ACE inhibitor; Ad, antidiabetic drugs; ARB, Angiotensin II receptor blocker; ATC, Anatomical Therapeutic Chemical (ATC) classification system for drugs; Bmi, body mass index; Bp, blood pressure; Copd, chronic obstructive pulmonary disease; Cvd, cardiovascular disease; DM, diabetes mellitus; DM1, diabetes type 1; DM2, diabetes type 2; Dvt, Deep venous thrombosis; Hdl, High-density lipoprotein; Hrt, hormone replacement therapy; Niad, non-insulin antidiabetics; Nmsc, non-melanoma skin cancer; NOS, Newcastle Ottawa Scale; ns, not specified; Oad, oral antidiabetics; Ses, socioeconomic status; tzd, thiazolidinedione.

* NOS vary in analyses depending on whether prior cancer is adjusted or excluded.

(3 of 3 populations below unity, 2significant). For the exposure contrast glargine versus non-glargine insulin use, 6 of 6 populations had risk estimate above unity for prostate cancer but none of the individual risk estimates were statistically significant.

14 cancer sites were only examined in one study per exposure contrast and were not included in pooled analyses: leukemia, Hodgkin's lymphoma (HL), multiple myeloma, brain, head-neck, skin, testis, ovarian, uterus, cervical, thyroid, oesophagus, gastrointestinal, and lymphoma. Results of these studies are presented in Supplementary Material 5.

Synthesis of Results (Meta-Analysis)

In total, 34 studies were included in pooled analyses. Table **3** presents the results of pooled analyses by random effects model for the 14 cancer sites and exposure contrasts with sufficient number of studies (populations). Significant increased risk of cancer for the exposure contrast insulin versus no insulin was found for cancer in pancreas, liver, kidney and the respiratory system, and a marginal significance for stomach cancer. A decreased risk was observed for prostate cancer. Non-significant results were observed for any cancer, bladder, colorectal, colon, rectal, non-Hodgkin's lymphoma, melanoma and breast cancer. For the exposure contrast insulin versus non-insulin antidiabetic drugs, significant increased risk of any cancer, pancreatic and colorectal cancer was observed, while results for prostate and breast cancer were not significant. Glargine use was associated with a significantly decreased risk of colon cancer compared to non-glargine use breast cancer were marginally significant, while any cancer, pancreatic, liver, bladder, colorectal, respiratory and prostate cancer was not statistically significant.

Additional fixed effects models were run for studies that did not exhibit significant heterogeneity ($p>0.05$, Table **3**). These analyses gave similar results as the random effects model except for an even higher risk for pancreatic cancer.

8 studies only provided risk estimates by dose or duration of exposure [33, 50, 52-55, 60, 66] while other studies provided dose or duration risk estimates in addition to average risk estimates. However, pooled analyses by dose or

Table 2. Characteristics of Case-Control Studies Included in the Systematic Review (15 Records)

Author (Country)	Study Design	Study Period	Data Source Population	Source Population	Source for Controls	Age Group	Matching Variables	Diabetes Type	Data Source Exposure	New/Prevalent Drug User	Data Source Outcome	Covariates	NOS
Bodmer 2010 (UK) [52]	case-control nested	1994-2005	physician database (GPRD)	nationwide	population (GPRD)	30-79	index date; age; sex; general practice;	DM2	Physician database (prescribed)	prevalent	Physician database	bmi; DM duration; HbA1c; metformin; sulfonylurea; tzd; prandial glucose regulators; acarbose; oestrogen; smoking;	9
Bodmer 2011 (UK) [53]	case-control nested	1995-2009 ?	physician database (GPRD)	nationwide	population (GPRD)	<90	index date; age; sex; general practice; years of history in database	Unspecified	Physician database (prescribed)	prevalent	Physician database	bmi; HbA1c; DM duration; metformin; sulfonylurea; smoking; oestrogens; oral contraceptives; history of hysterectomy/endometriosis/polycystic ovaries;	9
Bodmer 2012 (UK) [54]	case-control nested	1995-2009	physician database (GPRD)	nationwide	population (GPRD)	<90	index date; age; sex; general practice; years of history in database	Unspecified	Physician database (prescribed)	prevalent	Physician database	bmi; DM duration; HbA1c; metformin; sulfonylurea; smoking; aspirin; NSAIDs; statin;	9
Bodmer 2012 (UK) [55]	case-control nested	1995-2009	physician database (GPRD)	nationwide	population (GPRD)	<90	index date; age; sex; general practice; years of history in database	Unspecified	Physician database (prescribed)	prevalent	Physician database	bmi; metformin; sulfonylurea; smoking;	9
Bonelli 2003 (Italy) [56]	case-control	1992-1996	hospital records	ns (patients from 7 gastroenterology and endoscopy hospital units in Northern Italy)	hospital	18-75	ns	Unspecified	Interview	prevalent	hospital	age; sex; hospital; education; occupation; alcohol; smoking;	5
Chang 2012 (Taiwan) [57]	case-control nested	2000-2007	insurance database	nationwide	population	30-100	calendar time; age; gender; follow-up duration; (treatment duration)	DM2	insurance database (claims)	prevalent	Cancer register	Glitazones; metformin; sulfonylurea; glinides. varies by cancer site (stepwise selection): number of oad; statins; aspirin; beta-blockers; calcium-channel blockers; ACE; ARB; alpha-glucosidase inhibitors; chronic liver disease; chronic kidney disease; nephropathy; neuropathy; retinopathy; peripheral vascular disease; cerebrovascular disease; cvd; depression; chronic lung disease;	8

(Table 2) contd…..

