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Ebtihag O. Alenzi
West Virginia University

George A. Kelley
West Virginia University

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The association of hyperglycemia and diabetes mellitus and the risk of chemotherapy-induced neutropenia among cancer patients: A systematic review with meta-analysis

Ebtihag O. Alenzi[a,*] and **George A. Kelley**[b,1]

[a]Department of Pharmaceutical Systems and Policy, School of Pharmacy, West Virginia University, Morgantown, WV 26506, USA

[b]Department of Biostatistics, School of Public Health, West Virginia University, Morgantown, WV 26506-9190, USA

Abstract

Aim—Conduct a systematic review with meta-analysis to determine the association between incident chemotherapy-induced neutropenia (CIN) and either diabetes mellitus (DM) or hyperglycemia in patients with cancer.

Methods—Observational studies in cancer patients of any age receiving chemotherapy and having diabetes or hyperglycemia either during or before chemotherapy induction were included. Studies were retrieved by searching four databases (PubMed, EBSCO, ProQuest, and Cochrane) and cross-referencing. The metric for combining studies was the odds ratio (OR). Results were pooled using a random-effects model, while heterogeneity and inconsistency were assessed using the Q and I^2 statistic, respectively. Potential small-study effects were assessed using the funnel plot.

Results—Ten studies met the criteria for inclusion. Overall, the odds of having CIN were 32% higher among cancer patients with either DM or hyperglycemia compared with those without DM or hyperglycemia (OR = 1.32, 95% CI, 1.06–1.64). Statistically significant heterogeneity and inconsistency were found (Q = 33.15, $p < 0.05$, $I^2 = 72.9\%$). Funnel plot asymmetry reflecting potential small-study effects was observed.

Conclusions—Diabetes mellitus and hyperglycemia may be associated with an increased risk for CIN among cancer patients. However, additional well-designed studies are needed before any final and definitive recommendations can be made.

Keywords

Neutropenia; Systematic review; Chemotherapy; Diabetes mellitus; Hyperglycemia; Meta-analysis

[*]Corresponding author: eoalenzi@mix.wvu.edu, ebtihag2011@gmail.com (E.O. Alenzi), gkelley@hsc.wvu.edu (G.A. Kelley).
[1]Tel.: +1 304 293 6279.

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1. Introduction

Chemotherapy-induced neutropenia (CIN) is a hematologic toxicity caused by the cytotoxic effects of chemotherapy and which could lead to suppressing the production of neutrophils (Crawford, Dale, & Lyman, 2004). These cells are mature white blood cells made in the bone marrow and then released to the circulating blood as the first line of the body's defense against any infection (Crawford et al., 2004; “Neutropenia,” 2012). The threshold of absolute neutrophil count (ANC) in blood is approximately 2000 cells/mm^3 (Lyman, Lyman, & Agboola, 2005). Consequently, the reduction in neutrophil counts below this threshold could weaken the body's immunity and increase its susceptibility to infection, especially in cancer patients.

Among cancer patients, CIN is a major cause of morbidity, hospitalization, mortality, and costs after chemotherapy induction (Lyman & Kuderer, 2003; Pettengell et al., 2012). A study conducted in the United Kingdom (UK) showed that the incidence of CIN was 27% in breast cancer patients, 16% in lung cancer patients, and 13% in ovarian cancer patients, with an average length of stay in hospitals of 9.2 days and an average cost of £2353 per patient (Schelenz, Giles, & Abdallah, 2012). The substantial incidence of CIN during therapy could lead to an undesired delay in treatment or reduction in the chemotherapy dose, thus, compromising the potential benefits of cancer treatment (Chen, Chan, & Yap, 2013; Heuser & Ganser, 2005; Lyman, Dale, Friedberg, Crawford, & Fisher, 2004).

