Effect of Long-Acting Insulin Analogs on the Risk of Cancer: A Systematic Review of Observational Studies

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SYSTEMATIC REVIEW

OBJECTIVE

Observational studies examining the association between long-acting insulin analogs and cancer incidence have produced inconsistent results. We conducted a systematic review of these studies, focusing on their methodological strengths and weaknesses.

RESEARCH DESIGN AND METHODS

We systematically searched MEDLINE and EMBASE from 2000 to 2014 to identify all observational studies evaluating the relationship between the long-acting insulin analogs and the risk of any and site-specific cancers (breast, colorectal, prostate). We included cohort and case-control studies published in English on insulin glargine and detemir and any cancer incidence among patients with type 1 or 2 diabetes. The methodological assessment involved the inclusion of prevalent users, inclusion of lag periods, time-related biases, and duration of follow-up between insulin initiation and cancer incidence.

RESULTS

A total of 16 cohort and 3 case-control studies met our inclusion criteria. All studies evaluated insulin glargine, and four studies also examined insulin detemir. Follow-up ranged from 0.9 to 7.0 years. Thirteen of 15 studies reported no association between insulin glargine and detemir and any cancer. Four of 13 studies reported an increased risk of breast cancer with insulin glargine. In the quality assessment, 7 studies included prevalent users, 11 did not consider a lag period, 6 had time-related biases, and 16 had short (<5 years) follow-up.

CONCLUSIONS

The observational studies examining the risk of cancer associated with long-acting insulin analogs have important methodological shortcomings that limit the conclusions that can be drawn. Thus, uncertainty remains, particularly for breast cancer risk.

NPH insulin has been the mainstay treatment for type 1 diabetes and advanced type 2 diabetes since the 1950s. However, this insulin is associated with an increased risk of nocturnal hypoglycemia, and its relatively short half-life requires frequent administration (1,2). Consequently, structurally modified insulins, known as long-acting insulin analogs (glargine and detemir), were developed in the 1990s to circumvent these limitations. However, there are concerns that long-acting insulin

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analogs may be associated with an increased risk of cancer. Indeed, some laboratory studies showed long-acting insulin analogs were associated with cancer cell proliferation and protected against apoptosis via their higher binding affinity to IGF-I receptors (3,4).

In 2009, four observational studies associated the use of insulin glargine with an increased risk of cancer (5–8). These studies raised important concerns but were also criticized for important methodological shortcomings (9–13). Since then, several observational studies assessing the association between long-acting insulin analogs and cancer have been published but yielded inconsistent findings (14–28). Such discrepancies may be due to methodological limitations, including inadequate durations of follow-up between insulin initiation and cancer incidence, protopathic bias, detection bias, the inclusion of prevalent users, and time-related biases such as immortal time bias, time-window bias, and time-lag bias (29).

Randomized controlled trials (RCTs) have reported the effects of long-acting insulin analogs on the risk of any cancers (30–32), but most of these RCTs were designed to study efficacy (e.g., fasting plasma glucose level) and not designed to assess cancer. The most notable RCT, the Outcomes Reduction with Insulin Glargine Intervention (ORIGIN) trial, did not observe an effect of insulin glargine on the composite outcome of any cancer (33). Although the ORIGIN trial had several strengths, including the power to detect a clinically important effect of insulin glargine on any cancer and adjudication of cancer outcomes, it was not powered to detect site-specific cancers, and follow-up was relatively short ($<$7 years) given the long latency of cancer.

Several meta-analyses of observational studies have investigated the association between insulin glargine and cancer risk (34–37). These meta-analyses assessed the quality of included studies, but the methodological issues particular to pharmacoepidemiologic research were not fully considered. In addition, given the presence of important heterogeneity in this literature, the appropriateness of pooling the results of these studies remains unclear. We therefore conducted a systematic review of observational studies examining the association between long-acting insulin analogs and cancer incidence, with a particular focus on methodological strengths and weaknesses of these studies.

RESEARCH DESIGN AND METHODS

This systematic review was conducted following a prespecified protocol and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (38).