Author (Country)	Study Design	Study Period	Data Source Population	Source Population	Source for Controls	Age Group	Matching Variables	Diabetes Type	Data Source Exposure	New/Prevalent Drug User	Data Source Outcome	Covariates	NOS
Chang 2012 (Taiwan) [58]	case-control nested	2000-2007	insurance database	nationwide	population	30-100	index date; age; sex; dm duration	DM2	insurance database (claims)	prevalent	Cancer register	sulfonylurea; glinides; metformin; tzd; alpha-glucosidase inhibitors; statin; aspirin; beta-blockers; calcium-channel blockers; ACE; chronic liver disease; chronic kidney disease; nephropathy; cerebrovascular disease;	8
Cleveland 2012 (USA) [59]	case-control	1996-1997	rapid reporting system for cancer, interview	population (Nassau and Suffolk counties of Long Island)	population	all	age	DM2	Interview	prevalent	hospital, confirmed by physician records	bmi; metformin; insulin secretagogues (sulfonylurea); menopausal status; race;	5
Fortuny 2005 (Spain) [60]	case-control	1998-2002	hospital records	ns ("centres" in 4 cities (Barcelona, Tortosa, Reus and Madrid))	hospital	all	age; sex; centre;	DM2	interview	prevalent	hospital clinical data, verified by histology, immunohisto chemistry test, flow cytometry	age; sex; bmi; ad drugs; ses; study centre;	5
Kawaguchi 2010 (Japan) [61]	case-control nested	2004-2008	hospital (hepatitis C patients)	ns (patients from 3 hospitals specialized for liver diseases)	hospital	40+	no	DM2	ns	prevalent	hospital biopsy	age; sex; bmi; HbA1c; prior metastatic liver tumour; cholangiocellular carcinoma; history of pancreatic tumour; sulfonylurea (gliclazide or glibenclamide);cirrhosis ; albumin; alcohol?; AST; lactate dehydrogenase (LDH); alkaline phosphatase (ALP); platelet count; gamma-glutamyl transpeptidase?	7
Koro 2007 (USA) [62]	case-control nested	1997-2004	insurance database	ns (9 census regions, 30 different healthcare plans, 38 million patients (IHCIS))	population (insurance database)	18+	age; sex; index date; duration follow-up in database	DM2	insurance database (claims)	prevalent	insurance database	age	9

(Table 2) contd…..

Author (Country)	Study Design	Study Period	Data Source Population	Source Population	Source for Controls	Age Group	Matching Variables	Diabetes Type	Data Source Exposure	New/Prevalent Drug User	Data Source Outcome	Covariates	NOS
Li 2011 (USA) [63]	case-control (Pooled 3 case-control studies: MDACC; SFBA; NCI)	MDACC: 2001-2008; SFBA: 1995-1999; NCI: 1986-1989.	MDACC: outpatient clinic; SFBA: cancer register(?); NCI: cancer register.	MDACC: ns (one tertiary referral hospital); SFBA: population-based; NCI: population-based.	MDACC: hospital; SFBA, NCI: population.	MDACC: all; SFBA: 21-85; NCI: 21-79	age; sex; race (MDACC, NCI); geography (NCI);	Unspecified	Interview	prevalent	MDACC: hospital data with pathological confirmation. SFBA, NCI: cancer register.	age; sex; bmi; oad; race; education; smoking; alcohol; study site;	6
Mizuno 2013 (Japan) [64]	case-control	1999-2011	hospital records	ns (DM patients treated at specialized DM institute)	hospital	all	no	Unspecified	ns	prevalent	hospital data, verified by histology or clinical course	sulfonylurea; glinides; metformin; tzd; alpha-glucosidase inhibitors; family history with DM; statin;	4
Vinikoor 2009 (USA) [65]	case-control	2001-2006	rapid reporting system for cancer, interview	population-based (33 counties in North Carolina)	population	40-80	age; sex; race;	Unspecified	Interview	prevalent	Cancer register	age; sex; bmi; race; family history of colorectal cancer; NSAIDs; calcium intake; education;	7
Yang 2004 (UK) [66]	case-control nested	1990-2002	Physician database (GPRD)	nationwide	population (GPRD)	all	age; calendar period; duration follow-up in database	DM2	Physician database (prescribed)	prevalent	computerized medical records	sex; bmi; DM2 duration; metformin; sulfonylurea; cholecystectomy history; smoking; NSAIDs/aspirin;	9

Abbreviations: ACE, ACE inhibitor; Ad, antidiabetic drugs; ARB, Angiotensin II receptor blocker; Bmi, body mass index; Cvd, cardiovascular disease; DM, diabetes mellitus; DM1, diabetes type 1; DM2, diabetes type 2; NOS, Newcastle Ottawa Scale; ns, not specified; Oad, oral antidiabetics; Ses, socioeconomic status; tzd, thiazolidinedione.

duration was assessed as not feasible because these risk estimates were reported for different cancer sites, exposure contrasts and exposure definitions (e.g. mean or cumulative dose, duration since start exposure or cumulative duration. Dose and duration risk estimates were identified for any cancer, breast, pancreatic, prostate, liver, colorectal, ovarian, lung cancer and lymphoma (Supplementary Material 6).