Despite the high prevalence of CIN among cancer patients and its negative consequences on cancer outcomes, the possible risk factors associated with CIN have not been studied closely. In addition to common risk factors for the development of CIN such as age and the type of cancer, hyperglycemia and diabetes comorbidities could be associated with an increased risk in the incidence of CIN. Previous experimental studies have investigated that diabetes impairs neutrophil function by causing defects in chemotaxis and microbicidal activities (Alba-Loureiro et al., 2006; Bagdade, Nielson, & Bulger, 1972; Pereira, Sannomiya, & Leme, 1987). The metabolic disorders and changes in the processes of producing energy result in a reduction of neutrophil count since the generation of neutrophil cells requires energy (Alba-Loureiro et al., 2007). Therefore, it is plausible that diabetes and hyperglycemia may increase the risk of CIN among cancer patients as well. Hyperglycemia and diabetes mellitus (DM) could have a synergetic effect with chemotherapy on increasing the risk of CIN. However, since hyperglycemia and DM are previously unrecognized as risk factors for CIN, the collective evidence of their impact on developing CIN during chemotherapy among cancer patients is still lacking (Sonabend et al., 2008; Soysal et al., 2012).

To the best of the authors' knowledge, no previous systematic review with meta-analysis has examined the association between DM or hyperglycemia and the risk of developing CIN after chemotherapy induction in cancer patients. This is important in determining the overall magnitude of association, if any, between DM or hyperglycemia and the risk of developing CIN after chemotherapy induction in cancer patients. Thus, the purpose of this study was to conduct a systematic review with meta-analysis to determine the association between DM or

hyperglycemia and the risk of developing CIN after chemotherapy induction in cancer patients.

2. Methods

2.1. Study eligibility criteria

The a priori inclusion criteria for this meta-analysis were as follows: (1) observational studies in cancer patients of any age receiving chemotherapy, (2) cases defined as those who developed CIN after chemotherapy induction, (3) comparison group, defined as patients who did not develop CIN during or after chemotherapy induction, (4) having either DM or hyperglycemia during or before chemotherapy induction, (5) studies reported in any language, (6) data reported for chemotherapy-induced neutropenia (CIN), defined as a dichotomous variable (no or yes) for analysis. Although DM and hyperglycemia are clinically heterogeneous entities, both were included because they have similar pathophysiological features during chemotherapy that influence the development of CIN incidence (Dungan, Braithwaite, & Preiser, 2009). Eligible studies included articles published in peer-reviewed journals as well as unpublished work in the form of theses and dissertations. Because of the potential for publication bias, i.e., tendency for authors to submit, and editors to publish, studies that yield statistically significant results, unpublished work in the form of theses and dissertations were also considered eligible. This eligibility criterion may be especially relevant given the potential lack of eligible studies addressing the impact of DM and/or hyperglycemia on the risk of CIN. This meta-analysis was not registered in any trial registry.

2.2. Data sources

Studies were retrieved using the following 4 electronic databases: (1) PubMed, (2) EBSCO, (3) ProQuest Dissertation and Theses, and (4) Cochrane Library. The search strategy focused on hyperglycemia or diabetes before or during chemotherapy and the incidence of CIN. No date or language filters were applied. All databases were searched from their inception up to April 26th, 2016. The starting search dates for each database, based on their inception dates, were as follows: (1) PubMed (1966), (2) EBSCO (1984), (3) ProQuest Dissertation and Theses (1861), and (4) Cochrane Library (1992).When necessary, the full text was obtained for all potentially eligible articles. Although the search strategies used varied according to the requirements of the different databases searched, keywords centered on the terms ‘neutropenia’, ‘chemotherapy’ and ‘diabetes’ or ‘hyperglycemia’. An example of the search strategy for one database (PubMed) is as follows: “neutropenia AND (diabetes OR DM OR hyperglycemia) AND chemotherapy” Thereafter, a more general search was applied by focusing on the following since most cancer studies reported neutropenia cases under chemotherapy toxicity:

“(diabetes OR DM OR hyperglycemia) AND chemotherapy AND toxicity”

All database searches are shown in Supplementary file 1. In addition to electronic database searches, cross-referencing for potentially eligible studies and retrieved reviews was also conducted. All studies were stored in EndNote™ basic (“EndNote,” 2016). All searches were conducted by the first author with guidance from the second author.

