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Insulin glargine use and breast cancer: a systematic review and meta-analysis

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Type of article: Systematic review and meta-analysis

Abstract

Background: Insulin is widely used in the treatment of diabetes. There is an increasing concern regarding the association between insulin glargine use and breast cancer.

Aim: To systematically review the literature on insulin glargine use and breast cancer risk.

Methods: A systematic literature search on the relevant articles assessing insulin glargine use and breast cancer during the period from January 2008 to January 2018 was carried out. Studies on animals, human cell line, and humans, in English language that state the duration and dose of insulin glargine use, and the number of participants were retrieved from MEDLINE, Web Of Science, EMBASE, PubMed, and EBSCO, using the keywords insulin glargine, insulin Lantus, insulin analogs, breast neoplasia, and breast cancer.

Results: Out of 311 articles, 34 manuscripts stand after duplication removal and applying the inclusion and exclusion criteria (twelve experimental studies, eight reviews, and fourteen human studies). The reviews' results were inconclusive, human studies showed no relation of insulin glargine with breast cancer except at high dose and long duration of ≥ five years, and prior human insulin use, while the experimental studies showed a decreased breast cancer latency.

Conclusion: There is no association between insulin glargine and breast cancer. Some of the studies showed an association with a long duration of high doses and prior human insulin use. Treating physicians may need to use insulin glargine as the basal insulin of choice before human insulin, although the dose and duration need to be taken into consideration. Real-world studies are needed.

Keywords: Insulin glargine, Dose, and duration, Breast cancer

Note:
This study has followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement (http://www.prisma-statement.org). PRISMA is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses. PRISMA focuses on the reporting of reviews evaluating randomized trials, but can also be used as a basis for reporting systematic reviews of other types of research, particularly evaluations of interventions.

1. Introduction

Breast cancer is the most frequently occurring cancer in women. Currently, the number is 1,384,155 new cases worldwide with nearly 459,000 related deaths. The number is on the rise, and by the year 2050, the incidence is expected to reach 3.2 million new cases per year (1). Diabetes mellitus is the ninth primary cause of death, the number of people suffering from this lifelong chronic disease has quadrupled in the past three decades (2). Currently, more than nine percent of the population are affected worldwide, and the projection for the year 2030 is 438 million (2, 3). Epidemiological data has found an increased rate of breast cancer among patients with type 2 diabetes mellitus, metabolic abnormalities especially hyperinsulinemia create a favorable environment for tumorigenesis and induce metabolic reprogramming events required for the transformation of breast cancer cells (4). Recent literature found that women with diabetes have higher breast cancer-related mortality than their counterparts

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without diabetes (5). Furthermore, poor glycemic control was found to be associated with poor prognosis among patients with breast cancer, a recent study suggested a genetic polymorphism that predispose to diabetes and the risk of developing and dying from breast cancer (6, 7). Insulin glargine available in Gla-100 and Gla-300 concentrations is associated with lower risk of hypoglycemia, and weight gain compares to other types of insulin, but concern is raised due to its mitogenic potential, especially as regards breast cancer (8). The association of insulin glargine and breast cancer is a matter of controversy in the face of the limited control trials (9). Since the first published manuscripts in Diabetologia (2009) that showed contradicting results regarding the association of insulin glargine and breast cancer, many studies have been published, but the insecurity felt by users of insulin glargine is not resolved and the published in vitro studies showed contradicting results (9). Thus, we conducted this review of recent literature to examine whether insulin glargine is associated with breast cancer. In the current study, we systematically reviewed experimental studies and observational human studies regarding insulin glargine use and breast cancer in comparison to other diabetes medications focusing in particular on studies with a duration of five years or more, insulin dose, and prior use of insulin.

2. Material and Methods

2.1. Research design

An electronic systematic search was done for relevant literature published during the period from January 2008 to March 2018.

