SUPPLEMENTARY MATERIAL

Review and Meta-Analysis of Observational Studies

Øystein Karlstad¹, Jacob Starup-Linde², Peter Vestergaard³, Vidar Hjellvik¹, Marloes T. Bazelier⁵, Marjanka K. Schmidt⁶, Morten Andersen⁷, Anssi Auvina⁸, Jari Haukkaa⁹, Kari Furu¹, Frank de Vries⁵,¹⁰ and Marie L de Bruin⁵

¹Department of Pharmacoepidemiology, Norwegian Institute of Public Health, Oslo, Norway
²Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Denmark
³Clinical Institute, Aalborg University, Denmark
⁴Department of Endocrinology, Aalborg University Hospital, Denmark
⁵Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, the Netherlands
⁶Department of Molecular Pathology, Netherlands Cancer Institute, the Netherlands
⁷Centre for Pharmacoepidemiology, Karolinska Institute, Stockholm, Sweden
⁸School of Health Sciences, University of Tampere, Finland
⁹University of Helsinki, Finland
¹⁰Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre, Maastricht, the Netherlands

Supplementary Material 1: Search Strategy

Five databases were searched: Medline (PubMed), Embase (Ovid), Scopus (SciVerse), Web of Science WoS (ISI Web of Knowledge, Thomson Reuters) and the Cochrane Library (Wiley). All searches were performed on 27 November 2012 without restrictions on language, publication date, or publication status. MESH and Emtree terms were used (PubMed, Embase, Cochrane Library) with search filter “Humans” (Medline, Embase). In addition, free text search limited to records published during the last year was used to identify records not yet indexed with MESH and Emtree terms. For Scopus and Web of Science, only free-text searches were used. Search terms for diabetes, insulin and cancer (or similar terms) were used in all searches, while terms for risk or incidence were added in free text searches. The specific search strategy for each database is presented below.

Medline (PubMed)

MESH search combined with free text search and filter:
1. "Diabetes Mellitus"[Mesh]
2. "Insulins"[Mesh]
3. "Neoplasms"[Mesh]
4. risk OR risk* OR incidence OR inciden*
5. #1 AND #2 AND #3 AND #4
6. Filters: Humans
295 records

Free text search in all fields with filter on publication date 2012 :
1. diabetes OR diabetes* OR diabetic* OR diabet*
2. insulin OR insulin*
3. tumor OR tumor* OR tumour OR tumour* OR cancer OR cancer* OR neoplasm OR neoplasm* OR carcinoma OR carcinom* OR sarcoma OR sarcom* OR lymphoma OR lymphom* OR leukemia OR leukem* OR myeloma OR myelom*
4. risk OR risk* OR incidence OR inciden*
5. #1 AND #2 AND #3 AND #4
6. Filters: Publication date from 2012/01/01 to 2012/12/31
284 records

Embase (Ovid)

Emtree search with limit:
1. exp diabetes mellitus
2. exp insulin derivative
3. exp cancer incidence OR exp cancer risk OR exp carcinogenicity OR exp drug induced cancer OR exp drug carcinogenicity OR exp carcinogenesis
4. 1 AND 2 AND 3
5. limit 4 to human
816 records

Free text search in title / abstract / keywords with limit on publication year 2012:
1. "diabet*”.ti,ab,kw.
2. "insulin*”.ti,ab,kw.
3. (risk* or inciden*).ti,ab,kw.
4. (cancer* or neoplasm* or tumor* or tumour* or carcinom* or sarcom* or lymphom* or leukem* or myelom*).ti,ab,kw.
5. 1 AND 2 AND 3 AND 4
6. limit 5 to yr="2012 -Current"
295 records

Scopus (SciVerse)

Free text search search in title / abstract / keywords:
1. TITLE-ABS-KEY(*diabet*)
2. TITLE(*insulin*)
3. TITLE-ABS-KEY(risk* OR inciden*)
4. TITLE(*cancer* OR *neoplasm* OR *tumor* OR *tumour* OR *carcinom* OR *sarcom* OR *lymphom* OR *leukem* OR *myelom*)
5. 1 AND 2 AND 3 AND 4
313 records

Web of Science WoS (ISI Web of Knowledge, Thomson Reuters)

Free text search search in title / abstract / keywords (topic):
1. topic=(*diabet*)
2. title=(*insulin*)
3. topic=(risk* OR inciden*)
4. title=(*cancer* OR *neoplasm* OR *tumor* OR *tumour* OR *carcinom* OR *sarcom* OR *lymphom* OR *leukem* OR *myelom*)
5. 1 AND 2 AND 3 AND 4
239 records

The Cochrane Library (Wiley)

Databases selected: Cochrane Central Register of Controlled Trials (Clinical Trials), Cochrane Database of Systematic Reviews (Cochrane Reviews), Database of Abstracts of Reviews of Effects (Other Reviews), Cochrane Methodology Register (Methods
Studies), Health Technology Assessment Database (Technology Assessments), NHS Economic Evaluation Database (Economic Evaluations), About The Cochrane Collaboration (Cochrane Groups).

**MESH search:**
1. "Diabetes Mellitus"[Mesh]
2. "Insulins"[Mesh]
3. "Neoplasms"[Mesh]
4. 1 AND 2 AND 3

11 records

**Free text search search in title / abstract / keywords limited to dates 2011-2012:**
1. (*diabet*):ti,ab,kw
2. (*insulin*):ti,ab,kw
3. (risk* OR inciden*):ti,ab,kw
4. (*cancer* or *neoplasm* or *tumor* or *tumour* or *carcinom* or *sarcom* or *lymphom* or *leukem* or *myelom*):ti,ab,kw
5. 1 AND 2 AND 3 AND 4
6. Limit Dates 2011-2012

32 records
Supplementary Material 2: Newcastle – Ottawa Quality Assessment Scale

http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection
1) Is the case definition adequate?
   a) Yes, with independent validation *
   b) Yes, e.g. record linkage or based on self-reports *
   c) No description
2) Representativeness of the cases
   a) Consecutive or obviously representative series of cases *
   b) Potential for selection biases or not stated
3) Selection of Controls
   a) Community controls *
   b) Hospital controls
   c) No description
4) Definition of Controls
   a) No history of disease (endpoint) *
   b) No description of source

Comparability
1) Comparability of cases and controls on the basis of the design or analysis
   a) Study controls for age (user-defined) (Select the most important factor.) *
   b) Study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor.) *

Exposure
1) Ascertainment of exposure
   a) Secure record (e.g. surgical records) *
   b) Structured interview where blind to case / control status *
   c) Interview not blinded to case / control status
   d) Written self-report or medical record only
   e) No description
2) Same method of ascertainment for cases and controls
   a) Yes *
   b) No
3) Non-Response rate
   a) Same rate for both groups *
   b) Non-respondents described
   c) Rate different and no designation

COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection
1) Representativeness of the exposed cohort
   a) Truly representative of the average diabetic population using insulin (user-defined) in the community *
   b) Somewhat representative of the average diabetic population using insulin (user-defined) in the community *
   c) Selected group of users e.g. nurses, volunteers
   d) No description of the derivation of the cohort
2) Selection of the non-exposed cohort
Supplementary Material

Current Drug Safety, 2013, Vol. 8, No. 5

a) Drawn from the same community as the exposed cohort *
b) Drawn from a different source
c) No description of the derivation of the non-exposed cohort
3) Ascertainment of exposure
   a) Secure record (e.g. surgical records) *
   b) Structured interview *
   c) Written self-report
   d) No description
4) Demonstration that outcome of interest was not present at start of study
   a) Yes *
   b) No

Comparability
1) Comparability of cohorts on the basis of the design or analysis
   a) Study controls for age (user-defined) (select the most important factor) *
   b) Study controls for any additional factor (This criteria could be modified to indicate specific control for a
      second important factor.) *

Outcome
1) Assessment of outcome
   a) Independent blind assessment *
   b) Record linkage *
   c) Self-report
   d) No description
2) Was follow-up long enough for outcomes to occur
   a) Yes, > 5 years (user-defined) (select an adequate follow up period for outcome of interest) *
   b) No
3) Adequacy of follow up of cohorts
   a) Complete follow up - all subjects accounted for *
   b) Subjects lost to follow up unlikely to introduce bias (small number lost): >90 % (user-defined) - follow-up, or description provided of those lost *
   c) Follow up rate <10 % (user-defined) and no description of those lost
   d) No statement.

Supplementary Material 3

Presents all estimates extracted from each study for all cancer sites and exposure contrasts, sorted by author name and publication year. The same study can have several risk estimates for each combination of exposure contrast and cancer site if several study designs have been employed in the study (e.g. intention-to-treat and as-treated analysis, with and without latency periods, incident and prevalent users, diabetes types). If risk estimates for strata of dose / duration are presented, these are separated by “ / ” in tables.

1) Cohort studies (27 studies).