2.3. Study selection and data abstraction

The list of the both included and excluded studies as well as reasons for exclusion was stored by the first author in Microsoft Excel 2013. A codebook was created by the first author, with multiple items per each included study using Microsoft Excel 2013. The main variables that were coded included: (1) first author of study, (2) year when the studies' data was reported, (3) study design, (4) publication status, (5) country where the study was conducted, (6) funding, (7) age group (adults, elderly, or children), (8) definition of hyperglycemia or DM, (9) cutoff for having neutropenia based on ANC, (10) cancer type, and (11) number of patients included in each study. The primary outcome for this study was established a priori and defined as CIN incidence following chemotherapy for cancer patients. The main risk factor of interest was having either DM or hyperglycemia. Study selection and data abstraction were conducted by the first author with oversight from the second author.

2.4. Risk of bias

Risk of bias was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (STROBE, EQUATOR Network, 2016). The STROBE instrument is a checklist of 22 items that assesses cohort, case-control, and cross sectional studies (Elm et al., 2007). Items are related to components that include the title, abstract, introduction, methods, results, and discussion sections. Some items include multiple components where studies had to meet all criteria in order to receive a positive evaluation for the item (Elm et al., 2007). Risk of bias was assessed by the first author with oversight from the second author.

2.5. Statistical analysis

Odds ratios (ORs) with 95% confidence intervals were calculated from included studies and pooled using a random-effects model that incorporates between-study variance into the estimate (DerSimonian & Laird, 1986). Data were analyzed using the log odds ratio and then converted back to the odds ratio for ease of interpretation. Ninety-five percent confidence intervals that did not include 1 were considered statistically significant. Heterogeneity and inconsistency were assessed using Cochran's Q test and the I^2 statistic, respectively. An alpha value ≤0.10 on the Q test was considered to be representative of statistically significant heterogeneity, while an I^2 statistic greater than 50% was considered to be indicative of substantial inconsistency (Kim, Lee, Choi, Huh, & Park, 2015). Funnel plots were used to visually examine for potential small-study effects (publication bias, etc.). In addition, influence analysis with each result deleted from the model once, as well as cumulative meta-analysis, ranked by year, was conducted. Furthermore, stratified analyses were performed according to (1) country the study was conducted in (USA versus other), (2) risk factor (DM versus hyperglycemia) and (3) adjustment for potential confounders (yes versus no). All analyses were conducted using MetaXL, version 5.0, (Barendregt, 2016) within Microsoft Excel 2013.

3. Results

Of the 157 articles screened, 10 peer-reviewed articles involving 8688 cases of CIN met all eligibility criteria (Fig. 1). A list of the 12 studies that were excluded after reviewing the full text is shown in Supplementary file 2. Nine studies assessed the risk of neutropenia incidence as one of the primary outcomes of interest after chemotherapy induction (Abou-Saleh et al., 2013; Carmona-Bayonas et al., 2011; Chao et al., 2014; Chen et al., 2013; Crawford et al., 2008; Lyman et al., 2010; Sonabend et al., 2008; Soysal et al., 2012; Srokowski, Fang, Hortobagyi, & Giordano, 2009; Takenaka et al., 2013). One study used neutropenia as an exposure of interest to explore its impact on the overall mortality after chemotherapy reception (Lyman et al., 2010). Six studies reported DM as an exposure of interest or as one of the primary risk factors (Abou-Saleh et al., 2013; Carmona-Bayonas et al., 2011; Chao et al., 2014; Chen et al., 2013; Srokowski et al., 2009; Takenaka et al., 2013), while two studies used DM as just a patient characteristic included in the study (Crawford et al., 2008; Lyman et al., 2010). Only two studies assessed hyperglycemia as an exposure of interest (Sonabend et al., 2008; Soysal et al., 2012).