2.2. Search strategy and quality assessment

The Medline, EMBASE, and EBSCO database, the keywords insulin glargine, insulin Lantus, long-acting insulin analogs, breast cancer, and cancer of the breast were used along with the Boolean operators AND or OR. Articles in English on animals, human cells, and reviews were included, forward and backward chairing for articles cited in retrieved publication was applied to obtain relevant results. The two authors searched and recovered the manuscripts independently for the second stage selection process to avoid duplication of the titles and abstracts, analysis of the relevant data was done by the same authors. The study was conducted in accordance with PRISMA guidelines for systematic reviews and meta-analysis (10) (Figure 1).

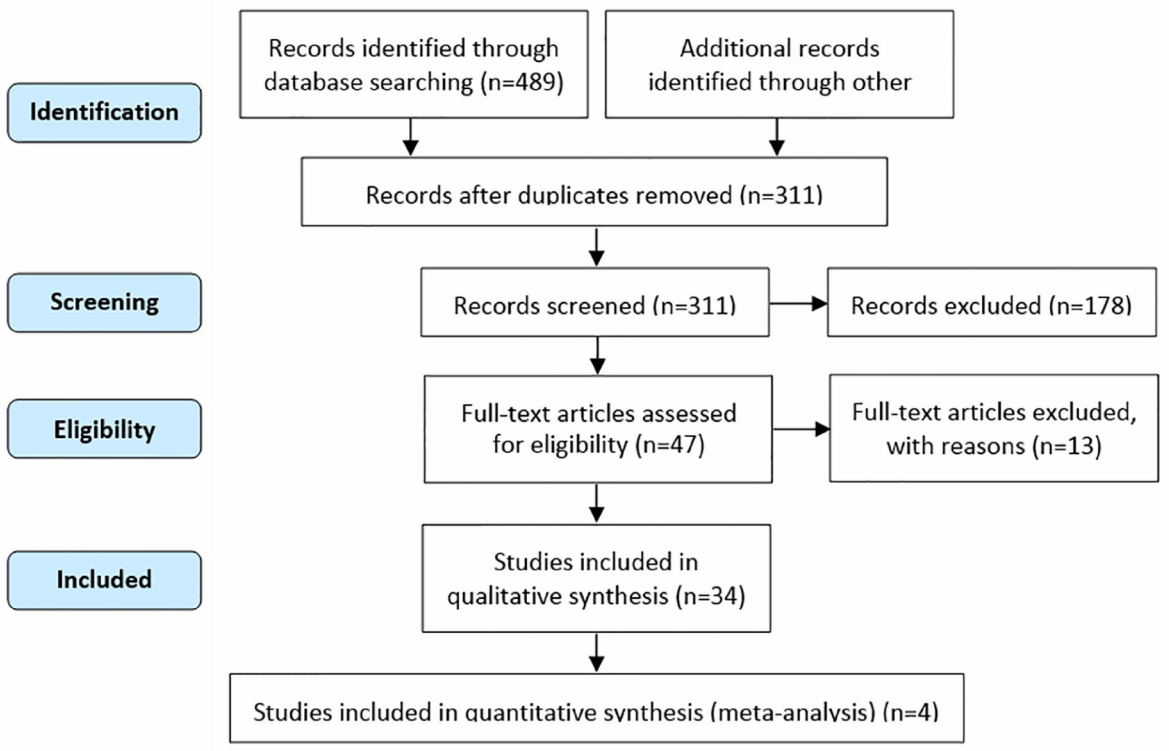

Figure 1. PRISMA Flow Diagram of events in literature search

2.3. Inclusion criteria
Prospective articles in English language that state the duration and dose of insulin glargine use and the number of participants. Previous reviews and experimental studies on animals and cancer cell lines.

2.4. Exclusion criteria
Retrospective studies, and studies not including the dose and duration of insulin glargine were excluded. The relevant evidence was selected after reading the titles and abstracts, to remove duplication and applying inclusion and exclusion criteria.

2.5. Statistical analysis
The IBM© SPSS© Statistics version 20 (IBM© Corp., Armonk, NY, USA) was used for the data analysis including the author's name, year of publication, number of participants, sex, the duration, and the dose of insulin glargine, and the relationship of insulin glargine to breast cancer and other types of cancer.