| Author (country) | Outcome | Exposure | Comparator | Gender | Risk estimate | 95% Confidence Interval |
|------------------|---------|----------|------------|--------|---------------|------------------------|
| Blin 2012 [25]   | any     | glargine only | human only | both   | 0.59          | 0.28 - 1.25             |
| Campbell 2010 [26] | colorectal | insulin | no insulin | men | 1.11          | 0.82 - 1.51             |
| Campbell 2010 [26] | colorectal | insulin | no insulin | women | 0.94 | 0.60 - 1.48 |
| Campbell 2010 [26] | colon    | insulin | no insulin | men | 1.13          | 0.79 - 1.61             |
| Campbell 2010 [26] | colon    | insulin | no insulin | women | 1.04 | 0.62 - 1.73 |
| Campbell 2010 [26] | rectal   | insulin | no insulin | men | 1.05          | 0.58 - 1.90             |
| Author (country) | Outcome | Exposure | Comparator | Gender Risk estimate | 95% Confidence Interval |
|-----------------|---------|----------|------------|----------------------|------------------------|
| Campbell 2010 [26] | rectal | insulin | no insulin | women | 0.65 | 0.24 | 1.75 |
| Carstensen 2012 [27] | any excl nmsc | insulin | no insulin | men | 1.14 | 1.08 | 1.20 |
| Carstensen 2012 [27] | any excl nmsc | insulin | no insulin | women | 1.23 | 1.16 | 1.30 |
| Carstensen 2013 [27] | oesophagus | insulin | no insulin | men | 0.98 | 0.67 | 1.43 |
| Carstensen 2013 [27] | oesophagus | insulin | no insulin | women | 1.19 | 0.57 | 2.49 |
| Carstensen 2013 [27] | stomach | insulin | no insulin | men | 1.23 | 0.90 | 1.68 |
| Carstensen 2013 [27] | stomach | insulin | no insulin | women | 1.43 | 0.89 | 2.28 |
| Carstensen 2013 [27] | colon | insulin | no insulin | men | 1.00 | 0.84 | 1.19 |
| Carstensen 2013 [27] | colon | insulin | no insulin | women | 0.90 | 0.73 | 1.12 |
| Carstensen 2013 [27] | rectal | insulin | no insulin | men | 0.98 | 0.77 | 1.24 |
| Carstensen 2013 [27] | rectal | insulin | no insulin | women | 0.91 | 0.62 | 1.32 |
| Carstensen 2013 [27] | colorectal | insulin | no insulin | men | 0.99 | 0.86 | 1.14 |
| Carstensen 2013 [27] | colorectal | insulin | no insulin | women | 0.90 | 0.75 | 1.09 |
| Carstensen 2013 [27] | liver | insulin | no insulin | men | 2.41 | 1.93 | 3.00 |
| Carstensen 2013 [27] | liver | insulin | no insulin | women | 2.59 | 1.58 | 4.23 |
| Carstensen 2013 [27] | pancreatic | insulin | no insulin | men | 2.92 | 2.49 | 3.42 |
| Carstensen 2013 [27] | pancreatic | insulin | no insulin | women | 3.30 | 2.77 | 3.93 |
| Carstensen 2013 [27] | respiratory | insulin | no insulin | men | 1.28 | 1.13 | 1.45 |
| Carstensen 2013 [27] | respiratory | insulin | no insulin | women | 1.31 | 1.11 | 1.54 |
| Carstensen 2013 [27] | melanoma | insulin | no insulin | men | 0.80 | 0.57 | 1.12 |
| Carstensen 2013 [27] | melanoma | insulin | no insulin | women | 1.10 | 0.76 | 1.60 |
| Carstensen 2013 [27] | kidney | insulin | no insulin | men | 1.39 | 1.06 | 1.83 |
| Carstensen 2013 [27] | kidney | insulin | no insulin | women | 2.04 | 1.45 | 2.86 |
| Carstensen 2013 [27] | bladder | insulin | no insulin | men | 0.91 | 0.75 | 1.10 |
| Carstensen 2013 [27] | bladder | insulin | no insulin | women | 1.13 | 0.77 | 1.64 |
| Carstensen 2013 [27] | brain | insulin | no insulin | men | 1.00 | 0.69 | 1.44 |
| Carstensen 2013 [27] | brain | insulin | no insulin | women | 1.47 | 1.00 | 2.18 |
| Carstensen 2013 [27] | thyroid | insulin | no insulin | men | 1.38 | 0.57 | 3.35 |
| Carstensen 2013 [27] | thyroid | insulin | no insulin | women | 2.05 | 1.07 | 3.90 |
| Carstensen 2013 [27] | HL | insulin | no insulin | men | 1.07 | 0.50 | 2.29 |
| Carstensen 2013 [27] | HL | insulin | no insulin | women | 0.52 | 0.12 | 2.22 |
| Carstensen 2013 [27] | NHL | insulin | no insulin | men | 0.85 | 0.60 | 1.19 |
| Carstensen 2013 [27] | NHL | insulin | no insulin | women | 1.18 | 0.81 | 1.73 |
| Carstensen 2013 [27] | multiple myeloma | insulin | no insulin | men | 0.92 | 0.57 | 1.49 |
| Author (country) | Outcome<sup>1</sup> | Exposure | Comparator | Gender Risk estimate<sup>1</sup> | 95% Confidence Interval |
|-----------------|---------------------|----------|------------|---------------------------------|------------------------|
| Carstensen 2013 [27] | multiple myeloma | insulin | no insulin | women 0.74 | 0.36 / 1.52 |
| Carstensen 2013 [27] | leukaemia | insulin | no insulin | men 1.01 | 0.72 / 1.43 |
| Carstensen 2013 [27] | leukaemia | insulin | no insulin | women 1.08 | 0.70 / 1.66 |
| Carstensen 2013 [27] | breast | insulin | no insulin | men 2.59 | 0.84 / 7.94 |
| Carstensen 2013 [27] | breast | insulin | no insulin | women 0.96 | 0.84 / 1.09 |
| Carstensen 2013 [27] | cervical | insulin | no insulin | women 1.37 | 0.89 / 2.09 |
| Carstensen 2013 [27] | uterus | insulin | no insulin | women 1.05 | 0.82 / 1.36 |
| Carstensen 2013 [27] | ovarian | insulin | no insulin | women 1.07 | 0.76 / 1.50 |
| Carstensen 2013 [27] | prostate | insulin | no insulin | men 0.79 | 0.69 / 0.90 |
| Carstensen 2013 [27] | testis | insulin | no insulin | men 0.57 | 0.25 / 1.28 |
| Chang 2011 [28] | any | glargine | human int-long-acting | both 0.86 | 0.73 / 1.02 |
| Chang 2011 [28] | liver | glargine | human int-long-acting | both 0.76 | 0.54 / 1.08 |
| Chang 2011 [28] | colorectal | glargine | human int-long-acting | both 0.78 | 0.49 / 1.26 |
| Chang 2011 [28] | pancreatic | glargine | human int-long-acting | both 1.85 | 1.06 / 3.22 |
| Chang 2011 [28] | lung | glargine | human int-long-acting | both 1.01 | 0.59 / 1.71 |
| Chang 2011 [28] | composite<sup>2</sup> | glargine | human int-long-acting | both 0.54 | 0.25 / 1.16 |
| Chang 2011 [28] | stomach | glargine | human int-long-acting | both 0.62 | 0.27 / 1.42 |
| Chang 2011 [28] | skin | glargine | human int-long-acting | both 1.08 | 0.48 / 2.46 |
| Chang 2011 [28] | breast | glargine | human int-long-acting | women 0.53 | 0.21 / 1.31 |
| Chang 2011 [28] | prostate | glargine | human int-long-acting | men 2.37 | 0.94 / 6.01 |
| Chang 2011 [28] | any | glargine | human int-long-acting | both 0.81 / 0.75 / 0.79 / 0.6 / 0.5 / 0.54 / 1.18 / 0.83 | 1.07 / 1.11 / cumulative dose (<50/50-135/135-300/300 DDD) |
| Chang 2011 [28] | pancreatic | glargine | human int-long-acting | both 1.23 / 1.19 / 1.15 / 0.53 / 0.34 / 0.27 / 0.79 / 2.84 / 4.17 / cumulative dose (<50/50-135/135-300/300 DDD) |
| Chang 2011 [28] | prostate | glargine | human int-long-acting | men 1.88 / 2.06 / 5.37 / 0.30 / 0.29 / 0.71 / 2.16 / 0.33 | 11.63 / 14.7 cumulative dose (<50/50-135/135-300/300 DDD) |
| Chang 2011 [28] | any | glargine | human int-long-acting | both 0.83 / 0.91 | 0.69 / 0.61 / 1.01 / 1.36 cumulative duration (<1/≥1 year) |
| Chang 2011 [28] | pancreatic | glargine | human int-long-acting | both 1.75 / 2.58 | 0.98 / 0.50 / 3.12 / 13.23 cumulative duration (<1/≥1 year) |
| Chang 2011 [28] | prostate | glargine | human int-long-acting | men 2.52 / 1.79 | 0.87 / 0.26 / 7.25 / 12.33 cumulative duration (<1/≥1 year) |
| Chang 2011 [28] | any | glargine | human int-long-acting | both 0.68 / 1.05 | 0.52 / 0.84 / 0.89 / 1.32 mean daily dose (<0.5/≥0.5 DDD/day) |
| Chang 2011 [28] | pancreatic | glargine | human int-long-acting | both 1.92 / 1.84 | 0.85 / 0.86 / 4.32 / 3.95 mean daily dose (<0.5/≥0.5 DDD/day) |
| Chang 2011 [28] | prostate | glargine | human int-long-acting | men 2.95 / 1.98 | 0.83 / 0.47 / 10.43 / 8.40 mean daily dose (<0.5/≥0.5 DDD/day) |
| Colhoun 2010 [29] | any excl nmsc | glargine only | non-glargine insulins only | both 1.64 | 1.05 / 2.54 |
| Colhoun 2010 [29] | any excl nmsc | glargine + non-glargine insulins | non-glargine insulins only | both 0.78 | 0.53 / 1.16 |
| Colhoun 2010 [29] | any excl nmsc | glargine | non-glargine insulins only | both 1.02 | 0.77 / 1.36 |
| Colhoun 2010 [29] | any excl nmsc | glargine | non-glargine insulins only | both 1.08 | 0.78 / 1.49 |
| Author (country) | Outcome\(^c\) | Exposure | Comparator | Gender Risk estimate\(^d\) | 95% Confidence Interval |
|-----------------|----------------|----------|------------|--------------------------|------------------------|
| Colhoun 2010 [29] | any excl nmsc | glargine only | non-glargine insulins only | both | 1.58 | 1.03 | 2.42 |
| Colhoun 2010 [29] | any excl nmsc | glargine | non-glargine insulins only | both | 1.02 | 0.50 | 2.09 |
| Colhoun 2010 [29] | any excl nmsc | glargine only | non-glargine insulins only | both | 1.73 | 0.98 | 3.05 |
| Colhoun 2010 [29] | any excl nmsc | glargine + non-glargine | non-glargine insulins only | both | 0.88 | 0.55 | 1.40 |
| Colhoun 2010 [29] | breast | glargine | non-glargine insulins only | women | 1.49 | 0.79 | 2.83 |
| Colhoun 2010 [29] | breast | glargine only | non-glargine insulins only | women | 3.65 | 1.05 | 12.68 |
| Colhoun 2010 [29] | breast | glargine + non-glargine | non-glargine insulins only | women | 1.10 | 0.38 | 3.16 |
| Colhoun 2010 [29] | prostate | glargine only | non-glargine insulins only | men | 1.16 | 0.16 | 8.50 |
| Colhoun 2010 [29] | prostate | glargine + non-glargine | non-glargine insulins only | men | 1.76 | 0.54 | 5.74 |
