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The anti-proliferative role of metformin in non-diabetic female patients with breast cancer: systematic review and meta-analysis of randomized control trials

ABSTRACT

Background. Usage of metformin in non-diabetic women with breast cancer is neither a common approach nor a conventional treatment modality. Metformin and chemotherapy have a high phenotypic variation in complete response rate among diabetic patients with different types of cancer. Although the results on salvage therapy were contradictory, we carried out a meta-analysis to evaluate the effect of the addition of metformin to conventional treatment on the prognosis in non-diabetic women who have breast cancer.

Methods. A consummate literature search of PubMed, EMBASE, grey literature, and web of science was conducted until 7th of March 2020. A total of 11 randomized control trials were included in this meta-analysis including references related to metformin, breast cancer, and prognosis. The search was limited to English language and human studies, including references related to metformin, breast cancer, and prognosis. We performed the meta-analysis using a random and fixed-effects model, with hazard ratios and 95% confidence intervals (95% CI) as effect measures.

Results. A total of 11 randomized control trials consisting of 1681 breast cancer patients without diabetes including 841 ones which received metformintreatement versus 840 ones not treated with metformin. The meta-analysis found that metformin has been linked with anti-proliferative role (HR 0.63, 95% CI 0.59–0.71). Subgroup analysis showed an increased average progression of free survival which demonstrates that metformin improves overall survival by 65% after correcting for hormone-receptor/gene expression (HR 0.35, 95% CI 0.15–0.84). Taking metformin as treatment of breast cancer has been related to extended survival rate.

Conclusion. This meta-analysis supports the potential role of metformin in the management of cancer, as it may increase progression free survival among non-diabetic patients with breast cancer. More clinical trials are needed for further exploration of metformin role, and to determine whether improvements in cancer care can be achieved with adding metformin to reduce mortality or to improve overall survival in patients with breast cancer. (Clin Diabetol 2021; 10; 3: 252–260)

Key words: apoptosis, metformin, non-diabetic, females, patients, breast cancer, systematic review, meta-analysis, randomized control trials

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Introduction

Available epidemiological data applicable to diabetes mellitus and insulin tolerance were related to bad prognosis in certain cancers such as breast cancer,

the most common neoplasm among females [1]. More attention has been paid to anti-diabetic drugs such as metformin in both cancer prevention and therapy. Nevertheless, an associated cancer-preventive benefit does not necessarily entail therapeutic efficacy in newly diagnosed patients with cancers. For cancer patients who are receiving conventional cancer care, better treatment results cannot be guaranteed by using metformin. This hypothesis, between acceptance and rejection, remains unexplained.

Pre-clinical research has demonstrated a positive effect of metformin on breast cancer [2] by indirect (insulin or sex hormones-mediated) implications or it may directly impact cell proliferation and cancer cell apoptosis [3, 4]. Jiralerspong et al. [5] reported that diabetic patients with breast cancer who received metformin had triple the pathological complete response rate in comparison with patients receiving neo-adjuvant chemotherapy alone (OR 2.95, 95% CI 1.07–8.17).

Metformin is considered to minimize gluconeogenesis and glycogenolysis in liver, it also increases the absorption of skeletal muscle glucose by triggering AMPK, a cell energy-sensing enzyme that controls cellular energy status by experiencing phosphorylation and raising activation when ATP levels are reduced and AMP levels rise. Shift in the ATP: AMP ratio is being used as an implicit energy deficit marker [6].

However, even after the rise in the absolute pathological response, metformin did not substantially increase the median 3-year duration relapse/free survival rate for this research. Multiple trials showed improved recovery among patients who were offered metformin than those who were not [7].

Hardly, evidence has been collected on the topic. A recent meta-analysis [8] has proved that metformin administered to patients with type 2 diabetes and cancer was associated with a 35% reduction in the risk of mortality compared to those who have not received metformin (HR 0.66, 95% CI 0.55–0.79). However, data about the effects of metformin on non-diabetic women with breast cancer was very scarce. No longevity gain has been shown in women with breast cancer, which could be attributed to the limited scale of the sample. Understanding the effectiveness of metformin for breast cancer may lead to improved treatment approaches of those patients. We then performed a meta-analysis to identify the interaction of metformin with the risk-specific recovery of non-diabetic women with breast cancer.