Search Strategy

We systematically searched MEDLINE and EMBASE via Ovid from 1 January 2000 to 8 October 2014 for observational studies examining the association between long-acting insulin analogs and cancer incidence. The detailed search strategy is reported in Supplementary Table 1. Briefly, the search included MeSH terms, Emtree terms, and keywords for diabetes, long-acting insulin analogs, neoplasm, and observational studies. The publication type search terms used in this search strategy were adopted from the Scottish Intercollegiate Guidelines Network (SIGN) group (39). The search was limited to articles published from 2000 onwards because long-acting insulin analogs were not available globally until after 2000. Our search was also limited to studies published in English. We hand-searched relevant systematic reviews and meta-analyses to identify additional articles that were not identified in our electronic literature search.

Inclusion and Exclusion Criteria

Cohort, case-control, and case-cohort studies evaluating the association of long-acting insulin analogs (glargine and/or detemir) and cancer incidence among patients with type 1 or 2 diabetes were eligible for inclusion. Inclusion was restricted to studies reporting any incident cancer or site-specific cancers as primary or secondary outcomes. Studies that did not exclude prevalent cancer cases were eligible for inclusion. We excluded studies that did not meet these inclusion criteria.

The literature search was conducted independently by two reviewers (J.W.W. and M.K.D.), who assessed the titles and/or abstracts of identified publications. The full text of any publication deemed potentially relevant by either reviewer at this stage was retrieved for detailed review. Discrepancies in determining whether the study met our inclusion criteria during the full-text review were resolved by consensus or, when necessary, a third reviewer (K.B.F.).

Data Extraction and Quality Assessment

We developed a data extraction form, which was pilot tested on six included studies. Two independent reviewers (J.W.W. and M.K.D.) extracted data, with disagreements resolved by consensus or a third reviewer (K.B.F., L.A., and S.S.). Disagreements could have occurred when extracting individual data points (e.g., study characteristics and measures of association) or when evaluating the quality of the studies.

Extracted information included the following:

1) study characteristics (source population, country, sample size, study design, type of database used to ascertain information about exposure and outcome);
2) patient characteristics (age);
3) exposure and comparator definitions (ever vs. never use, duration of use, dose, use of time-independent or -dependent approach);
4) incidence of any and/or site-specific cancers;
5) odds ratios, risk ratios, rate ratios, or hazard ratios (HRs) with corresponding 95% CIs;
6) methods of adjustment for confounders (matching, regression-based adjustments, propensity scores, disease risk scores) and list of potential confounders; and
7) quality of the studies.

We extracted any site-specific cancers but did not report on relative risks (RRs) for sites that were not commonly reported among the included studies.

No available quality assessment tool adequately captures the methodological issues and biases that are particular to pharmacoepidemiology. Therefore, we assessed the quality of studies for key components, including time-related biases (immortal time, time-lag, and time-window), inclusion of prevalent users, inclusion of lag periods, and length of follow-up between insulin initiation and cancer incidence.

Immortal time bias is defined by a period of unexposed person-time that is misclassified as exposed person-time or excluded, resulting in the exposure of interest appearing more favorable (40,41). Time-lag bias occurs when

treatments used later in the disease management process are compared with those used earlier for less advanced stages of the disease. Such comparisons can result in confounding by disease duration or severity of disease if duration and severity of disease are not adequately considered in the design or analysis of the study (29). This is particularly true for chronic disease with dynamic treatment processes such as type 2 diabetes. Currently, American and European clinical guidelines suggest using basal insulin (e.g., NPH, glargine, and detemir) as a last line of treatment if HbA_{1c} targets are not achieved with other antidiabetic medications (42). Therefore, studies that compare long-acting insulin analogs to nonbasal insulin may introduce confounding by disease duration. Time-window bias occurs when the opportunity for exposure differs between case subjects and control subjects (29,43).