Risk of Bias Across Studies

Egger's regression test did not reveal any significant ($p < 0.05$) publication bias for any cancer site.

DISCUSSION

Summary of Evidence

In the present meta-analysis, insulin exposure seems to be associated with an increased risk of cancer in pancreas, liver, kidney, stomach and respiratory system and decreased risk of prostate cancer, when compared to no insulin use. Compared to use of non-insulin antidiabetic drugs, insulin was associated with increased risk of any cancer, pancreatic and colorectal cancer. For users of glargine insulin compared to users of non-glargine insulin, a decreased risk of colon cancer as well as a marginally significant increased risk of breast cancer was observed. However, the results from individual studies reveal substantial variation in the reported cancer risk for most cancer sites. For 11 cancer sites results were only available in one population per exposure contrast.

The importance of assessing dose and duration of insulin use in addition to the average risk has been revealed in several studies observing an increased risk of cancer at different sites even in the initial period after treatment initiation or switch in therapy [27, 40, 50], and the exposure duration may be too short to be a causal factor for the occurrence of cancer. In particular, a substantial increased risk of pancreas cancer is observed and reverse casualty is important to consider for this cancer site. Analyses by

Table 3. Results of Pooled Analyses for Cancer Sites and Exposure Contrasts Examined in More than One Study. DerSimonian and Laird Random Effects Model and Fixed Effects Model

Cancer Site	Exposure Contrast	Number of Populations*	Random Effects Model		Fixed Effects Model‡		Heterogeneity†
			RR	[95% CI]	RR	[95% CI]	p
any	insulin *vs* no insulin	4	1.04	[0.75 , 1.45]			<0.001
	insulin *vs* niad	2	1.52	[1.16 , 2.00]			0.043
	glargine *vs* non-glargine	7	0.96	[0.83 , 1.10]			<0.001
stomach	insulin *vs* no insulin	3	1.65	[1.02 , 2.68]			0.002
	insulin *vs* niad	1	na	-			-
	glargine *vs* non-glargine	1	na	-			-
pancreatic	insulin *vs* no insulin	8	2.58	[2.05 , 3.25]			<0.001
	insulin *vs* niad	3	3.83	[1.43 , 10.23]	4.37	[2.62 , 5.67]	0.167
	glargine *vs* non-glargine	3	1.17	[0.78 , 1.77]	1.12	[0.86 , 1.46]	0.128
liver	insulin *vs* no insulin	6	1.84	[1.32 , 2.58]			<0.001
	insulin *vs* niad	1	na	-			-
	glargine *vs* non-glargine	2	0.89	[0.64 , 1.24]	0.88	[0.68 , 1.14]	0.203
kidney	insulin *vs* no insulin	4	1.38	[1.06 , 1.79]			0.002
	insulin *vs* niad	0	na	-			-
	glargine *vs* non-glargine	1	na	-			-
bladder	insulin *vs* no insulin	5	1.09	[0.93 , 1.28]	1.07	[0.98 , 1.17]	0.096
	insulin *vs* niad	0	na	-			-
	glargine *vs* non-glargine	2	1.34	[0.81 , 2.22]	1.32	[0.93 , 1.86]	0.150
colorectal	insulin *vs* no insulin	7	1.16	[0.87 , 1.55]			<0.001
	insulin *vs* niad	2	1.79	[1.36 , 2.36]	1.79	[1.36 , 2.36]	0.474
	glargine *vs* non-glargine	4	0.92	[0.75 , 1.13]	0.92	[0.75 , 1.13]	0.742
colon	insulin *vs* no insulin	5	1.02	[0.92 , 1.13]	1.02	[0.92 , 1.13]	0.675
	insulin *vs* niad	1	na	-			-
	glargine *vs* non-glargine	2	0.71	[0.56 , 0.91]	0.72	[0.58 , 0.89]	0.265
rectal	insulin *vs* no insulin	6	1.00	[0.85 , 1.17]	1.00	[0.85 , 1.17]	0.565
	insulin *vs* niad	0	na	-			-
	glargine *vs* non-glargine	0	na	-			-
respiratory	insulin *vs* no insulin	6	1.30	[1.14 , 1.47]			<0.001
	insulin *vs* niad	1	na	-			-
	glargine *vs* non-glargine	4	0.99	[0.83 , 1.17]	0.99	[0.83 , 1.17]	0.733
NHL	insulin *vs* no insulin	4	1.16	[0.83 , 1.62]			0.020
	insulin *vs* niad	0	na	-			-
	glargine *vs* non-glargine	0	na	-			-
melanoma	insulin *vs* no insulin	3	0.99	[0.80 , 1.22]	0.99	[0.81 , 1.20]	0.322
	insulin *vs* niad	0	na	-			-
	glargine *vs* non-glargine	0	na	-			-
prostate	insulin *vs* no insulin	3	0.80	[0.73 , 0.88]	0.80	[0.73 , 0.88]	0.825
	insulin *vs* niad	3	1.15	[0.86 , 1.54]	1.15	[0.86 , 1.54]	0.477
	glargine *vs* non-glargine	6	1.13	[0.98 , 1.32]	1.13	[0.98 , 1.32]	0.726
breast	insulin *vs* no insulin	7	0.90	[0.81 , 1.00]			0.033
	insulin *vs* niad	4	1.13	[0.88 , 1.45]	1.13	[0.88 , 1.45]	0.862
	glargine *vs* non-glargine	9	1.14	[1.01 , 1.29]	1.14	[1.01 , 1.29]	0.059