3. Results
The initial number of manuscripts was 489, the number was reduced to 47 after removing duplication, and stands at 34 after applying the inclusion and exclusion criteria of which twelve were experimental study, eight review articles, and fourteen prospective studies conducted among humans. Table 1 shows the articles that stated follow-up duration number, and sex of participants. The total number of participants was 2,557,177 patients. Two of the studies were conducted on men and women; two were published in the United Kingdom, one from the Netherlands, and the fourth from Sweden. Three studies (75%) concluded the association of glargine insulin use and breast cancer only after prolonged use of five years or more, especially with higher doses and prior human insulin use. The remaining study found an association irrespective of insulin dose and duration. It is interesting to note that the studies that included men showed favorable effects of insulin glargine on other tumors, especially colon and prostate.

Table 1. Studies with extended follow-up of patients using insulin glargine

Ref. no.	Year	Country	Sex	Participants	Duration	Results	Other cancer
11	2011	UK	Women	15227	Eight years	Increase breast cancer after five years especially with prior insulin use	
12	2012	Sweden	Women and men	7942 women and 11613 men	3.5 years for females and 3.4 years for males	Breast cancer does not increase, prostate cancer decrease	At higher doses increase breast and prostate cancer
13	2012	Netherlands	Men and women	2.5 million	Records	Increase breast cancer irrespective of dose	Other cancer decreased
14	2016	UK	Women	22395	12 years	Increase breast cancer after five years and after> thirty prescription	-

4. Discussion
4.1. Animals and experimental studies
Studies reviewed showed contradicting results regarding the association of insulin glargine and breast cancer, some studies showed an association on prolonged use of high doses, while experimental studies concluded the increased mitogenic potential and a decreased latency. Healthcare providers may need to reduce the dose and duration of insulin glargine, and use it before other human insulin. Eleven out of the twelve experimental studies concluded the mitogenic potential of insulin glargine on breast cell. Ter Braak et al. (15) tested the mechanism of insulin analogs tumor induction via the insulin-like growth factor 1 (IGF-1) and found a decreased mammary gland tumor latency, indicating a modulation of tumor progression rather than tumor induction. Another animal study (16) conducted on a type 2 diabetes mouse model injected with murine cancer cell lines, found that non-metabolisable glargine analog does not promote the progression of breast tumors. A further study (17) used p53R270H/$^{+}$WAPCre mouse cells and found a reduced breast cancer latency with IGF-1 and X10 but not insulin glargine. A study (18) used human breast cancer cell line and proposed a mitogenic classifier based on IGF-1 and X10 and found that insulin glargine is the most potent insulin analog. Similar studies (19-21) concluded the mitogenic potential of insulin glargine through IGF-1 activation. An experimental study (22) on human cells found that insulin glargine has the same affinity for insulin receptors and insulin-like growth factor 1 but insulin glargine is rapidly degraded to its metabolites M1 and

M2, thus, reduced mitogenic signaling through the IGF1R. Another study (21) published by Pierre-Eugene concluded similar observation. Teng et al. (22) conducted a research and found that glargine promote the proliferation of breast adenocarcinoma cells in vitro, probably by preventing apoptosis. Another study published by Rensing et al. (23) concluded similar results. A study (24) on C-peptide negative serum of patients with diabetes found that the serum of patients on glargine insulin is more mitogenic than those on detemir or human insulin.

4.2. Previous reviews

There is Heterogeneity regarding the eight retrieved previous reviews, with four reviews not supporting the mitogenic potential of insulin glargine, two reviews concluded the association of insulin glargine and breast cancer, and two cannot conclude due to methodological concerns. A review (25) published in Diabetologia 2009 concluded no association of insulin glargine with breast cancer. Call et al. (26) reviewed the literature and found evidence for insulin-induced mitogenicity appears to be most prevalent in the breast. Meta-analyses (10, 27) published in the year 2012 concluded that their results do not support the link between insulin glargine and breast cancer, and recommended further studies. A review (28) article published in 2015 found that insulin use is not related to breast cancer induction but may lead to tumor progression, on the other hand, Karlstad et al., (29) in their review, found that insulin glargine increased breast cancer and decreased colon cancer risk. Another review of observational studies published in Diabetes Care (14) 2016 stated that a conclusion could not be drawn due to a methodological shortcoming. Thus, uncertainty remains regarding the association of insulin Glargine with breast cancer. A similar conclusion was found by Hernández-Díaz et al. (30).