| Colhoun 2010 [29] | colorectal | glargine only | non-glargine insulins only | both | 1.43 | 0.45 | 4.57 |
| Colhoun 2010 [29] | colorectal | glargine + non-glargine | non-glargine insulins only | both | 0.36 | 0.09 | 1.45 |
| Colhoun 2010 [29] | lung | glargine only | non-glargine insulins only | both | 1.43 | 0.53 | 3.88 |
| Colhoun 2010 [29] | lung | glargine + non-glargine | non-glargine insulins only | both | 0.47 | 0.18 | 1.25 |
| Colhoun 2010 [29] | pancreatic | glargine only | non-glargine insulins only | both | - | - | - |
| Colhoun 2010 [29] | pancreatic | glargine + non-glargine | non-glargine insulins only | both | 0.54 | 0.08 | 4.32 |
| Colhoun 2010 [29] | any excl nmsc | glargine only | non-glargine insulins only | both | 0.87 | 0.63 | 1.21 |
| Colhoun 2010 [29] | any excl nmsc | glargine + non-glargine | non-glargine insulins only | both | 1.20 | 0.69 | 2.09 |
| Colhoun 2010 [29] | breast | glargine only | non-glargine insulins only | women | 1.47 | 0.59 | 3.64 |
| Colhoun 2010 [29] | breast | glargine + non-glargine | non-glargine insulins only | women | - | - | - |
| Colhoun 2010 [29] | any excl nmsc | glargine only | non-glargine insulins only | both | 1.49 | 1.09 | 2.03 |
| Colhoun 2010 [29] | any excl nmsc | glargine + non-glargine | non-glargine insulins only | both | 0.65 | 0.53 | 0.81 |
| Colhoun 2010 [29] | breast | glargine only | non-glargine insulins only | women | 1.99 | 0.88 | 4.49 |
| Colhoun 2010 [29] | breast | glargine + non-glargine | non-glargine insulins only | women | 1.19 | 0.72 | 1.94 |
| Colhoun 2010 [29] | prostate | glargine only | non-glargine insulins only | men | 1.14 | 0.45 | 2.84 |
| Colhoun 2010 [29] | prostate | glargine + non-glargine | non-glargine insulins only | men | 1.05 | 0.58 | 1.91 |
| Colhoun 2010 [29] | colorectal | glargine only | non-glargine insulins only | both | 1.13 | 0.62 | 2.04 |
| Colhoun 2010 [29] | colorectal | glargine + non-glargine | non-glargine insulins only | both | 0.58 | 0.36 | 0.93 |
| Colhoun 2010 [29] | pancreatic | glargine only | non-glargine insulins only | both | 1.34 | 0.64 | 2.78 |
| Colhoun 2010 [29] | pancreatic | glargine + non-glargine | non-glargine insulins only | both | 0.11 | 0.03 | 0.45 |
| Colhoun 2010 [29] | any excl nmsc | glargine | non-glargine insulins only | both | 0.69 | 0.60 | 0.79 |
| Currie 2009 [30] | any human long-acting only | glargine only | both | 1.24 | 0.90 | 1.70 |
| Currie 2009 [30] | any human biphasic glargine only | both | 0.88 | 0.66 | 1.19 |
| Currie 2009 [30] | analog biphasic glargine only | both | 1.02 | 0.76 | 1.37 |
| Currie 2009 [30] | insulin metformin only | both | 1.42 | 1.27 | 1.60 |
| Author (country) | Outcome | Exposure | Comparator | Gender Risk estimate | 95% Confidence Interval |
|-----------------|---------|----------|------------|----------------------|-------------------------|
| Currie 2009     | any     | insulin  | metformin only | both 1.35           | 1.19 / 1.54             |
| Currie 2009     | colorectal | insulin | metformin only | both 1.69           | 1.23 / 2.33             |
| Currie 2009     | pancreatic | insulin | metformin only | both 4.63           | 2.64 / 8.10             |
| Currie 2009     | prostate | insulin  | metformin only | men 1.10            | 0.79 / 1.52             |
| Currie 2009     | breast | insulin  | metformin only | women 1.07          | 0.79 / 1.44             |
| Currie 2009     | breast | glargine only | non-glargine insulin | women 0.86 | 0.42 / 1.75             |
| Currie 2009     | composite | human long-acting only | glargine only | both 1.17 | 0.70 / 1.94             |
| Currie 2009     | composite | human biphasic glargine only | both 0.76 | 0.47 / 1.24             |
| Currie 2009     | composite | analog biphasic glargine only | both 1.01 | 0.63 / 1.63             |
| Fagot 2012      | any     | glargine | other int-long-acting insulins | both 1.04 | 0.93 / 1.16             |
| Fagot 2012      | any     | glargine | other int-long-acting insulins | both 1.04 / 1.04 | 0.91 / 0.88 / 0.91 | 1.18 / 1.16 / cumulative dose (<14000/14000-27000/27000+ IU) |
| Fagot 2012      | any     | detemir  | other int-long-acting insulins | both 1.01 | 0.89 / 1.13             |
| Fagot 2012      | any     | detemir  | other int-long-acting insulins | both 1.05 / 0.91 | 0.88 / 0.73 / 0.85 | 1.23 / 1.12 / cumulative dose (<14000/14000-27000/27000+ IU) |
| Fagot 2012      | any     | human int-long-acting human int-long-acting | both 0.91 | 0.76 / 1.08             |
| Fagot 2012      | any     | human int-long-acting human int-long-acting | both 0.94 / 0.89 | 0.73 / 0.65 / 0.63 | 1.18 / 1.21 / cumulative dose (<14000/14000-27000/27000+ IU) |
| Fagot 2012      | breast | glargine | other int-long-acting insulins | women 1.08 | 0.72 / 1.62             |
| Fagot 2012      | breast | glargine | other int-long-acting insulins | women 0.88 / 1.02 | 0.84 / 0.54 / 0.91 | 1.45 / 1.67 / cumulative dose (<14000/14000-27000/27000+ IU) |
| Fagot 2012      | breast | detemir  | other int-long-acting insulins | women 1.08 | 0.72 / 1.62             |
| Fagot 2012      | breast | detemir  | other int-long-acting insulins | women 1.13 / 1.02 | 0.66 / 0.51 / 0.48 | 1.96 / 2.03 / cumulative dose (<14000/14000-27000/27000+ IU) |
| Fagot 2012      | breast | human int-long-acting human int-long-acting | women 1.03 | 0.56 / 1.88             |
| Fagot 2012      | breast | human int-long-acting human int-long-acting | women 1.21 / 1.51 | 0.56 / 0.61 / 0.56 / 1.26 / 3.72 / cumulative dose (<14000/14000-27000/27000+ IU) |
| Fagot 2012      | colorectal | glargine | other int-long-acting insulins | both 0.98 | 0.72 / 1.32             |
| Fagot 2012      | liver | glargine | other int-long-acting insulins | both 1.07 | 0.72 / 1.59             |
| Fagot 2012      | kidney | glargine | other int-long-acting insulins | both 1.11 | 0.54 / 2.26             |
| Fagot 2012      | bladder | glargine | other int-long-acting insulins | both 1.06 | 0.67 / 1.66             |
| Fagot 2012      | lung | glargine | other int-long-acting insulins | both 1.10 | 0.78 / 1.57             |
| Fagot 2012      | head+neck | glargine | other int-long-acting insulins | both 0.91 | 0.48 / 1.72             |
| Fagot 2012      | prostate | glargine | other int-long-acting insulins | men 1.01 | 0.68 / 1.48             |
| Ferrara 2011    | prostate | insulin | no insulin | men 0.80 | 0.70 / 0.90             |
| Ferrara 2011    | breast | insulin | no insulin | women 1.00 | 0.90 / 1.20             |
| Ferrara 2011    | lung+bronchus | insulin | no insulin | both 1.10 | 0.90 / 1.30             |
| Author (country)          | Outcome | Exposure | Comparator | Gender Risk estimate | 95% Confidence Interval |
|--------------------------|---------|----------|------------|----------------------|-------------------------|
| Ferrara 2011 colon [32]  |         | insulin  | no insulin | 1.10                 | 0.90 / 1.30             |
| Ferrara 2011 NHL [32]    |         | insulin  | no insulin | 1.00                 | 0.80 / 1.30             |
| Ferrara 2011 uterus [32] |         | insulin  | no insulin | 3.10                 | 2.40 / 4.00             |
| Ferrara 2011 pancreatic  | insulin | no insulin | both  | 1.30                 | 0.90 / 1.70             |
| Ferrara 2011 kidney+renal pelvis [32] | insulin | no insulin | both  | 1.00                 | 0.70 / 1.40             |
| Ferrara 2011 rectal [32] |         | insulin  | no insulin | 1.10                 | 0.80 / 1.50             |
| Ferrara 2011 melanoma [32] |      | insulin  | no insulin | 1.00                 | 0.80 / 1.30             |
| henkens 2009 [33]        |         | aspartat only | human only | both  | 1.00 / 1.02 / 1.04 | 0.82 / 0.85 / 0.87 / 1.21 / 1.22 / 1.24 / mean daily dose (10/30/50 IU mean daily dose) |
| henkens 2009 [33]        |         | lispro only | human only | both  | 0.99 / 0.98 / 0.98 | 0.82 / 0.83 / 0.83 / 1.19 / 1.16 / IU mean daily dose (10/30/50) |
| henkens 2009 [33]        |         | glargine only | human only | both  | 1.09 / 1.19 / 1.31 | 1.00 / 1.10 / 1.20 / 1.19 / 1.30 / 1.42 / mean daily dose (10/30/50 IU mean daily dose) |
| Hense 2011 any           |         | insulin only | no use human insulin | both  | 1.25                 | 1.17 / 1.33             |
| Hense 2011 any           |         | insulin analogs | no use insulin analogs | both  | 0.89                 | 0.79 / 1.01             |
| Hsieh 2012 any           |         | insulin only | metformin only | both  | 1.78                 | 1.41 / 2.26             |
| Hsieh 2012 colorectal    |         | insulin only | metformin only | both  | 2.14                 | 1.23 / 3.72             |
| Hsieh 2012 lung          |         | insulin only | metformin only | both  | 1.06                 | 0.51 / 2.18             |
| Hsieh 2012 liver         |         | insulin only | metformin only | both  | 1.82                 | 1.08 / 3.08             |
| Hsieh 2012 stomach       |         | insulin only | metformin only | both  | 1.86                 | 0.78 / 4.42             |