Only one study was a prospective cohort study (Crawford et al., 2008), while the remaining 9 were retrospective cohort studies (Abou-Saleh et al., 2013; Carmona-Bayonas et al., 2011; Chao et al., 2014; Chen et al., 2013; Lyman et al., 2010; Sonabend et al., 2008; Soysal et al., 2012; Srokowski et al., 2009; Takenaka et al., 2013). Two of ten studies adjusted for potential confounding factors such as sex, demographics, cancer characteristics, year of diagnosis, comorbidities, and type of chemotherapy (Chao et al., 2014; Srokowski et al., 2009), whereas the remaining studies reported crude OR or only frequencies of events (Abou-Saleh et al., 2013; Carmona-Bayonas et al., 2011; Chen et al., 2013; Crawford et al., 2008; Lyman et al., 2010; Sonabend et al., 2008; Soysal et al., 2012; Takenaka et al., 2013).

A summary of results using the STROBE instrument can be found in Supplementary file 3, while detailed study and item-level findings are shown in Supplementary file 4. Overall, all the included studies provided a background and rationale for their research, reported the results of their outcomes, and summarized the key results with reference to study objectives in the discussion. The majority of studies indicated the study design clearly (n = 7), provided a summary in the abstract (n = 7), stated their objectives (n = 9), and described the study setting (n = 9). However, few studies identified potential sources of bias (n = 2), provided the source of funding (n = 2), clearly defined the variable considered during the studies (outcomes, predictors, and covariates) (n = 4), and described the source of data used for each variable (n = 4).

Variation across included studies was observed for setting, populations studied (age and cancer type), definition of the risk factor (DM or hyperglycemia), and definition of CIN (Table 1). Cancer types in each study included acute leukemia (Sonabend et al., 2008), multiple types of cancer (Abou-Saleh et al., 2013; Carmona-Bayonas et al., 2011; Chao et al., 2014; Crawford et al., 2008; Lyman et al., 2010; Soysal et al., 2012), neck and head cancer (Takenaka et al., 2013), breast cancer (Chen et al., 2013; Srokowski et al., 2009), and lymphomas (Chen et al., 2013). Two of the 10 studies examined hyperglycemia as a primary risk factor of interest (Sonabend et al., 2008; Soysal et al., 2012), one examined DM as a

primary risk factor (Srokowski et al., 2009), whereas the remaining seven considered DM as a potential confounder based on another association of interest (Abou-Saleh et al., 2013; Carmona-Bayonas et al., 2011; Chao et al., 2014; Chen et al., 2013; Crawford et al., 2008; Lyman et al., 2010; Takenaka et al., 2013). One study considered only children (Sonabend et al., 2008), another study considered only elderly (Crawford et al., 2008), whereas other studies considered adults (Abou-Saleh et al., 2013; Carmona-Bayonas et al., 2011; Chao et al., 2014; Chen et al., 2013; Lyman et al., 2010; Soysal et al., 2012; Srokowski et al., 2009; Takenaka et al., 2013). Five studies were conducted in the US (Chao et al., 2014; Crawford et al., 2008; Lyman et al., 2010; Sonabend et al., 2008; Srokowski et al., 2009), while others were conducted in Spain (Carmona-Bayonas et al., 2011), Finland (Soysal et al., 2012), Singapore (Chen et al., 2013), Oman (Abou-Saleh et al., 2013), and Japan (Takenaka et al., 2013). For the definition of CIN, studies had different cut-off points for ANC and used different metrics. To facilitate the comparison between studies, all neutropenia metrics were converted into cells/mm^3 since the majority used this metric. However, a study conducted by Srokowski et al. (2009) identified neutropenia cases by ICD-9 code of 288.0, and thus, no conversion was possible.

Across all designs and categories, the odds of having CIN was statistically significant, being 32% higher among cancer patients when DM and hyperglycemia results were pooled together (Fig. 2). However, statistically significant heterogeneity and substantial inconsistency were observed. In addition, potential small-study effects were found (Fig. 3). With each study deleted from the model once, results remained statistically significant across all deletions (Supplementary file 5). Cumulative meta-analysis, ranked by year, revealed that results have remained statistically significant since only 2013 (Supplementary file 6).