The importance of considering a lag period is necessary for latency considerations (i.e., a minimum time between treatment initiation and the development of cancer) and to minimize protopathic and detection bias. Protopathic bias, or reverse causation, is present when a medication (exposure) is prescribed for early symptoms related to the outcome of interest, which can lead to an overestimation of the association. Lagging the exposure by a predefined time window in cohort studies or excluding exposures in a predefined time window before the event in case-control studies is a means of minimizing this bias (44). Detection bias is present when the exposure leads to higher detection of the outcome of interest due to the increased frequency of clinic visits (e.g., newly diagnosed patients with type 2 diabetes or new users of another antidiabetic medication), which also results in an overestimation of risk (45). Thus, including a lag period, such as starting follow-up after 1 year of the initiation of a drug, simultaneously considers a latency period while also minimizing protopathic and detection bias.

We also assessed the studies for traditional epidemiological biases such as selection bias, information bias, and confounding. For confounding, we considered three potential sources:

1) imbalances between measured baseline covariates that were not addressed analytically;
2) residual confounding due to unmeasured confounders; and
3) lack of adjustment for time-dependent confounders.

This assessment focused on the discussion of key components of design and analysis rather than on the creation of an aggregate score, as has been suggested elsewhere (46). We used the primary analysis of each included study for the qualitative assessment, but if the issue or bias was addressed in an appropriate sensitivity analysis, we considered this in the qualitative assessment.

Data Analysis

Given the methodological focus of this review and heterogeneity among published studies, we conducted a systematic review without a meta-analysis. Nonetheless, forest plots were constructed with Stata 13 software (StataCorp LP, College Station, TX) to graphically present the available data.

RESULTS

Study Selection

Our search of MEDLINE and EMBASE yielded 4,417 potentially relevant articles (Supplementary Fig. 1). Following our inclusion criteria, 16 cohort and 3 case-control studies were included in this systematic review (5–8,14–28). All studies evaluated insulin glargine, with four studies also investigating insulin detemir (15,17,25,28).

Study Characteristics and Effect Estimates

The study populations ranged from 1,340 to 275,164 patients (Table 1). The mean or median durations of follow-up and age ranged from 0.9 to 7.0 years and from 52.3 to 77.4 years, respectively. Thirteen studies examined ever use of long-acting insulin analogs, which was defined as at least one prescription, compared with nonuse, other, human, or NPH insulin (5–8,14,16,18,19,21,23,25–27). One study examined duration of time since starting long-acting insulin analogs, and one examined mean daily dose (22,28). Four studies used time-dependent exposure definitions (15,17,20,24). All included studies evaluated cancer incidence as a primary outcome.

Of the 16 studies that evaluated the relationship between long-acting insulin analogs and any, colorectal, and/or prostate cancer, 13 reported no associations (Fig. 1 and Supplementary Fig. 2) (5,8,14–17,19–21,23,25,26,28). Four of 13 studies reported an association of insulin glargine and breast cancer (8,19,21,24).

Quality Assessment

The different key components of the quality assessment are summarized in Table 2 and discussed in detail below.

Immortal Time Bias

Of the 19 studies in this review, immortal time bias may have been introduced in one study based on the time-independent exposure and cohort entry definitions that were used in this cohort study (14). For the exclusive user definition, patients needed to have insulin glargine or human insulin only between the first and last prescription to be considered exposed to that one insulin only. However, the follow-up started from the first insulin prescription, and as a result, the time before the last insulin prescription was misclassified as exposed when it should have been classified as unexposed. Similarly, for the predominant user definition, the patient needed to have at least 12 prescriptions of insulin and be exposed 80% of the follow-up time to be considered exposed, but the time before the 12th prescription and meeting the 80% exposure time should be considered unexposed (as depicted in Supplementary Fig. 3). As a result, the adjusted HRs for any cancer were ~0.60, although the results were not statistically significant.