| Hsieh 2012 pancreatic    |         | insulin only | metformin only | both  | 0.69                 | 0.09 / 5.55             |
| Hsieh 2012 breast        |         | insulin only | metformin only | women 1.63 | 0.60 | 4.40 / 4.40 |
| Hsieh 2012 prostate      |         | insulin only | metformin only | men 0.89 | 0.34 | 2.36 / 2.36 |
| Kostev 2012 breast       |         | glargine  | nph insulin | women 0.93 | 0.68 | 1.27 / 1.27 |
| Kostev 2012 breast       |         | detemir   | nph insulin | women 1.17 | 0.66 | 2.06 / 2.06 |
| Lai 2012 pancreatic      |         | insulin  | no insulin | both  | 2.20                 | 1.40 / 3.45             |
| Lai 2012 lung            |         | insulin  | no insulin | both  | 1.00                 | 0.68 / 1.45             |
| Lai 2012 hcc             |         | insulin  | no insulin | both  | 0.98                 | 0.74 / 1.28             |
| Lind 2012 breast         |         | glargine  | no glargine | women 1.54 | 0.90 | 2.67 / 2.67 |
| Lind 2012 prostate       |         | glargine  | no glargine | men 1.37 | 0.78 | 2.39 / 2.39 |
| Ljung 2011 any           |         | glargine only | non-glargine insulins only | both  | 1.10                 | 0.96 / 1.26             |
| Ljung 2011 gastrointestinal |     | glargine only | non-glargine insulins only | both  | 0.86                 | 0.61 / 1.23             |
| Ljung 2011 colorectal    |         | glargine only | non-glargine insulins only | both  | 0.88                 | 0.61 / 1.28             |
| Author (country) | Outcome ¹ | Exposure     | Comparator          | Gender Risk estimate ² | 95% Confidence Interval ³ |
|-----------------|-----------|--------------|---------------------|------------------------|--------------------------|
| Ljung 2011 [41]| pancreatic| glargine only| non-glargine        | both 1.52              | 0.82 / 2.33              |
| Ljung 2011 [41]| prostate  | glargine only| non-glargine        | men 1.11               | 0.81 / 1.52              |
| Ljung 2011 [41]| breast    | glargine only| non-glargine        | women 1.60             | 1.10 / 2.32              |
| Ljung 2011 [41]| breast    | glargine only| non-glargine        | women 1.58             | 1.09 / 2.32              |
| Ljung 2011 [41]| breast    | glargine only| non-glargine        | women 1.60             | 1.07 / 2.39              |
| Ljung 2011 [41]| any       | glargine only| non-glargine        | both 1.10              | 0.90 / 1.35              |
| Ljung 2011 [41]| gastrointestinal | glargine only | non-glargine  | both 0.80  | 0.46 / 1.38 |
| Ljung 2011 [41]| colorectal| glargine only| non-glargine        | both 0.76              | 0.41 / 1.38              |
| Ljung 2011 [41]| pancreatic| glargine only| non-glargine        | both 1.04              | 0.32 / 3.31              |
| Ljung 2011 [41]| prostate  | glargine only| non-glargine        | men 1.19               | 0.76 / 1.87              |
| Ljung 2011 [41]| breast    | glargine only| non-glargine        | women 0.87             | 0.41 / 1.85              |
| Morden 2011 [42]| any      | glargine only| non-glargine        | both 0.94              | 0.88 / 1.01              |
| Morden 2011 [42]| any      | glargine + non-glargin | non-glargine  | both 0.94  | 0.87 / 1.01 |
| Morden 2011 [42]| colon    | glargine only| non-glargine        | both 0.79              | 0.60 / 1.05              |
| Morden 2011 [42]| colon    | glargine + non-glargin | non-glargine  | both 0.95  | 0.74 / 1.23 |
| Morden 2011 [42]| pancreatic| glargine only| non-glargine        | both 0.95              | 0.67 / 1.35              |
| Morden 2011 [42]| pancreatic| glargine + non-glargin | non-glargine  | both 0.71  | 0.47 / 1.07 |
| Morden 2011 [42]| prostate | glargine only| non-glargine        | men 1.12               | 0.88 / 1.42              |
| Morden 2011 [42]| prostate | glargine + non-glargin | non-glargine  | men 0.89  | 0.68 / 1.18 |
| Morden 2011 [42]| breast   | glargine only| non-glargine        | women 1.03             | 0.83 / 1.29              |
| Morden 2011 [42]| breast   | glargine + non-glargin | non-glargine  | women 1.08  | 0.86 / 1.36 |
| Neumann 2012 [43]| bladder | insulin     | no insulin          | both 1.08              | 0.97 / 1.21              |
| Neumann 2012 [43]| colorectal| insulin     | no insulin          | both 1.05              | 1.01 / 1.11              |
| Neumann 2012 [43]| kidney   | insulin     | no insulin          | both 1.09              | 1.00 / 1.20              |
| Neumann 2012 [43]| lung     | insulin     | no insulin          | both 1.23              | 1.17 / 1.29              |
| Neumann 2012 [43]| head+neck| insulin     | no insulin          | both 1.24              | 1.14 / 1.36              |
| Neumann 2012 [43]| breast   | insulin     | no insulin          | women 0.86             | 0.81 / 0.91              |
| Newton 2012 [44]| bladder  | insulin     | no insulin          | both 1.70              | 1.13 / 2.54              |
| Oliveria 2008 [45]| bladder | insulin only | no insulin          | both 1.09              | 0.72 / 1.64              |
| Oliveria 2008 [45]| liver    | insulin only | no insulin          | both 1.19              | 0.54 / 2.65              |
| Oliveria 2008 [45]| pancreatic| insulin only | no insulin          | both 0.64              | 0.34 / 1.21              |
| Oliveria 2008 [45]| colorectal| insulin only | no insulin          | both 0.99              | 0.74 / 1.33              |
| Oliveria 2008 [45]| colorectal| insulin only | other ad drug       | both 1.48 / 1.24       | 0.58 / 0.57 / 3.78 / 2.68 | time of use (past/current) |
| Author (country) | Outcome | Exposure | Comparator | Gender Risk estimate | 95% Confidence Interval |
|-----------------|---------|----------|------------|----------------------|------------------------|
| Redaniel 2012 [46] | breast | insulin only | no ad drugs | women 0.72 | 0.60 / 0.87 |
| Redaniel 2012 [46] | breast | insulin only | sulfonylurea only | women 1.14 | 0.54 / 2.39 |
| Redaniel 2012 [46] | breast | insulin only | sulfonylurea only | women 1.33 | 0.63 / 2.83 |
| Redaniel 2012 [46] | breast | insulin only | sulfonylurea only | women 1.01 / 0.54 / 2.25 | 0.11 / 0.18 / 0.72 / 8.97 / 1.68 / duration since start exp / (<=1/5/>5 years) |
| Redaniel 2012 [46] | breast | insulin only | sulfonylurea only | women 1.33 | 0.63 / 2.78 |
| Redaniel 2012 [46] | breast | insulin only | sulfonylurea only | women 1.67 | 0.70 / 3.99 |
| Ruiter 2012 [47] | any | glargine only | human only | both 0.75 | 0.71 / 0.80 |
| Ruiter 2012 [47] | any | non-glargine analogs only | human only | both 0.85 | 0.82 / 0.89 |
| Ruiter 2012 [47] | colon | glargine only | human only | both 0.55 | 0.39 / 0.76 |
| Ruiter 2012 [47] | colon | non-glargine analogs only | human only | both 1.07 | 0.93 / 1.25 |
| Ruiter 2012 [47] | bladder | glargine only | human only | both 1.89 | 0.69 / 3.21 |
| Ruiter 2012 [47] | bladder | non-glargine analogs only | human only | both 0.48 | 0.34 / 0.69 |
| Ruiter 2012 [47] | respiratory | glargine only | human only | both 1.03 | 0.84 / 1.24 |
| Ruiter 2012 [47] | respiratory | non-glargine analogs only | human only | both 0.64 | 0.54 / 0.77 |
| Ruiter 2012 [47] | prostate | glargine only | human only | men 2.76 | 1.32 / 5.80 |
| Ruiter 2012 [47] | prostate | non-glargine analogs only | human only | men 0.83 | 0.70 / 1.03 |
| Ruiter 2012 [47] | breast | glargine only | human only | women 1.58 | 1.22 / 2.05 |
| Ruiter 2012 [47] | breast | non-glargine analogs only | human only | women 0.95 | 0.83 / 1.08 |
| Ruiter 2012 [47] | any | glargine | human | both 0.77 | 0.73 / 0.82 |
| Ruiter 2012 [47] | any | non-glargine analogs only | human | both 0.85 | 0.82 / 0.88 |
| Ruiter 2012 [47] | colon | glargine | human | both 0.61 | 0.43 / 0.88 |
| Ruiter 2012 [47] | colon | non-glargine analogs only | human | both 0.87 | 0.78 / 0.97 |
| Ruiter 2012 [47] | bladder | glargine | human | both 1.77 | 1.04 / 3.00 |
| Ruiter 2012 [47] | bladder | non-glargine analogs only | human | both 0.69 | 0.57 / 0.84 |
| Ruiter 2012 [47] | respiratory | glargine | human | both 0.92 | 0.74 / 1.16 |
| Ruiter 2012 [47] | respiratory | non-glargine analogs only | human | both 0.70 | 0.62 / 0.78 |
| Ruiter 2012 [47] | prostate | glargine | human | men 1.17 | 0.84 / 1.62 |
| Ruiter 2012 [47] | prostate | non-glargine analogs only | human | men 0.82 | 0.69 / 0.97 |
| Ruiter 2012 [47] | breast | glargine | human | women 1.39 | 1.08 / 1.79 |
| Ruiter 2012 [47] | breast | non-glargine analogs only | human | women 1.00 | 0.93 / 1.09 |
| Suissa 2012 [48] | breast | glargine | non-glargine insulins only | women 0.80 | 0.30 / 2.10 |
| Suissa 2012 [48] | breast | glargine | non-glargine insulins only | women 1.0 / 0.9 / 0.8 / 0.8 / 0.3 / 0.3 / 0.2 / 0.2 / 3.1 / 2.7 / 3.1 / ne | 1.40 / duration since start exp / (<=1/5/>5 years) |
| Suissa 2012 [48] | breast | glargine | non-glargine insulins only | women 1.00 | 0.70 / duration since start exp / (<=1/5/>5 years) |