Overall findings for stratified analyses are shown in Table 2, while study-level results are shown in Supplementary file 7. As can be seen, results were statistically significant and in the direction of an increased risk for CIN for other countries but not the United States. For risk factors, statistically significant odds ratios in the direction of increased risk were observed for hyperglycemia but not DM. In contrast, both crude and adjusted estimates were statistically significant and in the direction of an increased risk for CIN. No between-group differences, as judged by non-overlapping confidence intervals, were observed between any of the groups (Okera et al., 2011).

4. Discussion

4.1. Overall findings

This study set out to conduct a systematic review with meta-analysis to determine whether hyperglycemia and DM are associated with an increased risk for CIN among cancer patients. Overall, the results of this systematic review with meta-analysis of 10 observational studies suggest that DM and hyperglycemia may be associated with an increased risk for CIN among cancer patients after chemotherapy induction. These findings persisted when each study was deleted from the model once and have been statistically significant since 2013. Importantly, the use of a random-effects model incorporated between-study variance into the model, thus, resulting in more conservative findings when compared to a fixed-effect model.

4.2. Implications for research

The results of this study provide at least two implications for research. First, a statistically significant and substantial amount of unexplained heterogeneity and inconsistency was observed. Thus, while a random-effects model incorporates between-study heterogeneity into the model, it does not explain the source(s) from which such heterogeneity and inconsistency are derived. Along those lines, our stratified analyses suggested a continued association for CIN when (1) studies were conducted in countries other than the United States, (2) hyperglycemia but not DM was the risk factor examined, and (3) either crude or adjusted estimates were used. While these findings are interesting and may be worthy of further study, they are based on small samples and were examined separately versus being included in a larger multiple meta-regression model. However, as is the case with many meta-analyses, multiple meta-regression is often not possible due to the small number of studies included in a meta-analysis as well as missing data for different variables from different studies.

Second, the quality of reporting and/or conduct of studies on this topic could be improved. For example, based on the STROBE checklist, only five studies score at 75% or higher. More specifically, 40% or less of the included studies reported adequate information with respect to funding sources as well as methodological issues such as bias, data sources and variables. Given the former, it is suggested that future studies address these issues. More specifically, since only two of ten included studies adjusted for potential confounders (Chao et al., 2014; Srokowski et al., 2009), it is suggested that future studies on this topic include both crude and adjusted estimates.

4.3. Implications for practice

This finding supports a previous recommendation regarding pretreatment assessment of CIN risk factors such as hyperglycemia to avoid hospitalization and mortality associated with CIN incidence after chemotherapy induction (Crawford et al., 2008). Unfortunately, Sonabend et al. reported that although hyperglycemia was common among cancer patients who received chemotherapy induction, only a few were treated with insulin (Sonabend et al., 2008).

4.4. Strengths and limitations

From our perspective, the major strength of this study is the fact that to the best of our knowledge, this is the first systematic review with meta-analysis to examine the association between hyperglycemia and DM and the risk of CIN among cancer patients. Thus, this study provides important information for clinical consideration when prescribing chemotherapy as well as future research, both original and meta-analytic. Alternatively, there are at least five potential limitations to this study. First, given that only 10 studies met our inclusion criteria, it appears that the number of studies that have addressed this issue is small. Given the potential importance, it is suggested that future observational studies on this topic are needed. Second, like any aggregate data (not an individual patient data) meta-analysis, this study is prone to ecological fallacy. This suggests that our pooled findings may not occur at the individual level. Third, the included studies were heterogeneous in terms of the reasons why the studies were conducted, as well as the patients included in each study. Thus, it could

be argued that combining one or more of these studies in the current meta-analysis may not have been appropriate. Fourth, the odds ratios for 8 of the 10 included studies were unadjusted, thus, presenting the possibility of residual confounding. Fifth, since dual-selection, abstraction, and risk of bias assessment did not occur in the current meta-analysis, an increased risk of errors was possible.