Abbreviations: na, not applicable. NHL, non-Hodgkin's lymphoma. niad, non-insulin antidiabetic drugs. NOS, Newcastle Ottawa Scale.
Underlined estimates indicate statistical significance at 5% level.
* Some studies contribute more than one population in one analysis, e.g. if results in the original study is only presented stratified by gender.
‡ Only run for heterogeneous studies (test for heterogeneity p>0.05).
† Chi square test for heterogeneity.

duration of insulin exposure reveal specially high risk with shorter durations compared to longer durations [27, 63, 64, 68]. A similar increased risk is observed in the early period after diagnosis of diabetes [63, 81]. This could be a result of diabetes as an early sign of pancreatic cancer (protopathic bias) or ascertainment bias after diabetes diagnosis.

Confounding by severity or indication is a concern in pharmacoepidemiological studies, and could be more

pronounced when comparing a third-line therapy like insulin to first line therapies like metformin in patients with type 2 diabetes [14]. Characteristics of populations receiving these two therapies can be substantially different concerning diabetes duration, obesity and other factors. This effect may be less pronounced for use of specific insulin types compared to users of other insulin types, although physician preference for specific insulin types cannot be excluded. Furthermore, a protective effect from metformin use has been reported [6] and this is important to consider when insulin is compared to metformin or other oral antidiabetic drugs.

A few studies presented several results for the same comparison but from different study designs, e.g. intention-to-treat and as-treated analysis, with or without latency period, new user design or "prevalent users design". This enable assessment of the impact the choice of study design has on results. As an example, Colhoun *et al.* [29] reported results for use of "glargine only" and breast cancer risk that were substantially different by study design (range 1.47 to 3.65). Thus, if a different algorithm for selection of estimate to include in the present meta-analysis had been applied, the marginally significant results for glargine use and breast cancer could have been different. This is likely to apply for other comparisons as well.

During screening, only 2 randomized controlled trials (RCT) that assessed the risk of cancer in diabetes patients allocated to receive insulins were identified. The Origin trial [17] included 12,537 people with impaired glucose tolerance or diabetes type 2 for an average follow-up time of 6.2 years to study cardiovascular events as primary outcome. Participants were randomly allocated to receive insulin glargine or standard care and risk of new or recurrent cancer was a secondary outcome. There was no difference in risk of any cancer for the glargine group compared to the standard care group (Hazard Ratio 1.00 [95% CI, 0.88-1.13]). No significant difference in risk was reported for specific cancer sites: breast (1.01 [0.60-1.71]), lung (1.21 [0.87-1.67]), colon (1.09[0.79-1.51]), prostate (0.94 [0.70-1.26]), melanoma [0.88 [0.44-1.75]) or cancer at other sites [0.95 [0.80-1.14]). A long-term safety study designed to assess ocular complications followed 1,017 persons with type 2 diabetes (82). Participants were randomly assigned to insulin glargine or NPH insulin with a mean cumulative exposure of 4 years. As an additional outcome, malignant neoplasms reported as serious adverse events were assessed and occurred in 51 patients and with relative risk 0.63 [0.36-1.09] for glargine. Risk of benign and malignant neoplasms was 0.90 [0.64-1.26].

Two meta-analyses of RCT data from manufacturer's pharmacovigilance databases were also identified. Home *et al.* [15] analysed data from 12 phase 2-4 RCTs conducted by Sanofi-Aventis on insulin glargine versus any active comparator (insulin or oral antidiabetics) in type 1 and type 2 diabetes patients. Included studies were between 4 and 52 weeks duration except for the study by Rosenstock *et al.* [82] mentioned above, and data in the meta-analysis were primarily driven by those data. 10,880 patients were included and incident malignant cancer occurred in 91 patients with relative risk 0.90 [0.60-1.36] for glargine. Dejgaard *et al.* [16] performed a meta-analysis of 21 Novo Nordisk-sponsored RCTs of insulin detemir compared to NPH insulin (16 trials) or insulin glargine (5 trials) in patients with type 1 or type 2 diabetes. RCTs of at least 12 weeks duration were included, with median exposure to insulin of 24 weeks (max 115 weeks) in trials of detemir versus NPH insulin, and 51 weeks (max 64 weeks) in trials of detemir versus glargine. Malignant cancer occurred in 21 of 6,644 patients with Odds Ratio 2.44 [1.01-5.89] for NPH insulin versus detemir, and 16 events in 2,049 patients with Odds Ratio 1.47 [0.55-3.94] for glargine versus detemir.