**Supplementary Material**
### Supplementary Material

**Current Drug Safety, 2013, Vol. 8, No. 5**

| Author (country) | Outcome | Exposure | Comparator | Gender Risk estimate | 95% Confidence Interval |
|------------------|---------|----------|------------|----------------------|-------------------------|
| Tseng 2012 [49]  | NHL     | insulin  | no insulin | both                 | 2.52                    |
| Van Staa 2012 [50] | any excl nmsc | insulin only | metformin only | both             | 1.49 / 1.36 / 1.05 / 1.07 / 0.86 / 0.95 / 1.46 |
| Yang 2010 [51]   | any     | insulin  | no insulin | both                 | 0.17                    |
| Yang 2010 [51]   | digestive+peritoneum | insulin | no insulin | both                 | 0.19                    |

#### 2) Case control studies (15 studies)

| Author (country) | Outcome | Exposure | Comparator | Gender Risk estimate | 95% Confidence Interval | Dose/duration strata |
|------------------|---------|----------|------------|----------------------|-------------------------|----------------------|
| Bodmer 2010 [52] | breast  | insulin  | no insulin | women                | 1.74 / 1.30 / 1.17 / 1.07 / 1.00 / 0.72 / 0.54 / 0.31 / 0.22 | number of prescriptions (1-9/10-29/30+ rx) |
| Bodmer 2011 [53] | ovarian | insulin  | no insulin | women                | 4.67 / 1.17 / 0.59 / 0.75 / 0.61 / 0.73 / 0.66 / 0.86 / 0.95 / 1.07 / 1.28 | number of prescriptions (1-9/10-29/30+ rx) |
| Bodmer 2012 [54] | colorectal | Insulin | no insulin | both                 | 1.11 / 1.40 / 0.73 / 0.66 / 0.72 / 0.73 | number of prescriptions (1-9/10-29/30+ rx) |
| Bodmer 2012 [55] | lung    | Insulin  | no insulin | both                 | 1.64 / 1.16 / 1.12 / 1.05 / 1.17 / 1.21 | number of prescriptions (1-9/10-29/30+ rx) |
| Bonelli 2003 [56] | pancreatic | insulin | oad      | both                 | 7.68 / 1.67 / 35.40 / 1.73 / 1.21 / 1.93 | number of prescriptions (1-9/10-29/30+ rx) |
| Chang 2012 [57]  | liver   | human short-acting | no use human short-acting | both | 2.50 / 2.25 / 1.66 / 1.80 / 1.41 / 1.76 / 1.20 / 1.40 / 1.82 / 1.61 | cumulative dose (low/medium/high) |
| Chang 2012 [57]  | colorectal | human short-acting | no use human short-acting | both | 2.56 / 2.05 / 1.5 / 2.05 / 1.57 / 1.07 / 1.57 / 1.28 | cumulative duration (<1/1-2/2+ years) |
| Chang 2012 [57]  | lung    | human short-acting | no use human short-acting | both | 1.90 / 1.20 / 0.59 / 0.73 / 0.86 / 0.73 / 0.95 / 0.62 / 0.72 / 1.00 | cumulative duration (<1/1-2/2+ years) |
| Chang 2012 [58]  | bladder | human short-acting | no use human short-acting | both | 1.11 / 0.72 / 1.28 / 1.00 / 1.00 / 1.00 | cumulative duration (<1/1-2/2+ years) |
| Chang 2012 [58]  | any     | insulin  | no insulin | both                 | 1.97 / 1.97 / 1.85 / 1.92 / 1.90 / 1.85 / 1.78 / 0.95 / 0.69 / 1.25 | time of use (past/recent/current) |
| Chang 2012 [58]  | any     | insulin  | no insulin | both                 | 2.00 / 2.00 / 1.15 / 1.18 / 1.20 / 1.20 / 1.15 / 1.09 / 1.09 / 1.09 | cumulative duration (<1/1-2/2+ years) |
| Chang 2012 [58]  | colorectal | insulin | no insulin | both | 2.67 / 2.67 / 2.49 / 2.49 / 2.50 / 2.50 | cumulative duration (<1/1-2/2+ years) |
| Chang 2012 [58]  | lung    | insulin  | no insulin | both                 | 1.86 / 1.86 / 1.65 / 1.65 / 1.65 / 1.65 | cumulative duration (<1/1-2/2+ years) |
| Chang 2012 [58]  | breast  | insulin  | no insulin | both                 | 0.93 / 0.93 / 0.69 / 0.69 / 0.69 / 0.69 | cumulative duration (<1/1-2/2+ years) |
| Chang 2012 [58]  | prostate | insulin  | no insulin | men                  | 0.88 / 0.88 / 0.64 / 0.64 / 0.64 / 0.64 | cumulative duration (<1/1-2/2+ years) |
| Chang 2012 [58]  | stomach | insulin  | no insulin | both                 | 2.46 / 2.46 / 1.91 / 1.91 / 1.91 / 1.91 | cumulative duration (<1/1-2/2+ years) |
| Chang 2012 [58]  | pancreatic | insulin | no insulin | both | 3.75 / 3.75 / 2.53 / 2.53 / 2.53 / 2.53 | cumulative duration (<1/1-2/2+ years) |
| Chang 2012 [58]  | liver   | insulin  | no insulin | both                 | 1.98 / 1.98 / 1.72 / 1.72 / 1.72 / 1.72 | cumulative duration (<1/1-2/2+ years) |
| Author (country) | Outcome | Exposure | Comparator | Gender Risk estimate† | 95% Confidence Interval | Dose/duration strata† |
|----------------|---------|----------|------------|-----------------------|------------------------|----------------------|
| Chang 2012 [58] | liver   | insulin  | no insulin | both 1.11 / 1.74 / 10.28 | 0.92 / 1.32 / 7.68 | time of use (past/recent/current) |
| Chang 2012 [58] | liver   | insulin  | no insulin | both 2.15 / 1.84 / 1.94 | 1.74 / 1.48 / 1.54 | cumulative dose (low/intermediate/high) |
| Chang 2012 [58] | liver   | insulin  | no insulin | both 1.96 / 2.90 / 2.79 | 1.68 / 1.68 / 1.58 | cumulative duration (<1/1-2/2+ years) |
| Cleveland 2012 [59] | breast | insulin  | no insulin | women 1.15 | 0.40 | 3.40 | 0.00 |
| Fortuny 2005 [60] | lymphoma | insulin  | no insulin | both 0.73 / 0.36 | 0.23 / 0.07 | 2.33 / 1.79 | 0.00 |
| Kawaguchi 2010 [61] | hcc | Insulin  | No insulin | both 2.97 | 1.29 | 6.82 | 0.00 |
| Koro 2007 [62] | colon | insulin only | thiazolidinediones | both 4.46 | 1.05 | 19.00 | 0.00 |
| Koro 2007 [62] | colon | insulin only | thiazolidinediones | both 1.25 | 0.68 | 2.32 | 0.00 |
| Koro 2007 [62] | prostate | insulin only | thiazolidinediones | men 1.80 | 0.79 | 4.07 | 0.00 |
| Koro 2007 [62] | prostate | insulin only | thiazolidinediones | men 1.09 | 0.61 | 1.95 | 0.00 |
| Koro 2007 [62] | breast | insulin only | thiazolidinediones | women 1.27 | 0.61 | 2.67 | 0.00 |
| Koro 2007 [62] | breast | insulin only | thiazolidinediones | women 1.00 | 0.56 | 1.77 | 0.00 |
| Li 2011 [63] | pancreatic | insulin | no insulin | both 2.20 | 1.60 | 3.00 | 0.00 |
| Li 2011 [63] | pancreatic | insulin | no insulin | both 2.4 / 1.2 / 0.5 | 1.6 / 0.7 / 0.3 | 3.7 / 1.9 / 0.9 | 0.00 |
| Mizuno 2013 [64] | pancreatic | Insulin | No insulin | both 3.52 | 1.00 | 14.87 | 0.00 |
| Mizuno 2013 [64] | pancreatic | Insulin | No insulin | both 4.77 / 2.47 | 1.09 / 0.71 | 22.34 / 9.91 | 0.00 |
| Mizuno 2013 [64] | pancreatic | Insulin | No insulin | both 3.50 / 2.63 | 0.89 / 0.72 | 15.15 / 10.81 | cumulative dose (<30/30+ U/day) |
| Vinikoor 2009 [65] | rectal | insulin | no insulin | both 1.74 | 0.92 | 3.31 | 0.00 |
| Vinikoor 2009 [65] | rectal | insulin | no insulin | both 2.11 | 1.05 | 4.23 | 0.00 |
| Vinikoor 2009 [65] | rectal | insulin | no insulin | both 2.53 | 1.21 | 5.28 | 0.00 |
| Yang 2004 [66] | colorectal | insulin | no insulin | both 1.4 / 2.9 / 4.7 | 0.6 / 1.1 / 1.3 | 2.9 / 7.7 / 16.7 | cumulative duration (1-<3/3-<5/5+ years) |
| Yang 2004 [66] | colorectal | insulin | no insulin | both 1.21 | 1.03 | 1.42 | incremental duration (1-year increment) |
Supplementary Material 4: (Tables 1-14)

Presents estimates by 14 cancer sites examined in more than one study, sorted by type of exposure-comparator contrast (e.g. insulin vs. no insulin) and name of exposure. Only one risk estimate for each combination of cancer site and exposure contrast is included (chosen according to algorithm presented in article). These are the estimates preferred for inclusion in the pooled analyses, but note that pooled analyses were actually only performed for the 3 most frequently used exposure contrasts that were studied in several populations. See Supplementary Material 5 for cancer sites only examined in one study.

Abbreviations: ad, antidiabetic drug; excl, excluding; exp, exposure; Int-, intermediate-acting; ne, not estimable; niad, non-insulin antidiabetic drugs; oad, oral antidiabetic drug;

1) Any cancer (with or without exclusion of non-melanoma skin cancer)

| Author (country) | Exposure | Comparator | Gender | Risk  | [95% CI]   |
|------------------|----------|------------|--------|-------|------------|
| **Insulin vs. no insulin:** |          |            |        |       |            |
| Yang 2010 [51]   | insulin  | no insulin | both   | 0.17  | [0.09 , 0.32] |
| Carstensen 2012 [27] | insulin | no insulin | men    | 1.14  | [1.08 , 1.20] |
| Carstensen 2013 [27] | insulin | no insulin | women  | 1.23  | [1.16 , 1.30] |
| Chang 2012 [58]  | insulin  | no insulin | both   | 1.97  | [1.85 , 2.09] |
| **Insulin vs. niad:** |          |            |        |       |            |
| Currie 2009 [30] | insulin  | metformin only | both | 1.35  | [1.19 , 1.54] |
| Hsieh 2012 [35]  | insulin only | metformin only | both | 1.78  | [1.41 , 2.26] |
| **Insulin A vs. B:** |          |            |        |       |            |
| Currie 2009 [30] | analog biphasic | glargine only | both | 1.02  | [0.76 , 1.37] |
| Fagot 2012 [31]  | detemir  | other int-/long-acting insulins | both | 1.01  | [0.89 , 1.13] |
| Ruiter 2012 [47] | glargine | human | both | 0.77  | [0.73 , 0.82] |
| Chang 2011 [28]  | glargine | human int-/long-acting | both | 0.86  | [0.73 , 1.02] |
| Fagot 2012 [31]  | glargine | other int-/long-acting insulins | both | 1.04  | [0.93 , 1.16] |
| Blin 2012 [25]   | glargine only | human only | both | 0.59  | [0.28 , 1.25] |
| Colhoun 2010 [29] | glargine only | non-glargine insulins only | both | 1.64  | [1.05 , 2.54] |
| Morden 2011 [42] | glargine only | non-glargine insulins only | both | 0.94  | [0.88 , 1.01] |
| Ljung 2011 [41]  | glargine only | non-glargine insulins only | both | 1.10  | [0.96 , 1.26] |
| Currie 2009 [30] | human biphasic | glargine only | both | 0.88  | [0.66 , 1.19] |
| Fagot 2012 [31]  | human int-/long-acting | other int-/long-acting insulins | both | 0.91  | [0.76 , 1.08] |
| Currie 2009 [30] | human long-acting only | glargine only | both | 1.24  | [0.90 , 1.70] |
| Ruiter 2012 [47] | non-glargine analogs only | human | both | 0.85  | [0.82 , 0.88] |
| **Insulin A vs. B or no insulin:** |          |            |        |       |            |
| Hense 2011 [34]  | insulin analogs | no use insulin analogs | both | 0.89  | [0.79 , 1.01] |
| Hense 2011 [34]  | human only | no use human insulin | both | 1.25  | [1.17 , 1.33] |
2) Breast cancer

| Author                     | Exposure    | Comparator       | Gender | Risk     | [95% CI]      |
|----------------------------|-------------|------------------|--------|----------|---------------|
| Neumann 2012 [43]          | insulin     | no insulin       | women  | 0.86     | [0.81, 0.91]  |
| Carstensen 2013 [27]       | insulin     | no insulin       | men    | 2.59     | [0.84, 7.94]  |
| Carstensen 2013 [27]       | insulin     | no insulin       | women  | 0.96     | [0.84, 1.09]  |
| Ferrara 2011 [32]          | insulin     | no insulin       | women  | 1.00     | [0.90, 1.20]  |
| Chang 2012 [58]            | insulin     | no insulin       | both?  | 0.93     | [0.69, 1.25]  |
| Cleveland 2012 [59]        | insulin     | no insulin       | women  | 1.15     | [0.40, 3.40]  |
| Redaniel 2012 [46]         | insulin only| no ad drugs      | women  | 0.72     | [0.60, 0.87]  |