Time-Lag Bias

Time-lag bias may have occurred in four studies that compared insulin glargine to human or other (nonbasal) insulin or highest-to-lowest duration of insulin use without adjusting or matching on diabetes duration (7,14,23,28). The presence of time-lag bias is well illustrated in a cohort study in which individuals who received human insulin or any type of insulin analog for the first time were included in the cohort. Such individuals could be at earlier stages of the disease than those who received insulin glargine (as depicted in Supplementary Fig. 4). Unfortunately, diabetes duration was not reported. This study observed an association between insulin glargine and cancer (HR 1.19 [95% CI 1.09–1.29]), but it is possible that more cases of cancer occurred in the insulin glargine group due

Table 1—Characteristics of observational studies examining the association between long-acting insulin analogs and cancer incidence

Source	Study design	Follow-up (years)*	Age (years)*	Study sample size	Type of database		Exposure vs. comparator†	Type of cancer(s)‡
					Exposure	Outcome		
Colhoun (5)	Cohort	~3.0	54.7	36,524 patients with DM	Health research database	Disease registry	Insulin glargine vs. other insulin§	Any, breast, CRC, lung, pancreas, prostate
Currie (6)	Cohort	2.4	62.0	62,809 patients with DM	Health research database	Health research database	Insulin glargine vs. other insulin§	Breast
Hemkens (7)	Cohort	1.6	68.0	127,031 insulin users	Health administrative database	Health administrative database	Insulin glargine vs. human insulin	Any
Jonasson (8)	Cohort	~2.0	n/a	114,841 insulin users	Pharmacy dispensing records	Disease registry	Insulin glargine vs. other insulin§	Any, breast, GI, prostate
Mannucci (22)	Nested CC	6.3	63.1	1,340 patients with DM Case subjects: 112; control subjects: 370	Medical records	Health administrative database, disease registry	Mean daily dose of insulin glargine (≥0.3 vs. <0.3 IU/kg/day)	Any
Buchs (15)	Cohort	4.5	60.0	36,342 patients with DM	Pharmacy dispensing records	Disease registry	Total purchases of insulin glargine/detemir	Any
Chang (16)	Cohort	1.7	61.4	59,443 new insulin users	Health administrative database	Disease registry	Insulin glargine vs. intermediate/ long-acting human insulin	Any, bladder or kidney, breast, CRC, liver, lung, pancreas, prostate, skin, stomach
Ljung (21)	Cohort	~3.0	n/a	114,838 insulin users	Pharmacy dispensing records	Disease registry	Insulin glargine vs. other insulin§	Any, breast, CRC, GI, pancreas, prostate
Morden (23)	Cohort	1.9	77.4	81,681 patients with DM	Health administrative database	Health administrative database	Insulin glargine vs. other insulin§	Any, breast, colon, pancreas, prostate
Suissa (27)	Cohort	~4.0	65.0	15,227 female, insulin users	Health research database	Health research database	Insulin glargine vs. other insulin	Breast
Blin (14)	Cohort	1.4	68.9	6,649 insulin users	Health administrative database	Health administrative database	Insulin glargine vs. human insulin (≥2 prescriptions)	Any
Lind (20)	Cohort	7.0	52.3	7,942 (breast) and 11,613 (prostate) patients with DM	Health research database	Disease registry	Current use of insulin glargine	Breast, prostate
Ruiter (24)	Cohort	3.1	63.3	19,337 patients with DM	Pharmacy dispensing records	Medical records	Cumulative duration of insulin glargine	Any, bladder, breast, colon, endometrial, pancreas, prostate, respiratory
van Staa (28)	Cohort	4.0	65.0	23,005 insulin users	Health research database	Health research database, disease registry	6–24, 25–60, or >60 vs. 0–6 months since starting insulin glargine/detemir	Any
Fagot (17)	Cohort	2.8	63.2	70,027 insulin users	Health administrative database	Health administrative database	Cumulative dose of insulin glargine/ detemir	Any, bladder, breast, CRC, head and neck, kidney, liver, lung, prostate