Methods

Search strategy and data sources

We reported this systematic review and meta-analysis according to the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [9]. Institutional review board (IRB) and ethics commission agreement has been fulfilled and was granted guaranteed by the IRB-King Abdullah International Medical Research Center (KAIMRC) with code number IRBC/1783/19, and protocol number RC19/369/R.

We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science (Thomson Reuters), and grey literature from inception to 7th of March 2020, for articles evaluating the effect of Metformin on any prognostic outcome in non-diabetic patients with breast cancer. The following main keywords with corresponding MeSH terms and Boolean operators were used: "Metformin", and breast cancer (e.g., "breast", and "cancer", or "malignancy", or "tumor", or "neoplasm"), and prognosis (e.g., "prognosis", "mortality", "survival"). Reference lists of the included publications were also searched. The search was carried out on randomized controlled trials with English language and human studies restrictions. Research about the assessment of the association between metformin and result of breast cancer, including recovery, diagnostic steps and option of medication, were reviewed and listed to be critically appraised.

Our comprehensive search strategies included synonym terms for metformin, cancer breast (e.g. "Adenocarcinoma", "Carcinoma", "Cancer" and "Breast" Prognosis (e.g. "mortality", "survival", "prognosis"). Reference lists of the included publications were also searched. No language bias or restrictions on the type of publication or publication bias have been imposed.

Study selection

Our cumulative search selected articles describing research studies that (a) Assessed any prognostic outcome through metformin application, (b) Evaluated population of non-diabetic patients with breast cancer, (c) Evaluated only the direct effect of metformin on neoplastic tissue, and (d) Encompassed the original analysis of data. To avoid overlapping of patients' population, we compared data on recruitment years, data source and geographical location. Duplicate articles were trimmed by keeping the most notable ones, those with a bigger study population, or with a multivariate-adjusted population estimate.

Articles that encountered at least three of those conditions laid out above and that noted all-cause/cancer-specific or overall mortality/Survival were preserved. To be part of our meta-analysis, articles had to report an estimate of the risk e.g., hazard ratio. Metformin use for eventual death by means of survival analysis, regression models with precision estimation, such as SE or 95

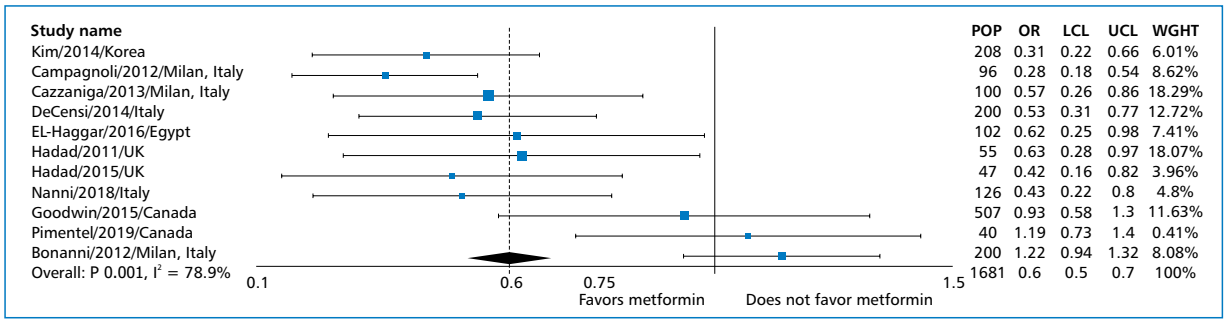

Figure 1. Meta-analysis and pooled hazard ratio of long-term, all-cause mortality in 11 studies comparing breast cancer patients with and without metformin

percent of the CI has been calculated by random and fixed models. Articles with missing risk estimates have also been included in the meta-analysis in case, if the risk estimates were obtained by the author's contact.

Data extraction and quality assessment

Abstracts and full articles were reviewed independently by two authors. Any dispute was settled by consensus or a third review for adjudication. Data derived from relevant publications included data on publishing, first author's last name, year of publishing and country of research community. Others include report development (clinical or population-based observational studies), sample size, data line, recruitment year report, follow-up length, and calculated result, risk assessments with their related CIs, and the variables on which they are regulated in the case of a multivariate scheme.