Limitations

Potential flaws in observational studies of insulin use and risk of cancer have been extensively debated, and the quality of studies included in the present systematic review is a concern. As a measure of the quality of each study, we used the NOS score and most studies could be considered as fair to high quality. However, it can be argued that NOS score is a crude quality measure. Generally, NOS takes into account the quality of the underlying data sources but does not fully account for important issues in pharmacoepidemiological studies, such as definition of drug exposure and time-related biases. For instance, the study by Yang *et al.* [51] reported a substantial decreased risk of cancer for insulin users compared to nonusers (HR 0.17 [0.09-0.32]). Potentially serious flaws in the study design have been pointed out [13, 83] but the study was nevertheless scored as NOS 9. Potential time-related and other biases of other studies included in the present systematic review have been discussed [10, 12, 14] and these studies also received high NOS scores [30, 33, 52]. Thus, the NOS do not seem to fully reflect important aspects of quality of the studies of the present review and has low granularity to distinguish studies of higher and lower quality.

The availability of covariates to adjust for confounding varied substantially in included studies (Table **1** and **2**). The NOS score does to some extent take into account confounder adjustment, however, adjustment for age and one other factor gave full score on this NOS item. The most important cofounders to adjust for may vary by cancer site and a more thorough assessment of confounder adjustment is desirable. Included studies examined a wide variety of exposures and comparators and this is useful for assessing consistency of the association of insulin and cancer. However, there were too few studies (populations) for most combinations of cancer site and exposure contrast to perform pooled analyses, and additional subgroup or meta-regression analyses could not be performed to assess possible determinants of cancer risk such as diabetes type, gender, age, incident or prevalent insulin use and study design. Egger's regression test did not reveal any significant publication bias for any cancer site. However, the number of studies in each analysis was low and the test may not have sufficient power to distinguish chance from real asymmetry [19]. Selective reporting was observed within some published studies as only the analyses with significant results were reported [44, 64, 79].

Conclusions

The results from individual studies in the present review revealed substantial variation in reported risk of cancer

associated with use of insulin, and varied by type of comparison group for the insulin users. Many studies are too small to make any firm conclusions. The pooled analyses revealed significantly increased or decreased risk of cancer at several sites for insulin users. However, there were few available studies in each pooled analysis, and subgroup analyses of possible determinants of cancer risk like diabetes type was not feasible. It is imperative to consider the data quality and conduct of individual studies when interpreting these results and the choice of study design in individual studies may have an effect on the estimated cancer risk. Extensive review of the quality of methods, design and conduct of studies was not the aim of the present review. A fit-for-purpose system for evaluating the quality of pharmacoepidemiological studies would be useful in any further evaluation of whether the observed associations can be attributed to issues with study design, analysis and low quality of data.

CONFLICT OF INTEREST

Marloes T Bazelier and Frank de Vries 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). Marie L 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.

The other Co-authors do not have any conflict of interest to declare.

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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.

REFERENCES

[1] Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer 2009; 16: 1103-23.

[2] Giovannucci E, Harlan DM, Archer MC, *et al.* Diabetes and Cancer: A consensus report. Diabetes Care 2010; 33: 1674-85.

[3] Nicolucci A. Epidemiological aspects of neoplasms in diabetes. Acta Diabetol 2010; 47: 87-95.

[4] Pollak M, Russell-Jones D. Insulin analogs and cancer risk: cause for concern or cause célèbre? Int J Clin Pract 2010; 64: 628-36.

[5] Home P. Insulin Therapy and Cancer. Diabetes Care 2013; 36: S240-S244.

[6] DeCensi A, Puntoni M, Goodwin P, *et al.* Metformin and Cancer Risk in Diabetic Patients: A Systematic Review and Meta-analysis. Cancer Prevent Res 2010; 3: 1451-61.

[7] Colmers IN, Bowker SL, Johnson JA. Thiazolidinedione use and cancer incidence in type-2 diabetes: A systematic review and meta-analysis. Diabet & Metabol 2012; 38: 475-84.

[8] Soranna D, Scotti L, Zambon A, *et al.* Cancer Risk Associated with Use of Metformin and Sulfonylurea in Type 2 Diabetes: A Meta-Analysis. Oncologist 2012; 17: 813-22.

[9] Smith U, Gale EAM. Does diabetes therapy influence the risk of cancer? Diabetologia 2009; 52: 1699-708.

[10] Pocock SJ, Smeeth L. Insulin glargine and malignancy: an unwarranted alarm. Lancet 2009; 374: 511-3.

[11] Gale EA. Insulin glargine and cancer: another side to the story? Lancet 2009; 374: 521.