Continued on p. 490

Table 1—Continued

Source	Study design	Follow-up (years)*	Age (years)*	Study sample size	Type of database		Exposure vs. comparator†	Type of cancer(s)‡
					Exposure	Outcome		
Habel (19)	Cohort	3.3	n/a	115,514 patients with DM	Pharmacy dispensing records	Disease registry	Insulin glargine vs. NPH insulin (≥2 prescriptions)	Any, breast, CRC, prostate
Simó (25)	Nested CC	~2.0	72	275,164 patients with DM Case subjects: 764; control subjects: 2,292	Pharmacy dispensing records	Disease registry	Insulin glargine/ detemir vs. nonuse‖	Any
Stürmer (26)	Cohort	0.9	60.1	52,453 patients with DM	Health administrative database	Health administrative database	Insulin glargine vs. NPH insulin (≥2 prescriptions)	Any, breast, colon, prostate
Grimaldi-Bensouda (18)	CC	n/a	66.4	Cases subjects: 775 Control subjects: 3,050	Questionnaire	Medical records, health research database	Insulin glargine vs. other insulin§	Breast

~Indicates that it was estimated from the start and end of the study or total person-time; CC, case-control; CRC, colorectal cancer; DM, diabetes mellitus; GI, gastrointestinal cancer; n/a, not available. *Reported as means, medians, or maximum range. †Ever vs. never exposure definitions were reported unless the study only reported other exposure definitions. ‡All cancers that were reported in the study are presented, but only the RRs of the four most common cancer sites among the included studies were reported. §Other insulin comparator definitions in the study can include rapid-acting, short-acting, other basal (NPH, detemir), premixed, inhaled, and animal insulin. ‖Nonuse can include noninsulin antidiabetic medication and other insulins as listed above.

to the longer diabetes duration rather than due to exposure to insulin glargine.

A variation of time-lag bias was observed in a cohort study of new insulin users (28). For the exposure definition, highest duration since the start of insulin use was compared with the lowest. It is expected that the risk of cancer would increase with longer duration of insulin use; however, the opposite was reported (with RRs ranging from 0.50 to 0.90). The protective association observed could be due to competing risks (e.g., death from cardiovascular-related events) (47,48). Patients with diabetes have a higher risk of cardiovascular-related deaths compared with patients with no diabetes (49,50). Therefore, patients with diabetes who die of cardiovascular-related events do not have the opportunity to develop cancer, resulting in an underestimation of the risk of cancer.

Time-Window Bias

Time-window bias was observed in two studies (18,22). In one of the two studies, despite matching on calendar time, time-window bias was potentially present because case and control subjects were not matched on diabetes duration (as depicted in Supplementary Fig. 5) (18). Consequently, the opportunity for exposure differed between the case and control subjects due to the varying diabetes durations (a mean of 14.5 years among case subjects and 13.2 among control subjects). Although one would expect an increased risk due to the time-window bias, a null effect was observed. This suggests that other biases, such as selection bias resulting from selection of case and control subjects from different study bases, may also be present.

Residual Confounding

We evaluated the patient characteristics in each of the 19 studies and observed that the measured covariates (e.g., age, sex, HbA_{1c}, diabetes duration, comorbidities, prior medication use, smoking status, and/or alcohol use) were generally balanced between groups (either exposed vs. comparator or case subjects vs. control subjects, depending on the study design). However, residual confounding may have resulted due to the presence of unmeasured confounders. HbA_{1c} and diabetes duration were not accounted for in 15 of the 19 studies, resulting in likely residual confounding (7,8,14–18,20–26,28). In addition, residual confounding may have occurred in all 19 studies because none of these studies adjusted for time-dependent covariates, such as the addition of short-acting insulins or other antidiabetic medication (e.g., metformin), at all or appropriately (e.g., used a marginal structural model and inverse probability weighting to adjust for time-dependent confounders in the causal pathway).

Other Methodological Issues

Seven studies included prevalent users of insulin (8,15,18,20,21,23,25), which is problematic because of the corresponding depletion of susceptible subjects in other insulin groups compared with long-acting insulin analogs. Protopathic or detection bias could have resulted in 11 of the 19 studies because a lag period was not incorporated in the study design (6,7,14–16,18–21,23,28). Furthermore, given the cancer latency and the time required to observe all the cancers that will occur in patients in these studies, short follow-up (defined here as <5 years) was an issue in 16 studies, whose follow-up time (reported as mean, median, or maximum duration of follow-up) ranged from 0.9 to 4.5 years (5–8,14–17,19,21,23–28). Only one of the studies observed an association between insulin glargine and breast cancer among prevalent users and after 5 years of use (HR 2.7 [95% CI 1.1–6.5]), which may highlight the importance of using a new user study design and having longer follow-up (27).