In relation to eligibility requirements for the analysis, when there are many projections reported in the same post, the most accurate adjusted estimate (i.e., a multivariate model was selected over the distribution of univariate) was selected . Where an article has mentioned several figures by subgroup only, such figures were entered in our respective meta-analysis data collection independently. For each sample, we selected the risk levels that exhibited the maximum degree of regulation for potential confounders in it. Quality was determined by the usage of the elements strengthening the coverage of empirical findings report on epidemiology (STROBE) [10]. To judge the quality, we looked at the information on patients' characteristics (including data sources, inclusion and exclusion criteria) exposure to metformin, strategies for evaluating the result, whether or not metformin was the main treatment vector part of the prognostic variables community, and statistical adjustment to the Confounders [11].

We used Newcastle–Ottawa scale as a metric to determine the consistency of randomized control trials published in a systematic-reviews and/or meta-analysis. Using the instrument, each sample is tested on eight elements, grouped into three groups: the collection of the research groups; the comparability of the groups; and the assessment of any participation or result of significance in case-control or longitudinal studies. The points awarded for each quality object work as a simple visual evaluation. Points are graded in such a manner that the best performing experiments are given up to nine points.

Data analyses

For the meta analyses, P values are given below the defined values. Cochran and I^2Q predictions have been made in a heterogeneity review [12]. Random-effects of Der-Simonian-Laird formula was used to measure the HR combined. Meta-analysis was done using Stata Version 12.0 program. (Stata-Corp-College-Station-TX-http:/www.state.com). We used the "metan" command to pool ln HR through the sample. Forest plots were used for visual evaluation of HR forecasts and around 95 percent of CIs in both tests. We performed an evaluation of the impact of the content of the sensitivity research that ignored low-quality tests.

Publication bias was tested using Begg's funnel plot and the Egger check [12, 13]. We did the Duval and Non-parametric tweedie trim and filling procedure [14] to further assess the possible consequences of the prejudice of reporting. For all tests two-sided P value of less than 0.05 was considered statistically significant. Funnel plot is a simple scatter plot of the intervention effect estimates from individual studies against some measure of each study's size or precision. In common with forest plots, it is most common to plot the effect estimates on the horizontal scale, and thus the measure of study size on the vertical axis (Fig. 1).

Results

As described in the PRISMA flowchart, the flow diagram depicts the flow of information through the

different phases of a systematic review. It maps out the number of records identified, included and excluded, and the reasons for exclusions. Out of the 5757 titles and abstracts screened, 4937 titles and records were identified through databases searching, and 820 additional records were identified through other sources. 4907 Records were excluded because of different topics, and 112 duplicate records removed. Also, 738 full-text articles were assessed for eligibility, 518 full-text articles excluded due to participation of diabetic patients, and 196 full-text articles excluded due to different study designs. Studies included in qualitative synthesis were 24. (supplementary material A) We excluded 13 studies that addressed other types of cancer other than breast cancer. The remaining 11 Studies were included in quantitative synthesis (meta-analysis) (Table 1, Fig. 2) [15–25].

Description of studies

The 11 quantitative RCT studies of our cumulative meta-analysis of total survival included 1,681 non-diabetic female patients with breast cancer including 841 patients that took metformin and 840 patients that did not take metformin. The selected researches were performed in Italy (n5), Canada (n2), UK (n2), Korea (n1), and Egypt (n1). Follow-up time differed through the respective studies. Time basis for survival analysis was calculated, this was usually the time of cancer treatment, particularly in the case of medical treatment under which the date of incidence happened. The studies were characterized by high level of homogeneity; all of the patients were almost of the same age, and dose. The duration of metformin was approximately equal 500–850 mg for 2–4 weeks; and all of the patients were postmenopausal, non-diabetic females with breast cancer.

Sensitivity analysis

We performed a sensitivity analysis to check robustness. All the 11 studies, with 8 estimates, concentrated on one point: the anti-proliferative role and apoptotic effect of metformin. And they were all agreed upon the fact that metformin decreases the tumor size by 65% and decrease mortality rate by 45%; Pooled HR (95% CI); 0.6 (0.52–0.71), I^2 (%);78.9, P value = .001, apart from two studies [15, 24]. The results of the meta-analysis were shown in Figure 3. In spite of almost absence of variations between the studies, we performed Egger's test (P = .001), and Begg's funnel plot (p5.827), which suggested the possible presence of publication bias (Fig. 1).