[12] Hernández-Díaz S, Adami HO. Diabetes therapy and cancer risk: causal effects and other plausible explanations. Diabetologia 2010; 53: 802-8.

[13] Renehan AG. Insulin analogs and cancer risk: the emergence of second-generation studies. Diabetologia 2012; 55: 7-9.

[14] Suissa S, Azoulay L. Metformin and the Risk of Cancer: Time-related biases in observational studies. Diabetes Care 2012; 35: 2665-73.

[15] Home PD, Lagarenne P. Combined randomised controlled trial experience of malignancies in studies using insulin glargine. Diabetologia 2009; 52: 2499-506.

[16] Dejgaard A, Lynggaard H, Rastam J, Krogsgaard TM. No evidence of increased risk of malignancies in patients with diabetes treated with insulin detemir: a meta-analysis. Diabetologia 2009; 52: 2507-12.

[17] Gerstein HC, Bosch J, Dagenais GR, *et al.* Basal insulin and cardiovascular and other outcomes in dysglycemia. New Engl J Med 2012; 367: 319-28.

[18] Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6: e1000097.

[19] The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 [updated March 2011]. Available from www.cochrane-handbook.org. 2011.

[20] Karlstad Ø, Hjellvik V, Furu K, *et al.* Use of insulin and insulin analogs and risk of cancer. PROSPERO 2012: CRD42012002428. PROSPERO International prospective register of systematic reviews 2013; cited 2013 Oct 20: Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002428.

[21] Starup-Linde J, Karlstad O, Aistrup Eriksen S, *et al.* 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. Curr Drug Saf 2013; 8: 296-332.

[22] Wells GA, Shea B, O'Connell D, *et al.* The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute (OHRI) 2013; Available from: http://www.ohri.ca/Programs/clinical_epidemiology/oxford.asp

[23] Böhning D. Computer-assisted analysis of mixtures and applications: meta-analysis, disease mapping and others. Monographs on statistics and applied probability. Boca Raton, FL: Chapman & Hall/CRC; 2000. p. 1-232.

[24] Matthias E, George DS, Martin S, Christoph M. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-34.

[25] Blin P, Lassalle R, Dureau-Pournin C, Ambrosino B, Bernard MA, Abouelfath A, *et al.* Insulin glargine and risk of cancer: A cohort study in the French National Healthcare Insurance Database. Diabetologia 2012; 55: 644-53.

[26] Campbell PT, Deka A, Jacobs EJ, *et al.* Prospective study reveals associations between colorectal cancer and type 2 diabetes mellitus or insulin use in men. Gastroenterology 2010; 139: 1138-46.

[27] Carstensen B, Witte DR, Friis S. Cancer occurrence in Danish diabetic patients: duration and insulin effects. Diabetologia 2012; 55: 948-58.

[28] Chang CH, Toh S, Lin JW, *et al.* Cancer risk associated with insulin Glargine among adult type 2 diabetes patients - a nationwide Cohort study. PLoS ONE 2011; 6: e21368.

[29] Colhoun HM. Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group. Diabetologia 2009; 52: 1755-65.

[30] Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia 2009; 52: 1766-77.

[31] Fagot JP, Blotiere PO, Ricordeau P, Weill A, Alla F, Allemand H. Does Insulin Glargine Increase the Risk of Cancer Compared With Other Basal Insulins?: A French nationwide cohort study based on national administrative databases. Diabetes Care 2012; 10: doi: 10.2337/dc12-0506.

[32] Ferrara A, Lewis JD, Quesenberry CP, *et al.* Cohort Study of Pioglitazone and Cancer Incidence in Patients With Diabetes. Diabetes Care 2011; 34: 923-9.

[33] Hemkens LG, Grouven U, Bender R, *et al.* Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. Diabetologia 2009; 52: 1732-44.

[34] Hense HW, Kajuter H, Wellmann J, Batzler W. Cancer incidence in type 2 diabetes patients - first results from a feasibility study of the D2C cohort. Diabetol Metab Syndr 2011; 3: 15.

[35] Hsieh MC, Lee TC, Cheng SM, Tu ST, Yen MH, Tseng CH. The influence of type 2 diabetes and glucose-lowering therapies on cancer risk in the Taiwanese. Exp Dia Res 2012; 2012: 413782.

[36] Kostev K. Risk of breast cancer in patients on long-acting insulin analogs in comparison with those on human insulin. Diabetologia 2012; 55: 1554-5.

[37] Lai HC, Tsai IJ, Chen PC, *et al.* Gallstones, a cholecystectomy, chronic pancreatitis, and the risk of subsequent pancreatic cancer in diabetic patients: a population-based cohort study. J Gastroenterol 2012; 48(6): 721-7.

[38] Lai SW, Liao KF, Chen PC, Tsai PY, Hsieh DPH, Chen CC. Antidiabetes Drugs Correlate With Decreased Risk of Lung Cancer: A Population-Based Observation in Taiwan. Clin Lung Cancer 2012; 13: 143-8.