5. Conclusions

The results of this systematic review with meta-analysis suggest that DM and hyperglycemia may be associated with an increased risk of CIN among cancer patients. However, given the substantial heterogeneity observed, additional well-designed studies are needed before any final and definitive recommendations can be made.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies | the EQUATOR Network. 2016. Retrieved from http://www.equator-network.org/reporting-guidelines/strobe/

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jdiacomp.2016.09.006.

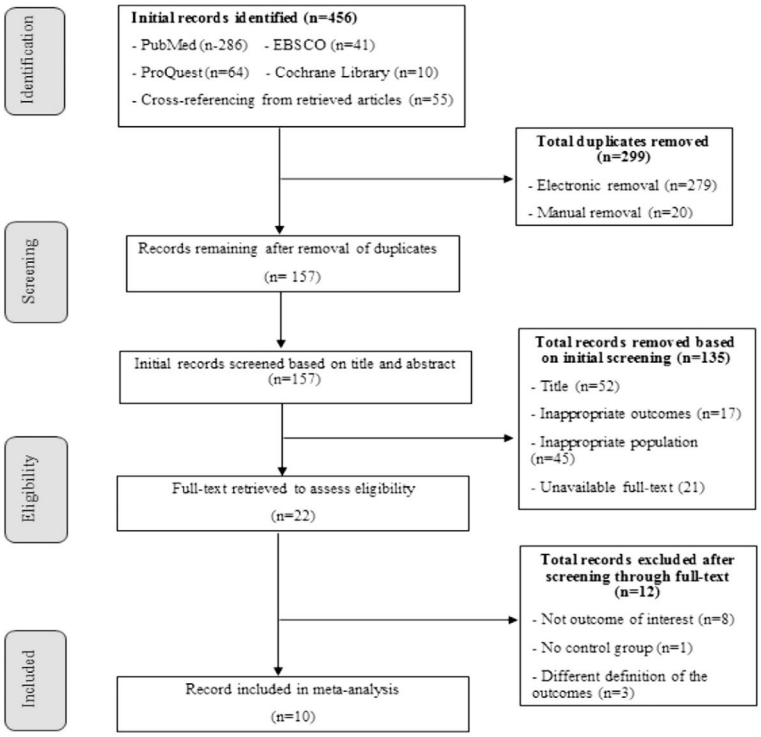

Fig. 1.
Flow diagram that describes the search process.

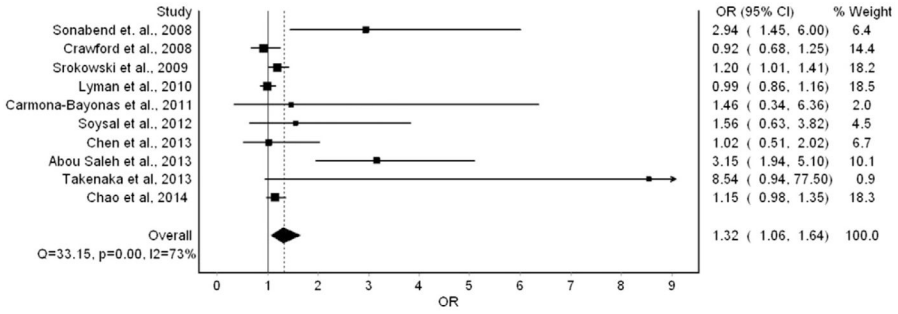

Fig. 2.

Forest plot of the association between DM/hyperglycemia and CIN in cancer patients. OR and 95% CI indicate odds ratio and 95% confidence interval.