Subgroup analysis in Table 2 showed the pooled hazard ratios of all-cause mortality in non-diabetic female patients with breast cancer with and without metformin. There were two studies involving patients aged less than 50 years [20, 21]. Estimates adjusted for age 50–70 years, 9 studies showed that old aged patients had more effect than younger patients, HR (95% CI); 0.53 (0.39–0.71), I^2 80.3, P = .001. There were 6 studies that addressed the hormone receptors and metabolic effect. They showed significant dual effect on breast cancer growth according to insulin resistance status [17]; significant reduction of insulin level by 25%; significant reduction of testosterone level by 23%, as well as free androgen index [16]. Significant increase of the apoptotic inducer IGFBP-3 or/and the significant reduction of mitogenic insulin, IGF-1, free bioactive IGF-1, FBG [19] significantly improved weight, insulin, glucose, leptin, and CRP [20]. Up-regulation of tumor pAMPK, down-regulation of pAkt, and alteration in molecular assays. Pooled HR (95% CI) 0.35 (0.15–0.84), I^2 60.2, P value 057 [23, 25]. After adjusting for Ki67, PFS, HOMI, and TUNEL, were HR (95% CI) 0.48 (0.23–1.00), I^2 9.1, P value .033; HR (95%CI) 0.66 (0.48–0.91), I^2 81.3, P value .001; HR (95% CI) 0.49 (0.27–0.87) I^2 84.0, P value.001; and HR (95% CI) 0.87 (0.67–1.13), I^2 76.5, P value 0.39, respectively. Adjustment of duration and dose of metformin did not reveal significant effects, HR (95% CI) 0.43 (0.34–0.55), I^2 0, P value .771 and HR (95% CI) 0.40(0.30–0.54), I^2 32.4, P value .170, respectively.

Discussion

Metformin is a commonly prescribed oral medicine that is used as a front-line treatment of diabetes mellitus. Studies have shown that the drug can also prevent the development of cancer cell lines in both in vitro, like the breast cancer lines and in vivo versions of the tumors [2].

Metformin stimulated the activation of AMPK in cells other than liver cells can lead to the stimulation of cell proliferation, which is also assisted, and has demonstrated that metformin stimulation of the AMPK mechanism is not limited to liver cells but it can also be seen in endothelial and epithelial cells. In addition, the influence of AMPK stimulations in endothelial and epithelial cells, like breast carcinoma, may result in reduced proliferation, a general decrease in the translation of mRNA and protein metabolism [15].

Population and history studies have shown that metformin decreases incidence of cancer and mortality correlated with cancer, and increased response to neo-adjuvant chemotherapy patients. Metformin induces activation of AMPK which reduces insulin resistance and contributes to protein synthesis inhibition, decreasing the proliferation and development of cancer

Table 1. Spreadsheet characteristics of RCT about anti-proliferative role of metformin (MF) in non-diabetic patients with breast cancer (n =11)

	Author/ publication year/ country	Patients number (case/control)	Mean age ± SD (yr.) (case/control)	Gender (M/F)% (case/ control)	Duration of MF (w)	Dose of MF	Intervention	End point	Outcome measures	Results	NOS scale
1	Bernardo Bonanni/ 2012/ Italy	200 (100/100)	53 ± 10/52 ± 10	200 women	4	850 mg/twice per day	200 non-diabetic women with operable breast cancer Metformin (100)/placebo (100)	Breast cancer treatment and prognosis	Difference between arms in Ki67	MF not significantly affects Ki67 overall, but showed significantly different effects according to insulin resistance, particularly in luminal B tumors	8
2	Carlo Campagnoli/ 2012/ Italy	125–108–96 (43/53)	< 70 years	125 women	9	500–1000–1500 mg/d	124 have 500mg for 3 m, then 108 of them 1000 mg for 1 m, then assigned to 2 groups for 5 m (1500/1000 mg)	Breast CA prognosis Novel approach to management of BC	Weight, BMI, waist circumference, glycaemia concentration, Insulin level, HOMA-IR index Testosterone level, FAI, SHBG level	Who took 1500 mg/d, significant reduction of insulin level by 25%, HOMA-IR index, testosterone level, by 23%, and free androgen index	7
3	Cazzaniga/ 2013/ Italy	100 (45/42)	50 [45–62]/ /49 [45–57] Med [IQR]	100 women	4	850 mg	850 mg tablets once daily for 3 days followed by 850 mg bid. *vs.* placebo	Treatment of BC cells by apoptosis	Ki67, TUNEL levels, HOMA index, apoptotic cell nuclei by TUNEL from core biopsies and their paired surgical sample	Apoptosis was significantly higher in surgical specimens compared with baseline biopsy and was directly correlated with Ki67. There was a dual effect on BC growth according to insulin resistance status	7
4	DeCensi/2014/ Italy	200 (100/100)	65 [56–73]/ /62 [57–71] Med [IQR]	200 women	4	850 mg	850 mg tablets/bid *vs.* placebo	BC treatment	Ki67, weight, BMI, GLU, HOMA	Decreased Ki67 only in women with insulin resistance orHER2-positive tumors. Whereas a trend to anincrease of Ki67 in the others	8
5	EL-Haggar/ 2016/Egypt	102 (51/51)	49.78 ± 7.57/48.84 ± 7.49	102 women	48	850 mg	850 mg tablets/bid *vs.* placebo	BC treatment and prevent metastasis	IGF binding protein-3, insulin, fasting blood glucose, the molar ratio of IGF-1 to IGFBP-3, HOMA-IR and metastasis	Significant increase of the apoptotic inducer IGFBP-3 or/ and the significant reduction of mitogenic insulin, IGF-1, free bioactive IGF-1, FBG and HOMA-IR	8