[39] Lai SW, Chen PC, Liao KF, Muo CH, Lin CC, Sung FC. Risk of hepatocellular carcinoma in diabetic patients and risk reduction associated with anti-diabetic therapy: A population-based cohort study. Am J Gastroenterol 2012; 107: 46-52.

[40] Lind M, Fahlen M, Eliasson B, Oden A. The relationship between the exposure time of insulin glargine and risk of breast and prostate cancer: an observational study of the time-dependent effects of antidiabetic treatments in patients with diabetes. Prim Care Diabetes 2012; 6: 53-9.

[41] Ljung R, TalbAck M, Haglund B, Jonasson JM, Gudbjornsdottir S, Steineck G. Insulin glargine use and short-term incidence of malignancies - A three-year population-based observation. Acta Oncol 2011; 50: 685-92.

[42] Morden NE, Liu SK, Smith J, Mackenzie TA, Skinner J, Korc M. Further exploration of the relationship between insulin glargine and incident cancer: A retrospective cohort study of older medicare patients. Diabetes Care 2011; 34: 1965-71.

[43] Neumann A, Weill A, Ricordeau P, Fagot JP, Alla F, Allemand H. Pioglitazone and risk of bladder cancer among diabetic patients in France: A population-based cohort study. Diabetologia 2012; 55: 1953-62.

[44] Newton CC, Gapstur SM, Campbell PT, Jacobs EJ. Type 2 diabetes mellitus, insulin-use and risk of bladder cancer in a large cohort study. Int J Cancer 2013; 132: 2186-91.

[45] Oliveria SA, Koro CE, Ulcickas YM, Sowell M. Cancer incidence among patients treated with antidiabetic pharmacotherapy. Diabetes Metab Syndr Clin Res Rev 2008; 2: 47-57.

[46] Redaniel MT, Jeffreys M, May MT, Ben-Shlomo Y, Martin RM. Associations of type 2 diabetes and diabetes treatment with breast cancer risk and mortality: a population-based cohort study among British women. Cancer Causes Control 2012; 23: 1785-95.

[47] Ruiter R, Visser LE, van Herk-Sukel MP, *et al.* Risk of cancer in patients on insulin glargine and other insulin analogs in comparison with those on human insulin: results from a large population-based follow-up study. Diabetologia 2012; 55: 51-62.

[48] Suissa S, Azoulay L, Dell'Aniello S, Evans M, Vora J, Pollak M. Long-term effects of insulin glargine on the risk of breast cancer. Diabetologia 2011; 54: 2254-62.

[49] Tseng CH. Diabetes and non-Hodgkin's lymphoma: analyses of prevalence and annual incidence in 2005 using the National Health Insurance database in Taiwan. Ann Oncol 2012; 23: 153-8.

[50] Van Staa TP, Patel D, Gallagher AM, De Bruin ML. Glucose-lowering agents and the patterns of risk for cancer: A study with the General Practice Research Database and secondary care data. Diabetologia 2012; 55: 654-65.

[51] Yang X, Ko GTC, So WY, *et al.* Associations of hyperglycemia and insulin usage with the risk of cancer in type 2 diabetes: The Hong Kong diabetes registry. Diabetes 2010; 59: 1254-60.

[52] Bodmer M, Meier C, Krahenbuhl S, Jick SS, Meier CR. Long-term metformin use is associated with decreased risk of breast cancer. Diabetes Care 2010; 33: 1304-8.

[53] Bodmer M, Becker C, Meier C, Jick SS, Meier CR. Use of metformin and the risk of ovarian cancer: A case-control analysis. Gynecol Oncol 2011; 123: 200-4.

[54] Bodmer M, Becker C, Meier C, Jick SS, Meier CR. Use of metformin is not associated with a decreased risk of colorectal cancer: A case-control analysis. Cancer Epidemiol Biomarkers Prev 2012; 21: 280-6.

[55] Bodmer M, Becker C, Jick SS, Meier CR. Metformin does not alter the risk of lung cancer: A case-control analysis. Lung Cancer 2012; 78: 133-7.

[56] Bonelli L, Aste H, Bovo P, *et al.* Exocrine pancreatic cancer, cigarette smoking, and diabetes mellitus: A case-control study in Northern Italy. Pancreas 2003; 27: 143-9.

[57] Chang CH, Lin JW, Wu LC, Lai MS, Chuang LM, Arnold CK. Association of thiazolidinediones with liver cancer and colorectal cancer in type 2 diabetes mellitus. Hepatology 2012; 55: 1462-72.

[58] Chang CH, Lin JW, Wu LC, Lai MS, Chuang LM. Oral insulin secretagogues, insulin, and cancer risk in type 2 diabetes mellitus. J Clin Endocrinol Metab 2012; 97: E1170-E1175.

[59] Cleveland RJ, North KE, Stevens J, Teitelbaum SL, Neugut AI, Gammon MD. The association of diabetes with breast cancer incidence and mortality in the Long Island Breast Cancer Study Project. Cancer Causes Control 2012; 23: 1193-203.