4.3. Studies on humans

Fourteen surveys were seen, all the prospective studies except two found no association between glargine use and breast cancer. Three studies (Table 1) with a follow-up duration of five years or more concluded the association of glargine insulin use and breast cancer only after five years, in particular among those using higher doses and prior human insulin use, while Ruiter et al. (13) from Netherlands reviewed the records of 2.5 million women and men and reported the association of insulin glargine and breast cancer irrespective of dose. A retrospective cohort (31) including 81,681 patients followed for 23.1 months observed a higher risk of breast cancer among those using insulin combinations but not insulin glargine. An extensive French study (32) included 70,027 patients and followed for 2.7 years, found no association of insulin glargine with breast cancer. A cohort comprised of 15,227 women from the United Kingdom (11) found no association of insulin glargine and breast cancer, but an increased risk was observed among those who used glargine for more than five years mainly if they were on longstanding insulin use before starting insulin glargine. Peeters et al. (33) conducted a study including 12,468 insulin users, the study concluded no association of insulin glargine use and breast cancer even after five years exposure in insulin-naïve patients, but an increased link was observed among previous insulin users, in particular for prolonged, extensive exposure. Habel et al., (34) in his comparative study (27,418 glargine users vs. 100,757 NPH users followed for 3.3 years) found an increased breast cancer among glargine users depending on duration and the combined use with NPH. The authors stated that the results should be approached with caution due to the short period of glargine exposure and a large number of potential associations examined. A recent extensive study (22,395 participants) (35) with twelve years duration conducted among women with type 2 diabetes, found that insulin glargine was associated with breast cancer mainly after five years and thirty prescriptions, furthermore, prior insulin users were at a higher risk than non-insulin users. In a previous study (12) conducted in Sweden among 7,942 women with diabetes mellitus and followed for 3.5 years, no association was found between insulin glargine use and breast cancer, while the risk was more with higher insulin doses. A further Swedish study (38) included 114,838 participants and was followed for 2.5 years and observed no association between breast cancer and insulin glargine use. Another study in Sweden (37) included 114,841 participants in 2006-2007 and found an increased rate of breast cancer among women on insulin glargine compared to other types of insulin. A nationwide diabetes study in Scotland (38) conducted among 49,108 participants and followed for four years found no association between insulin glargine and breast cancer. Currie et al., (39) in their research, included 62,809 participants and found that metformin monotherapy carries the lowest risk of cancer; furthermore, metformin combined with sulphonylureas or insulin lower the risk of solid tumors. The study found no association between human insulin or glargine with breast cancer. Another case-control (775 breast cancer patients vs. 3,050 patients with diabetes) multi-center study (40) conducted in Canada, United Kingdom, and France found no association between insulin glargine use and breast cancer, furthermore, insulin dose and duration did not change the results. Similar findings were observed by Stürmeret al., (41) who conducted a study on 34,306 patients on glargine and 9,147 on NPH and followed for 1.2 years. They found that patients on glargine are not at an increased risk for breast cancer, the results were consistent for the different

durations of treatment. Ioacara et al. (44) assessed cancer mortality among 79,869 patients and concluded a decreased mortality from breast cancer in patients taking insulin glargine.

5. Limitation

Regarding the study limitation, because the review network was observational, we cannot conclude a cause and effect. Incomplete retrieval of identified research, and reporting bias are major limitations of the present review.

6. Conclusions

No association between insulin glargine use and breast cancer except after the use of high doses for ≥ five years especially among prior use of human insulin. The association observed may be due to the increased breast cancer incidence among patients with diabetes, hyperglycemia, the polymorphism shared by diabetes and breast cancer, or other confounders including a high body mass index. Physicians taking care of patients with diabetes may need to use insulin glargine before human insulin in a shorter duration and small doses, until real-world data are available.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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