CONCLUSIONS

Summary

Our systematic review identified 16 cohort and 3 case-control studies on long-acting insulin analogs and cancer risk. We have shown that 7 studies included prevalent users, 11 did not incorporate a lag period, 6 were subject to time-related

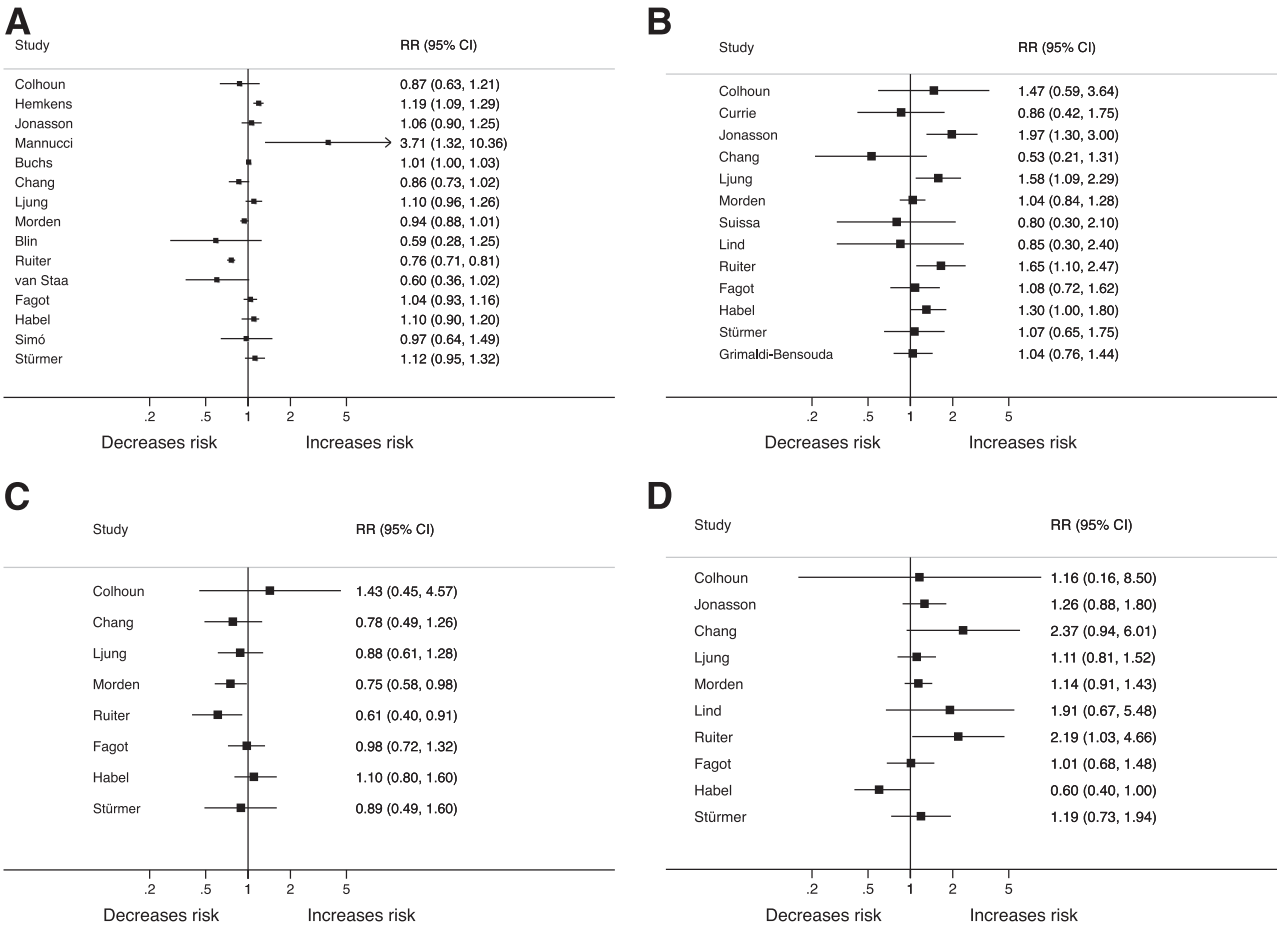

Figure 1—Forest plots of RRs (solid squares) and 95% CIs (solid horizontal lines) from studies on insulin glargine and any (*A*), breast (*B*), colorectal (*C*), and prostate (*D*) cancers. For exposure and comparator definitions in each study, please refer to Table 1.

biases (4 of which had time-lag bias), and 16 had short follow-up (<5 years). The RRs reported in the existing literature on long-acting insulin analogs and cancer suggests there is no increased risk for any, colorectal, or prostate cancers, but four studies observed an increased risk for breast cancer when insulin glargine was compared with other insulins. However, the conclusions that can be drawn from observational studies on long-acting insulin analogs and cancer are limited due to the methodological issues.

Implications and Solutions to the Methodological Issues

Given the methodological issues present in many of the existing studies, the currently available evidence is insufficient to draw definitive conclusions regarding the association between long-acting insulin analogs and cancer. The U.S. Food and Drug Administration arrived at similar conclusions (51–53). In contrast, the European Medicines Agency concluded that insulin glargine does not increase the risk of cancer (54). Given the limitations of the existing literature, there remains a need for methodologically rigorous studies conducted with longer follow-up to clearly evaluate the relationship between long-acting insulin analogs and site-specific cancers. Such studies must use study designs and analytical approaches that consider the biases and issues that were discussed in detail above and summarized in Supplementary Table 2.

Previous Observational Studies, Reviews, and RCTs on Antidiabetic Medications and Cancer