**Insulin vs. no insulin:**

| Author                     | Exposure    | Comparator       | Gender | Risk     | [95% CI]      |
|----------------------------|-------------|------------------|--------|----------|---------------|
| Currie 2009 [30]           | insulin     | metformin only   | women  | 1.07     | [0.79, 1.44]  |
| Koro 2007 [62]             | insulin only| thiazolidinediones| women  | 1.27     | [0.61, 2.67]  |
| Hsieh 2012 [35]            | insulin only| metformin only   | women  | 1.63     | [0.60, 4.40]  |
| Redaniel 2012 [46]         | insulin only| sulfonylurea only| women  | 1.14     | [0.54, 2.39]  |

**Insulin A vs. B:**

| Author                     | Exposure    | Comparator       | Gender | Risk     | [95% CI]      |
|----------------------------|-------------|------------------|--------|----------|---------------|
| Kostev 2012 [36]           | detemir     | nph insulin      | women  | 1.17     | [0.66, 2.06]  |
| Fagot 2012 [31]            | detemir     | other int- / long-acting insulins | women  | 1.08     | [0.72, 1.62]  |
| Ruiter 2012 [47]           | glargine    | human            | women  | 1.39     | [1.08, 1.79]  |
| Chang 2011 [28]            | glargine    | human int- / long-acting | women  | 0.53     | [0.21, 1.31]  |
| Suissa 2012 [48]           | glargine    | non-glargine insulins only | women  | 0.80     | [0.30, 2.10]  |
| Kostev 2012 [36]           | glargine    | nph insulin      | women  | 0.93     | [0.68, 1.27]  |

**Insulin A vs. B or no insulin:**

| Author                     | Exposure    | Comparator       | Gender | Risk     | [95% CI]      |
|----------------------------|-------------|------------------|--------|----------|---------------|
| Lind 2012 [40]             | glargine    | no glargine      | women  | 1.54     | [0.90, 2.67]  |

3) Prostate cancer

| Author                     | Exposure    | Comparator       | Gender | Risk     | [95% CI]      |
|----------------------------|-------------|------------------|--------|----------|---------------|
| Carstensen 2013 [27]       | insulin     | no insulin       | men    | 0.79     | [0.69, 0.90]  |
| Ferrara 2011 [32]          | insulin     | no insulin       | men    | 0.80     | [0.70, 0.90]  |
| Chang 2012 [58]            | insulin     | no insulin       | men    | 0.88     | [0.64, 1.20]  |

**Insulin vs. no insulin:**

| Author                     | Exposure    | Comparator       | Gender | Risk     | [95% CI]      |
|----------------------------|-------------|------------------|--------|----------|---------------|
| Currie 2009 [30]           | insulin     | metformin only   | men    | 1.10     | [0.79, 1.52]  |
| Koro 2007 [62]             | insulin only| thiazolidinediones| men    | 1.80     | [0.79, 4.07]  |
| Hsieh 2012 [35]            | insulin only| metformin only   | men    | 0.89     | [0.34, 2.36]  |

**Insulin A vs. B:**

| Author                     | Exposure    | Comparator       | Gender | Risk     | [95% CI]      |
|----------------------------|-------------|------------------|--------|----------|---------------|
| Ruiter 2012 [47]           | glargine    | human            | men    | 1.17     | [0.84, 1.62]  |

**Insulin A vs. B or no insulin:**

| Author                     | Exposure    | Comparator       | Gender | Risk     | [95% CI]      |
|----------------------------|-------------|------------------|--------|----------|---------------|
| Lind 2012 [40]             | glargine    | no glargine      | men    | 1.37     | [0.78, 2.39]  |
### 4) Stomach cancer

| Author (country) | Exposure | Comparator | Gender | Risk  | [95% CI]       |
|------------------|----------|------------|--------|-------|----------------|
| **Insulin vs. no insulin:** |          |            |        |       |                |
| Carstensen 2013 [27] | insulin | no insulin | men    | 1.23  | [0.90 , 1.68]  |
| Carstensen 2013 [27] | insulin | no insulin | women  | 1.43  | [0.89 , 2.28]  |
| Chang 2012 [58] | insulin | no insulin | both   | 2.46  | [1.91 , 3.17]  |
| **Insulin vs. niad:** |          |            |        |       |                |
| Hsieh 2012 [35] | insulin only | metformin only | both | 1.86  | [0.78 , 4.42]  |
| **Insulin A vs. B:** |          |            |        |       |                |
| Chang 2011 [28] | glargine | human int- / long-acting | both | 0.62  | [0.27 , 1.42]  |

### 5) Pancreatic cancer

| Author (country) | Exposure | Comparator | Gender | Risk  | [95% CI]       |
|------------------|----------|------------|--------|-------|----------------|
| **Insulin vs. no insulin:** |          |            |        |       |                |
| Lai 2012 [37] | insulin | no insulin | both   | 0.98  | [0.74 , 1.28]  |
| Carstensen 2013 [27] | insulin | no insulin | men    | 2.92  | [2.49 , 3.42]  |
| Carstensen 2013 [27] | insulin | no insulin | women  | 3.30  | [2.77 , 3.93]  |
| Ferrara 2011 [32] | insulin | no insulin | both   | 3.10  | [2.40 , 4.00]  |
| Chang 2012 [58] | insulin | no insulin | both   | 3.75  | [2.61 , 5.38]  |
| Li 2011 [63] | insulin | no insulin | both   | 2.20  | [1.60 , 3.00]  |
| Mizuno 2013 [64] | Insulin | No insulin | both   | 3.52  | [1.00 , 14.87] |
| Oliveria 2008 [45] | insulin only | no insulin | both | 0.64  | [0.34 , 1.21]  |
| **Insulin vs. niad:** |          |            |        |       |                |
| Currie 2009 [30] | insulin | metformin only | both | 4.63  | [2.64 , 8.10]  |
| Bonelli 2003 [36] | insulin | oad | both | 7.68  | [1.67 , 35.40] |
| Hsieh 2012 [35] | insulin only | metformin only | both | 0.69  | [0.09 , 5.55]  |
| **Insulin A vs. B:** |          |            |        |       |                |
| Chang 2011 [28] | glargine | human int- / long-acting | both | 1.85  | [1.06 , 3.22]  |
| Morden 2011 [42] | glargine only | non-glargine insulins only | both | 0.95  | [0.67 , 1.35]  |
| Ljung 2011 [41] | glargine only | non-glargine insulins only | both | 1.52  | [0.82 , 2.83]  |

### 6) Liver cancer

| Author (country) | Exposure | Comparator | Gender | Risk  | [95% CI]       |
|------------------|----------|------------|--------|-------|----------------|
| **Insulin vs. no insulin:** |          |            |        |       |                |
| Lai 2012 [39] | insulin | no insulin | both   | 0.98  | [0.74 , 1.28]  |
| Carstensen 2013 [27] | insulin | no insulin | men    | 2.41  | [1.93 , 3.00]  |
| Carstensen 2013 [27] | insulin | no insulin | women  | 2.59  | [1.58 , 4.23]  |
| Chang 2012 [58] | insulin | no insulin | both   | 1.98  | [1.71 , 2.31]  |
| Kawaguchi 2010 [61] | Insulin | No insulin | both   | 2.97  | [1.29 , 6.82]  |
| Oliveria 2008 [45] | insulin only | no insulin | both | 1.19  | [0.54 , 2.65]  |
| **Insulin vs. niad:** |          |            |        |       |                |
| Hsieh 2012 [35] | insulin only | metformin only | both | 1.82  | [1.08 , 3.08]  |
| **Insulin A vs. B:** |          |            |        |       |                |
| Chang 2011 [28] | glargine | human int- / long-acting | both | 0.76  | [0.54 , 1.08]  |
| Fagot 2012 [31] | glargine | other int- / long-acting insulins | both | 1.07  | [0.72 , 1.59]  |
| **Insulin A vs. B or no insulin:** |          |            |        |       |                |
| Chang 2012 [57] | human short-acting | no use human short-acting | both | 2.35  | [2.21 , 2.49]  |
### Colorectal cancer

| Author (country) | Exposure | Comparator | Gender | Risk   | [95% CI]     |
|------------------|----------|------------|--------|--------|--------------|
| **Insulin vs. no insulin:** |          |            |        |        |              |
| Campbell 2010 [26] | insulin | no insulin | men    | 1.11   | [0.82, 1.51] |
| Campbell 2010 [26] | insulin | no insulin | women  | 0.94   | [0.60, 1.48] |
| Neumann 2012 [43] | insulin | no insulin | both   | 1.05   | [1.01, 1.11] |
| Carstensen 2013 [27] | insulin | no insulin | men    | 0.99   | [0.86, 1.14] |
| Carstensen 2013 [27] | insulin | no insulin | women  | 0.90   | [0.75, 1.09] |
| Chang 2012 [58] | insulin | no insulin | both   | 2.67   | [2.29, 3.12] |
| Oliveria 2008 [45] | insulin only | no insulin | both   | 0.99   | [0.74, 1.33] |
| **Insulin vs. niad:** |          |            |        |        |              |
| Campbell 2010 [26] | insulin | no insulin | men    | 1.13   | [0.79, 1.61] |
| Campbell 2010 [26] | insulin | no insulin | women  | 1.04   | [0.62, 1.73] |
| Carstensen 2013 [27] | insulin | no insulin | men    | 1.00   | [0.84, 1.19] |
| Carstensen 2013 [27] | insulin | no insulin | women  | 0.90   | [0.73, 1.12] |
| Ferrara 2011 [32] | insulin | no insulin | both   | 1.10   | [0.90, 1.30] |
| **Insulin A vs. B:** |          |            |        |        |              |
| Chang 2011 [28] | glargine | human int- / long-acting | both   | 0.78   | [0.49, 1.26] |
| Fagot 2012 [31] | glargine | other int- / long-acting insulins | both   | 0.98   | [0.72, 1.32] |
| Colhoun 2010 [29] | glargine only | non-glargine insulins only | both   | 1.43   | [0.45, 4.57] |
| Ljung 2011 [41] | glargine only | non-glargine insulins only | both   | 0.88   | [0.61, 1.28] |
| **Insulin A vs. B or no insulin:** |          |            |        |        |              |
| Chang 2012 [57] | human short-acting | no use human short-acting | both   | 2.56   | [2.40, 2.72] |

### Colon cancer

| Author (country) | Exposure | Comparator | Gender | Risk   | [95% CI]     |
|------------------|----------|------------|--------|--------|--------------|
| **Insulin vs. no insulin:** |          |            |        |        |              |
| Campbell 2010 [26] | insulin | no insulin | men    | 1.13   | [0.79, 1.61] |
| Campbell 2010 [26] | insulin | no insulin | women  | 1.04   | [0.62, 1.73] |
| Carstensen 2013 [27] | insulin | no insulin | men    | 1.00   | [0.84, 1.19] |
| Carstensen 2013 [27] | insulin | no insulin | women  | 0.90   | [0.73, 1.12] |
| Ferrara 2011 [32] | insulin | no insulin | both   | 1.10   | [0.90, 1.30] |
| **Insulin vs. niad:** |          |            |        |        |              |
| Koro 2007 [62] | insulin only | thiazolidinediones | both   | 4.46   | [1.05, 19.00] |
| **Insulin A vs. B:** |          |            |        |        |              |
| Ruiter 2012 [47] | glargine | human | both   | 0.61   | [0.43, 0.88] |
| Morden 2011 [42] | glargine only | non-glargine insulins only | both   | 0.79   | [0.60, 1.05] |
| Ruiter 2012 [47] | non-glargine analogs only | human | both   | 0.87   | [0.78, 0.97] |