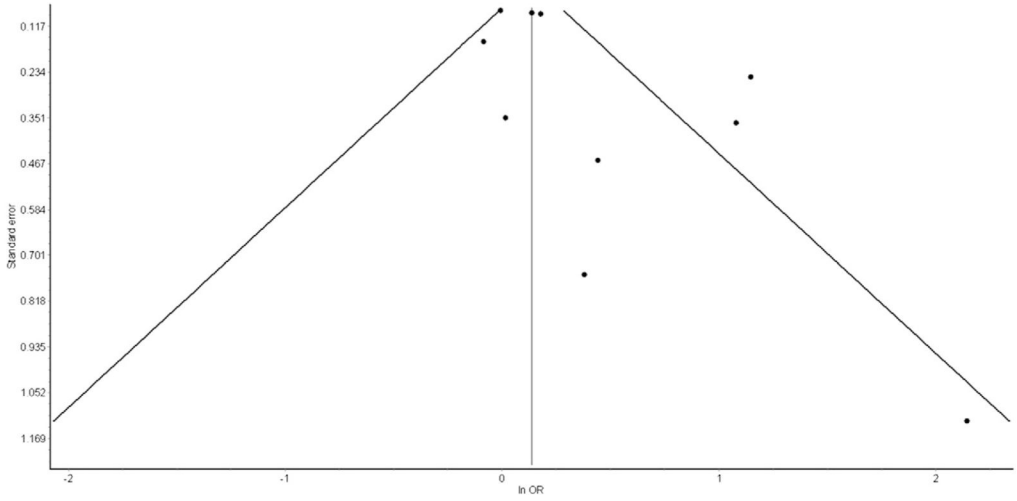

Fig. 3.
Funnel plot for small-study effects.

Table 1

Characteristics of the included studies.

Source	Study design	Country	Age group	Patients (#)	BGL	Neutropenia	Cancer type
Sonabend et al., 2008	Retrospective cohort	US	Children	135	BGL >140 mg/dl	ANC of <1000 cells/mm^3	AL
Crawford et al., 2008	Prospective cohort	US	Elderly	2692	DM	ANC of <1000 cells/mm^3	MT
Srokowski et al., 2009	Retrospective cohort	US	Adults	11,826	DM	ICD-9-CM Code 288.0	BC
Lyman et al., 2010	Retrospective cohort	US	Adults	11,980	DM	ANC of <1000 cells/mm^3	MT
Carmona-Bayonas et al., 2011	Retrospective cohort	Spain	Adults	173	DM	ANC of <1000 cells/mm^3	MT
Soysal et al., 2012	Retrospective cohort	Finland	Adults	86	BGL >140 mg/dl	ANC of <100 cells/mm^3	MT
Chen et al., 2013	Retrospective cohort	Singapore	Adults	583	DM	ANC of <500 cells/mm^3	BC & L
Abou-Saleh et al., 2013	Retrospective cohort	Oman	Adults	1357	DM	ANC of <500 cells/mm^3	MT
Takenaka et al., 2013	Retrospective cohort	Japan	Adults	71	DM	ANC of <500 cells/mm^3	HC & NC
Chao et al., 2014	Retrospective cohort	US	Adults	19,160	DM	ANC of <1000 cells/mm^3	MT

BGL: blood glucose level, DM: diabetes mellitus, ANC: absolute neutrophils count, MT: multiple types, HC: head cancer, NC: neck cancer, BC: breast cancer, L: lymphoma, AL: acute leukemia.

Table 2

Stratified analyses for CIN.

Group	Studies (#)	OR (95% CI)	Cochran Q	Q(p)	I^2 (%)
Country					
-United States	5	1.13 (0.95, 1.33)	11.7	0.02**	66
-Other	5	1.94 (1.04, 3.61)*	9.2	0.06**	57
Risk factor					
-DM	8	1.22 (0.99, 1.51)	25.8	<0.001**	73
-Hyperglycemia	2	2.28 (1.23, 4.20)*	1.2	<0.28	16
Crude vs. adjusted					
-Crude	8	1.55 (1.03, 2.32)*	32.7	<0.001**	79
-Adjusted	2	1.17 (1.04, 131)*	0.1	0.73	0

Notes: OR, odds ratios; CI, confidence intervals.

*Statistically significant (confidence intervals do not include 1).

**Statistically significant at $p \leq 0.1$.