To the best of our knowledge, this is the first systematic review of the methodological strengths and limitations of existing studies on long-acting insulin analogs and cancer. However, earlier editorials and narrative reviews have criticized the four cohort studies on insulin glargine and cancer for their methodological shortcomings, which included reverse causation, lack of lag periods, inclusion of prevalent insulin users, and concerns about the data analysis (9–13). In our systematic review, we also identified the lack of lag periods used and the inclusion of prevalent users as additional limitations in a few studies.

One of the insulin glargine and breast cancer studies only observed an association among prevalent users of insulin after 5 or more years of use (27). This study suggests that duration of insulin use could be an effect measure modifier of the insulin glargine and breast cancer relationship and that studies with shorter follow-up may not be sufficient to observe these effects. Moreover, it also highlights the importance of separating new or first-time users from patients who are switchers from one type of insulin to another because the risk may not be uniform across user types. Along with using more appropriate comparators, one of the strengths of a recent study by Habel et al. (19) was the separation of new users and switchers. Studies only

Table 2—Pharmacoepidemiology biases in studies examining the association between long-acting insulin analogs and cancer incidence

					Time-related biases			
Study	Short follow-up*	Prevalent insulin users†	Lack of lag period	Residual confounding‡	Immortal time	Time-lag	Time-window	Main limitation§
Colhoun (5)	•			•				Short follow-up
Currie (6)	•		•	•				Short follow-up
Hemkens (7)	•		•	•		•		Time-lag bias
Jonasson (8)	•	•		•				Inclusion of prevalent users
Mannucci (22)				•			•	Time-window bias
Buchs (15)	•	•	•	•				Inclusion of prevalent users
Chang (16)	•		•	•				Selection bias and lack of lag period
Ljung (21)	•	•	•	•				Inclusion of prevalent users
Morden (23)	•	•	•	•		•		Time-lag bias
Suissa (27)	•			•				Short follow-up
Blin (14)	•		•	•	•	•		Immortal time bias
Lind (20)		•	•	•				Inclusion of prevalent users
Ruiter (24)	•			•				Short follow-up
van Staa (28)	•		•	•		•		Time-lag bias
Fagot (17)	•			•				Short follow-up
Habel (19)	•		•	•				Lack of lag period
Simó (25)	•	•		•				Inappropriate comparator
Stürmer (26)	•			•				Short follow-up
Grimaldi-Bensouda (18)		•	•	•			•	Selection bias