### Rectal cancer

| Author (country) | Exposure | Comparator | Gender | Risk   | [95% CI]     |
|------------------|----------|------------|--------|--------|--------------|
| **Insulin vs. no insulin:** |          |            |        |        |              |
| Campbell 2010 [26] | insulin | no insulin | men    | 1.05   | [0.58, 1.90] |
| Campbell 2010 [26] | insulin | no insulin | women  | 0.65   | [0.24, 1.75] |
| Carstensen 2013 [27] | insulin | no insulin | men    | 0.98   | [0.77, 1.24] |
| Carstensen 2013 [27] | insulin | no insulin | women  | 0.91   | [0.62, 1.32] |
| Ferrara 2011 [32] | insulin | no insulin | both   | 1.00   | [0.70, 1.40] |
| Vinikoor 2009 [65] | insulin | no insulin | both   | 1.74   | [0.92, 3.31] |
10) Respiratory cancer

| Author (country) | Exposure | Comparator | Gender | Risk  | [95% CI] |
|------------------|----------|------------|--------|-------|----------|
| **Insulin vs. no insulin:** | | | | | |
| Lai 2012 [38] | insulin | no insulin | both | 1.00 | [0.68, 1.45] |
| Neumann 2012 [43] | insulin | no insulin | both | 1.23 | [1.17, 1.29] |
| Carstensen 2013 [27] | insulin | no insulin | men | 1.28 | [1.13, 1.45] |
| Carstensen 2013 [27] | insulin | no insulin | women | 1.31 | [1.11, 1.54] |
| Ferrara 2011 [32] | insulin | no insulin | both | 1.10 | [0.90, 1.30] |
| Chang 2012 [58] | insulin | no insulin | both | 1.86 | [1.56, 2.23] |
| **Insulin vs. niad:** | | | | | |
| Hsieh 2012 [35] | insulin only | metformin only | both | 1.06 | [0.51, 2.18] |
| **Insulin A vs. B:** | | | | | |
| Ruiter 2012 [47] | glargine | human int- / long-acting insulins | both | 1.77 | [1.04, 3.00] |
| Fagot 2012 [31] | glargine | other int- / long-acting insulins | both | 1.06 | [0.67, 1.66] |
| Ruiter 2012 [47] | non-glargine analogs only | human | both | 0.69 | [0.57, 0.84] |
| **Insulin A vs. B or no insulin:** | | | | | |
| Chang 2012 [57] | human short-acting | no use human short-acting | both | 1.90 | [1.76, 2.03] |

11) Bladder cancer

| Author (country) | Exposure | Comparator | Gender | Risk  | [95% CI] |
|------------------|----------|------------|--------|-------|----------|
| **Insulin vs. no insulin:** | | | | | |
| Neumann 2012 [43] | insulin | no insulin | both | 1.08 | [0.97, 1.21] |
| Carstensen 2013 [27] | insulin | no insulin | men | 0.91 | [0.75, 1.10] |
| Carstensen 2013 [27] | insulin | no insulin | women | 1.13 | [0.77, 1.64] |
| Newton 2012 [44] | insulin | no insulin | both | 1.70 | [1.13, 2.54] |
| Oliveria 2008 [45] | insulin only | no insulin | both | 1.09 | [0.72, 1.64] |
| **Insulin A vs. B:** | | | | | |
| Ruiter 2012 [47] | glargine | human int- / long-acting insulins | both | 1.06 | [0.67, 1.66] |
| Fagot 2012 [31] | glargine | other int- / long-acting insulins | both | 0.69 | [0.57, 0.84] |
| **Insulin A vs. B or no insulin:** | | | | | |
| Chang 2012 [57] | human short-acting | no use human short-acting | both | 1.11 | [0.96, 1.28] |

12) Kidney cancer

| Author (country) | Exposure | Comparator | Gender | Risk  | [95% CI] |
|------------------|----------|------------|--------|-------|----------|
| **Insulin vs. no insulin:** | | | | | |
| Neumann 2012 [43] | insulin | no insulin | both | 1.09 | [1.00, 1.20] |
| Carstensen 2013 [27] | insulin | no insulin | men | 1.39 | [1.06, 1.83] |
| Carstensen 2013 [27] | insulin | no insulin | women | 2.04 | [1.45, 2.86] |
| Ferrara 2011 [32] | insulin | no insulin | both | 1.30 | [0.90, 1.70] |
| **Insulin A vs. B:** | | | | | |
| Fagot 2012 [31] | glargine | other int- / long-acting insulins | both | 1.11 | [0.54, 2.26] |
13) Melanoma

| Author (country) | Exposure | Comparator | Gender | Risk  | [95% CI] |
|------------------|----------|------------|--------|-------|----------|
| Carstensen 2013 [27] | insulin | no insulin | men    | 0.80  | [0.57, 1.12] |
| Carstensen 2013 [27] | insulin | no insulin | women  | 1.10  | [0.76, 1.60] |
| Ferrara 2011 [32] | insulin | no insulin | both   | 1.10  | [0.80, 1.50] |

14) Non-Hodgkin’s lymphoma (NHL)

| Author (country) | Exposure | Comparator | Gender | Risk   | [95% CI] |
|------------------|----------|------------|--------|--------|----------|
| Carstensen 2013 [27] | insulin | no insulin | men    | 0.85   | [0.60, 1.19] |
| Carstensen 2013 [27] | insulin | no insulin | women  | 1.18   | [0.81, 1.73] |
| Tseng 2012 [49] | insulin | no insulin | both   | 2.52   | [1.37, 4.64] |
| Ferrara 2011 [32] | insulin | no insulin | both   | 1.00   | [0.80, 1.30] |

**Supplementary Material 5**

Presents results for the cancer sites that were only examined in one study per exposure contrast, i.e. no pooled analyses could be performed for these cancer sites.

In addition to these cancer sites, lymphoma was examined in only one study and risk by strata of duration of exposure is presented in Appendix 6 (Fortuny 2005 [60]).

**Abbreviations:** HL, Hodgkin's lymphoma; Int-, intermediate-acting;

| Author (country) | Outcome | Exposure | Comparator | Gender | Risk | [95% CI] |
|------------------|---------|----------|------------|--------|------|----------|
| Carstensen 2013 [27] | leukaemia | insulin | no insulin | men    | 1.01 | [0.72, 1.43] |
| Carstensen 2013 [27] | leukaemia | insulin | no insulin | women  | 1.08 | [0.70, 1.66] |
| Carstensen 2013 [27] | HL | insulin | no insulin | men    | 1.07 | [0.50, 2.29] |
| Carstensen 2013 [27] | HL | insulin | no insulin | women  | 0.52 | [0.12, 2.22] |
| Carstensen 2013 [27] | multiple myeloma | insulin | no insulin | men    | 0.92 | [0.57, 1.49] |
| Carstensen 2013 [27] | multiple myeloma | insulin | no insulin | women  | 0.74 | [0.36, 1.52] |
| Carstensen 2013 [27] | brain | insulin | no insulin | men    | 1.00 | [0.69, 1.44] |
| Carstensen 2013 [27] | brain | insulin | no insulin | women  | 1.47 | [1.00, 2.18] |
| Neumann 2012 [43] | head+neck | insulin | no insulin | both   | 1.24 | [1.14, 1.36] |
| Fagot 2012 [31] | head+neck | glargine | other int-/long-acting insulins | both   | 0.91 | [0.48, 1.72] |
| Chang 2011 [28] | skin | glargine | human int-/long-acting | both   | 1.08 | [0.48, 2.46] |
| Carstensen 2013 [27] | testis | insulin | no insulin | men    | 0.57 | [0.25, 1.28] |
| Carstensen 2013 [27] | ovarian | insulin | no insulin | women  | 1.07 | [0.76, 1.50] |
| Carstensen 2013 [27] | uterus | insulin | no insulin | women  | 1.05 | [0.82, 1.36] |
| Ferrara 2011 [32] | uterus | insulin | no insulin | women  | 1.00 | [0.80, 1.30] |
| Carstensen 2013 [27] | cervical | insulin | no insulin | women  | 1.37 | [0.89, 2.09] |
| Carstensen 2013 [27] | thyroid | insulin | no insulin | men    | 1.38 | [0.57, 3.35] |
| Carstensen 2013 [27] | thyroid | insulin | no insulin | women  | 2.05 | [1.07, 3.90] |
| Carstensen 2013 [27] | oesophagus | insulin | no insulin | men    | 0.98 | [0.67, 1.43] |
| Carstensen 2013 [27] | oesophagus | insulin | no insulin | women  | 1.19 | [0.57, 2.49] |
| Ljung 2011 [41] | gastrointestinal | glargine only | non-glargine insulins only | both   | 0.86 | [0.61, 1.23] |
| Yang 2010 [51] | digestive+peritoneum | insulin | no insulin | both   | 0.19 | [0.08, 0.46] |
Supplementary Material 6

Presents estimates for strata of dose or duration of insulin exposure for all cancer sites and exposure contrasts.

Abbreviations: ad, antidiabetic drug; excl, excluding; exp, exposure; Int-, intermediate-acting; ne, not estimable; niad, non-insulin antidiabetic drugs; nmse, non-melanoma skin cancer; rx, prescription.