[60] Fortuny J, Benavente Y, Bosch R, Garcia-Villanueva M, de Sevilla AF, de SS. Type 2 diabetes mellitus, its treatment and risk for lymphoma. Eur J Cancer 2005; 41: 1782-7.

[61] Kawaguchi T, Taniguchi E, Morita Y, *et al.* Association of exogenous insulin or sulphonylurea treatment with an increased incidence of hepatoma in patients with hepatitis C virus infection. Liver Int 2010; 30: 479-86.

[62] Koro C, Barrett S, Qizilbash N. Cancer risks in thiazolidinedione users compared to other anti-diabetic agents. Pharmacoepidemiol Drug Saf 2007; 16: 485-92.

[63] Li D, Tang H, Hassan M, Holly E, Bracci P, Silverman D. Diabetes and risk of pancreatic cancer: a pooled analysis of three large case-control studies. Cancer Causes Control 2011; 22: 189-97.

[64] Mizuno S, Nakai Y, Isayama H, *et al.* Risk factors and early signs of pancreatic cancer in diabetes: screening strategy based on diabetes onset age. J Gastroenterol 2013; 48: 238-46.

[65] Vinikoor LC, Long MD, Keku TO, Martin CF, Galanko JA, Sandler RS. The association between diabetes, insulin use, and colorectal cancer among Whites and African Americans. Cancer Epidemiol Biomarkers Prev 2009; 18: 1239-42.

[66] Yang YX, Hennessy S, Lewis JD. Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. Gastroenterology 2004; 127: 1044-50.

[67] Blin P, Lassalle R, Dureau-Pournin C, *et al.* Insulin glargine and risk of cancer: A cohort study in the french national healthcare insurance database. Fund Clin Pharmacol 2012; 26: 1-122.

[68] Li D, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies affect risk of pancreatic cancer. Gastroenterology 2009; 137: 482-8.

[69] Silverman DT, Schiffman M, Everhart J, *et al.* Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. Br J Cancer 1999; 80: 1830-7.

[70] Jonasson JM, Ljung R, Talback M, Haglund B, Gudbjornsdottir S, Steineck G. Insulin glargine use and short-term incidence of malignancies a population-based follow-up study in Sweden. Diabetologia 2009; 52: 1745-54.

[71] Ljung R, Talback M, Haglund B, Jonasson JM, Gudbjornsdottir S, Steineck G. Insulin glargine use and short-term incidence of breast cancer - a four-year population-based observation. Acta Oncol 2012; 51: 400-2.

[72] Liao KF, Lai SW, Li CI, Chen WC. Diabetes mellitus correlates with increased risk of pancreatic cancer: A population-based cohort study in Taiwan. J Gastroenterol Hepatol 2012; 27: 709-13.

[73] Liao KF, Lai SW, Li CI. The impact of anti-diabetic drugs on colorectal cancer risk in a large cohort of women with diabetes. Libyan J Med 2012; 7: doi: 10.3402/ljm.v7i0.17532.

[74] Monami M, Lamanna C, Pala L, *et al.* Treatment with insulin secretagogues and cancer-related mortality in type 2 diabetic patients a retrospective cohort study. Exp Clin Endocrinol Diabetes 2008; 116: 184-9.

[75] Monami M, Lamanna C, Balzi D, Marchionni N, Mannucci E. Sulphonylureas and cancer: a case-control study. Acta Diabetol 2009; 46: 279-84.

[76] Buchs AE, Silverman BG. Incidence of malignancies in patients with diabetes mellitus and correlation with treatment modalities in a large Israeli health maintenance organization: A historical cohort study. Metabolism 2011; 60: 1379-85.

[77] Chuang TY, Lewis DA, Spandau DF. Decreased incidence of nonmelanoma skin cancer in patients with type 2 diabetes mellitus using insulin: a pilot study. Brit J Dermatol 2005; 153: 552-7.

[78] Donadon V, Balbi M, Valent F, Avogaro A. Glycated hemoglobin and antidiabetic strategies as risk factors for hepatocellular carcinoma. World J Gastroenterol 2010; 16: 3025-32.

[79] Bodmer M, Becker C, Meier C, Jick SS, Meier CR. Use of Antidiabetic Agents and the Risk of Pancreatic Cancer: A Case-Control Analysis. Am J Gastroenterol 2012; 107: 620-6.

[80] Mannucci E, Monami M, Balzi D, *et al.* Doses of insulin and its analogs and cancer occurrence in insulin-treated type 2 diabetic patients. Diabetes Care 2010; 33: 1997-2003.

[81] Johnson JA, Bowker SL, Richardson K, Marra CA. Time-varying incidence of cancer after the onset of type 2 diabetes: evidence of potential detection bias. Diabetologia 2011; 54: 2263-71.

[82] Rosenstock J, Fonseca V, McGill JB, *et al.* Similar risk of malignancy with insulin glargine and neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes: findings from a 5 year randomised, open-label study. Diabetologia 2009; 52: 1971-3.

[83] Carstensen B. Associations of Hyperglycemia and Insulin Usage With the Risk of Cancer in Type 2 Diabetes: The Hong Kong Diabetes Registry. Diabetes 2010; 59: e17-e18.

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