•Indicates presence of the methodological issue or bias in the study. *Short follow-up is defined as <5 years of follow-up. †Prevalent insulin users refers to the study not distinguishing between prevalent and new insulin users. ‡Residual confounding as a result of unmeasured confounders (HbA_{1c} and diabetes duration) or lack of adjustments for time-dependent confounders. §Main limitation refers to bias or methodological issue that changed the RR.

considering new users may not provide adequate evidence for decision making in a real-world setting because the risk of cancer may differ among patients who switch from other insulins to long-acting insulin analogs.

The methodological limitations, particularly time-related biases, of previous studies of antidiabetic medications and cancer incidence were discussed previously in a review of observational studies of metformin and cancer (29). Compared with the literature examining the association between metformin and cancer incidence, we observed a smaller prevalence of time-related biases. However, we identified the presence of other methodological issues not addressed in this previous work. Importantly, unlike the previous review, the present methodological assessment was conducted in the context of a systematic review.

Similar to observational studies, RCTs assessing long-acting insulin analogs among patients with diabetes did not observe an increased risk of cancer (30–32), but these RCTs were designed to study efficacy (e.g., improvements in fasting plasma glucose level) and not cancer outcomes. The most notable RCT was the ORIGIN trial, which had 12,537 patients in whom 953 new or recurrent cancers occurred during 7 years of follow-up (33). This secondary analysis of the ORIGIN trial had 90% power to detect a 20% increased risk of cancer with use of insulin glargine, and cancer outcomes were adjudicated by an assessor blinded to treatment assignment. Despite these strengths, the study was insufficiently powered to conclusively assess site-specific cancers. Furthermore, given the long latency of cancer, the duration of follow-up of ORIGIN (a median of 6.2) was likely insufficient to conclusively assess cancer risk.

Strengths and Limitations

Our study has several important strengths. First, to our knowledge, it is the first systematic review to methodologically assess the literature on long-acting insulin analogs and their effects on cancer in patients with type 1 or 2 diabetes. This includes the assessment of biases and methodological issues that are particularly prevalent in pharmacoepidemiologic research. Second, a prespecified protocol was used to conduct the systematic review. Finally, our systematic search was conducted in duplicate, ensuring the inclusion of all relevant studies in the present systematic review.

There are also some potential limitations. First, we did not search the gray literature, contact other experts in the field, or attempt to obtain unpublished work. Second, the search was restricted to studies published in English; however, this restriction did not result in the exclusion of a large number of studies. Third, the presence of residual confounding due to unmeasured confounders was evaluated based on confounders (i.e., HbA_{1c} and diabetes duration) previously identified in the literature, and conclusions could vary based on the assessment of other potential confounders. Fourth, this systematic review focused on the association between long-acting insulin analogs and cancer incidence. Consequently, it did not assess the literature in which the cancer risk of any insulin

was compared with that of no insulin, an area that warrants further investigation, particularly given the emergence of new medications for patients with type 2 diabetes. Finally, as is true with any systematic review, there is the potential for publication bias. However, given our focus on the methodological aspects of the literature on this topic and the large number of included studies with null results, the effect of publication bias on the current study was likely minimal.

Conclusion

We identified several methodological issues in observational studies on long-acting insulin analogs and cancer incidence, including the inclusion of prevalent users, lack of lag periods, and time-lag bias. In addition to these three prevalent methodological issues, most studies had short follow-up, which could prevent the observation of a relationship given the long latency of cancer. Therefore, the conclusions that can be drawn from existing observational studies of long-acting insulin analogs and cancer are limited. Future studies addressing these issues must use appropriate study designs and analytical approaches that address these limitations to conclusively address the potential association between long-acting insulin analogs and cancer incidence.

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