† Numbers separated by " / " are estimates by different strata of dose or duration. Note that the same study may have several dose and / or duration analyses for the same cancer site and exposure contrast.

| Author (country) | Outcome¹ | Exposure | Comparator | Dose / duration strata² | Risk estimates³ | 95% Confidence Interval (CI) | Gender | diabetes type |
|------------------|----------|----------|------------|--------------------------|-----------------|-------------------------------|--------|--------------|
| Chang 2012 [58]  | any      | insulin  | no insulin | time of use (past / recent / current) cumulative dose (low / intermediate / high) | 1.03 / 1.32 / 0.94 | 0.95 / 1.18 / 0.893 / 1.49 / 11.08 / 1.22 | both | DM2          |
| Chang 2012 [58]  | any      | insulin  | no insulin | cumulative duration (<1 / 1-2 / 2+ years) | 2.23 / 1.93 / 1.73 | 2.05 / 1.77 / 1.57 / 2.43 / 2.11 / 1.90 | both | DM2          |
| Chang 2012 [58]  | any excl | insulin only | metformin only | duration since start exp (<273 / 274-546 / 547-1001 / 1002-1547 / 1548+ days) | 2.00 / 2.00 / 1.53 | 1.27 / 1.15 / 0.86 / 1.17 | both | DM2          |
| Chang 2011 [28]  | any      | glargine | human int- / long-acting | cumulative dose (<50 / 14000 / 14000-27000 / 27000+ IU) | 1.81 / 0.75 / 0.79 | 0.6 / 0.5 / 0.54 / 1.11 / 0.83 / 1.16 | both | DM2          |
| Chang 2011 [28]  | any      | glargine | human int- / long-acting | mean daily dose (<0.5 / 135-300 / >300 DDD) | 0.68 / 1.05 | 0.52 / 0.84 / 0.89 / 1.32 | both | DM2          |
| Fagot 2012 [31]  | any      | glargine | human int- / long-acting | cumulative duration (<1 / 1-21 year) | 0.83 / 0.91 | 0.69 / 0.61 / 1.01 / 1.16 / 0.91 / 1.24 | both | DM2          |
| Fagot 2012 [31]  | any      | detemir  | other int- / long-acting insulins | cumulative dose (<14000 / 14000-27000 / 27000+ IU) | 1.05 / 0.91 / 1.06 | 0.88 / 0.73 / 1.23 / 1.12 / 0.85 / 1.32 | both | DM2          |
| Fagot 2012 [31]  | any      | human int- / long-acting insulins | cumulative dose (<14000 / 14000-27000 / 27000+ IU) | 0.93 / 0.89 | 0.73 / 0.65 | 1.18 / 1.21 / 0.63 | 1.24 | both | DM2          |
| Bodmer 2010 [52] | breast   | insulin  | no insulin | cumulative duration since start exp (<1 / 1-5 / >5 years) number of prescriptions (1-9 / 10-29 / 30+) | 1.74 / 1.30 / 1.51 | 0.95 / 0.62 / 0.76 / 2.70 / 3.21 / 4.01 | women | DM2          |
| Redaniel 2012 [46] | breast | insulin only | sulfonylurea only | cumulative duration since start exp (<1 / 1-5 / >5 years) | 1.01 / 0.54 / 2.25 | 0.11 / 0.18 | 8.97 / 1.68 / 6.99 | women | DM2          |
| Fagot 2012 [31]  | breast   | detemir  | other int- / long-acting insulins | cumulative dose (<14000 / 14000-27000 / 27000+ IU) | 1.13 / 1.02 / 1.04 | 0.66 / 0.51 / 0.48 / 1.96 / 2.03 / 2.26 | women | DM2          |
| Fagot 2012 [31]  | breast   | human int- / long-acting insulins | cumulative dose (<14000 / 14000-27000 / 27000+ IU) | 1.21 / 1.51 / - | 0.56 / 0.61 / 2.60 / 3.72 / - | women | DM2          |
| Fagot 2012 [31]  | breast   | glargine | other int- / long-acting insulins | cumulative dose (<14000 / 14000-27000 / 27000+ IU) | 0.88 / 1.02 / 1.49 | 0.54 / 0.62 / 0.91 / 1.45 / 1.67 / 2.45 | women | DM2          |
| Suisse 2012 [48] | breast   | glargine | non-glargine insulins only | cumulative duration since start exp (<1 / 1-3 / 3-5 / >5 years) | 1.0 / 0.9 / 0.8 | 0.3 / 0.3 / 0.3 / 0.76 / 2.76 / 2.45 | women | DM2          |
| Suisse 2012 [48] | breast   | glargine | non-glargine insulins only | cumulative duration since start exp (<1 / 1-3 / 3-5 / >5 years) | 0.9 / 1.0 / 0.8 / 1.8 | 0.5 / 0.6 / 0.5 / 1.5 / 1.7 / 1.6 | women | DM2          |

¹ Outcome: breast, colon, lung, ovary, prostate, rectum, stomach, uterus.
² Dose / duration strata: low, intermediate, high.
³ Risk estimates: stratum-specific relative risk estimates, with 95% confidence intervals.
| Author (country) | Outcome | Exposure | Comparator | Dose / duration strata | Risk estimates | 95% Confidence Interval | Gender | diabetes type |
|------------------|---------|----------|------------|------------------------|---------------|------------------------|--------|--------------|
| Chang 2011 [28] | pancreatic | glargine | human int- / long-acting | cumulative dose (<50 / 50-135 / 135-300 / >300 DDD) | 1.23 / 1.19 / 1.15 / 7.90 | 0.53 / 0.34 / 0.27 / 2.64 | both | DM2 |
| Chang 2011 [28] | pancreatic | glargine | human int- / long-acting | cumulative duration (<1 / ≥1 year) mean daily dose (<0.5 / ≥0.5 DDD / day) | 1.75 / 2.58 | 0.98 / 0.50 | 3.12 / 1.23 | both | DM2 |
| Chang 2011 [28] | pancreatic | glargine | human int- / long-acting | cumulative duration (<1 / ≥1 year) mean daily dose (<0.5 / ≥0.5 DDD / day) | 1.92 / 1.84 | 0.85 / 0.86 | 4.32 / 3.95 | both | DM2 |
| Li 2011 [63] | pancreatic | insulin | no insulin | length of use (< 3 years / 3-9 / ≥10 years) cumulative duration (<5 / 5+ years) mean daily dose (<30 / 30+ U / day) cumulative dose (<50 / 50-135 / 135-300 / >300 DDD) | 2.4 / 1.2 / 0.5 | 1.6 / 0.7 / 0.3 | 3.7 / 1.9 / 0.9 | both | Unspecified |
| Mizuno 2013 [64] | pancreatic | insulin | no insulin | length of use (< 3 years / 3-9 / ≥10 years) cumulative duration (<5 / 5+ years) mean daily dose (<30 / 30+ U / day) cumulative dose (<50 / 50-135 / 135-300 / >300 DDD) | 4.77 / 2.47 | 1.09 / 0.71 | 22.34 / 9.91 | both | Unspecified |
| Chang 2011 [28] | pancreatic | insulin | no insulin | length of use (< 3 years / 3-9 / ≥10 years) cumulative duration (<5 / 5+ years) mean daily dose (<30 / 30+ U / day) cumulative dose (<50 / 50-135 / 135-300 / >300 DDD) | 3.50 / 2.63 | 0.89 / 0.72 | 15.15 / 10.81 | both | DM2 |
| Chang 2011 [28] | prostate | glargine | human int- / long-acting | cumulative duration (<1 / ≥1 year) mean daily dose (<0.5 / ≥0.5 DDD / day) | 2.52 / 1.79 | 0.87 / 0.26 | 7.25 / 12.33 | men | DM2 |
| Chang 2011 [28] | prostate | glargine | human int- / long-acting | cumulative duration (<1 / ≥1 year) mean daily dose (<0.5 / ≥0.5 DDD / day) | 2.95 / 1.98 | 0.83 / 0.47 | 10.43 / 8.40 | men | DM2 |
| Chang 2012 [58] | liver | insulin | no insulin | time of use (past / recent / current) cumulative duration (low / intermediate / high) cumulative duration (<1 / 1-2 / ≥2 years) cumulative duration (1-<3 / 3-<5 / 5+ years) number of prescriptions (1-9 / 10-29 / 30-49 / 50+ rx) | 1.11 / 1.74 / 10.28 | 0.92 / 1.32 / 13.74 | 1.35 / 2.31 / 7.68 | both | DM2 |
| Chang 2012 [58] | liver | insulin | no insulin | time of use (past / recent / current) cumulative duration (low / intermediate / high) cumulative duration (<1 / 1-2 / ≥2 years) cumulative duration (1-<3 / 3-<5 / 5+ years) number of prescriptions (1-9 / 10-29 / 30-49 / 50+ rx) | 2.15 / 1.84 / 1.94 | 1.74 / 1.48 / 2.66 | 2.6 / 2.3 / 1.48 | both | DM2 |
| Chang 2012 [58] | liver | insulin | no insulin | time of use (past / recent / current) cumulative duration (low / intermediate / high) cumulative duration (<1 / 1-2 / ≥2 years) cumulative duration (1-<3 / 3-<5 / 5+ years) number of prescriptions (1-9 / 10-29 / 30-49 / 50+ rx) | 1.96 / 2.90 / 2.79 | 1.68 / 1.68 / 2.28 | 4.99 / 2.24 / 1.58 | both | DM2 |
| Yang 2004 [66] | colorectal | insulin | no insulin | length of use (< 3 years / 3-9 / ≥10 years) cumulative duration (1-<3 / 3-<5 / 5+ years) number of prescriptions (1-9 / 10-29 / 30-49 / 50+ rx) | 1.4 / 2.9 / 4.7 | 1.1 / 0.64 / 1.07 | 1.64 / 0.85 / 1.57 | both | DM2 |
| Bodmer 2012 [54] | colorectal | Insulin | no insulin | length of use (< 3 years / 3-9 / ≥10 years) cumulative duration (1-<3 / 3-<5 / 5+ years) number of prescriptions (1-9 / 10-29 / 30-49 / 50+ rx) | 1.11 / 0.64 / 1.07 / 0.90 | 0.73 / 0.75 / 0.73 / 0.63 | 1.64 / 0.85 / 1.57 / 1.57 | both | Unspecified |
| Oliveria 2008 [45] | colorectal | insulin only | other ad drug | time of use (past / current) number of prescriptions (1-9 / 10-29 / 30-49 / 50+ rx) | 1.48 / 1.24 | 0.58 / 0.57 | 3.78 / 2.68 | both | Unspecified |
| Bodmer 2011 [53] | ovarian | insulin | no insulin | number of prescriptions (1-9 / 10-29 / 30+ rx) number of prescriptions (1-9 / 10-29 / 30+ rx) number of prescriptions (1-14 / 10-39 / 40+ rx) | 4.67 / 1.17 / 1.46 | 1.07 / 0.43 / 0.54 | 20.42 / 3.14 / 3.98 | women | Unspecified |
| Bodmer 2012 [55] | lung | Insulin | no insulin | length of use (1-9 / 9+ years) cumulative duration (1-<3 / 3-<5 / 5+ years) number of prescriptions (1-9 / 10-29 / 30+ rx) | 1.64 / 1.16 / 1.53 | 1.20 / 0.84 / 1.18 | 2.24 / 1.59 / 1.99 | both | Unspecified |
| Fortuny 2005 [60] | lymphoma | insulin | no insulin | cumulative duration (1-<3 / 3-<5 / 5+ years) number of prescriptions (1-9 / 10-29 / 30+ rx) number of prescriptions (1-14 / 10-39 / 40+ rx) | 0.73 / 0.36 | 0.23 / 0.07 | 2.33 / 1.79 | both | DM2 |
Supplementary Material 7

List of records excluded because of using same data as one of the records included in the review and study the same cancer site and exposure.

‡ Mannucci study [80] was in final analysis excluded because of ambiguous or insufficient reporting of the comparator group.

| Excluded study       | Included study       |
|----------------------|----------------------|
| Blin 2012 [67]       | Blin 2012 [25]       |
| Li 2009 [68]         | Li 2011 [63]         |
| Silverman 1999 [69]  | Li 2011 [63]         |
| Jonasson 2009 [70]   | Ljung 2011 [41]      |
| Ljung 2012 [71]      | Ljung 2011 [41]      |
| Liao 2012 [72]       | Lai 2012 [37]        |
| Liao 2012 [73]       | Chang 2012 [58]      |
| Monami 2008 [74]     | Mannucci 2010 [80]‡  |
| Monami 2009 [75]     | Mannucci 2010 [80]‡  |