→

Table 1 (cont.). Spreadsheet characteristics of RCT about anti-proliferative role of metformin (MF) in non-diabetic patients with breast cancer (n =11)

	Author/ publication year/ country	Patients number (case/control)	Mean age ± SD (yr.) (case/control)	Gender (M/F)% (case/ control)	Duration of MF (w)	Dose of MF	Intervention	End point	Outcome measures	Results	NOS scale
6	Hadad/2011/ UK	55 (25/30)	NA	55 women	5	500 mg	500 mg tablets once daily *vs.* no treatment	BC treatment	Ki67 and gene expression in primary breast cancer	Significant biomarker and genetic evidence for anti-proliferative effects of metformin in women with breast cancer and provides support for therapeutic trials of metformin	6
7	Hadad/2015/ UK	47 (24/23)	NA	47 women	2	500 mg	500 mg daily for 1 week then 1 g twice daily for a further week *vs.* Placebo	BC treatment	Phospho-AMPK (pAMPK), phospho-Akt (pAkt), insulin receptor, cleaved caspase-3, and Ki67	Up-regulation of tumor pAMPK, down-regulation of pAkt, and significant falls in Ki67 and cleaved caspase-3	6
8	Nanni/ 2018/Italy	126 (59/67)	57 (50–68)/ /61 (54–66)	Females with BC	156	2000 mg	2000 mg/day+ CT *vs.* CT alone	1-year PFS rate of HER2 -ve metastatic BC	HOMA index, Adverse event, Efficacy, mortality, survival rate	No anticancer activity of MF in combination with first line CT in BC. Sig shorter PFS in IR patients (HOMAI > 2.5), MF had sig effect on CT induced NP	8
9	Goodwin/ /2015/Canada	507 (249/258)	52.1 ± 9.5/ /52.6 ± –9.8	Females with BC	24	850 mg	850 mg caplet *p.o.* bid *vs.* placebo	Weight and metabolic factors	Weight, BMI, glucose, insulin, HOMAI, Leptin, CRP	Significantly improved weight, insulin, glucose, leptin, and CRP at six months	6
10	Pimentel/2019/ Canada	40 (22/18)	55 (39–75)/ /57 (41–73)	Females with BC	28	850 mg	850 mg *p.o.* bid *vs.* placebo bid. Both groups on CT	1-year (PFS) rate of met BC	OS, RR, QOL, HR	MF showed no significant effect on RR, PFS or OS	8
11	Kim/ 2014/ Korea	208 (104/104)	> 60 yrs	Females with BC	24	500 1wk, 1500 1wk, 2000 mg 22wk	Lt with MF *vs.* Lt with placebo	RR	Pathologic complete response rate, breast conserving rate, change in Ki67 expression, breast density change, and toxicity profile Molecular assays	MF has Anti-tumor effect in non-diabetic, postmenopausal patients with ER-positive breast cancer	8

MF — metformin; NOS — Newcastle-Ottawa Scale; BMI — body mass index; MO — month; M/F — male/female; μM — micro mole; SD — standard deviation; NA — not available; TUNEL — terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling; ACF — colorectal aberrant crypt foci; PCNA — proliferative cell nuclear antigen; HOMA-IR — homeostatic model assessment of insulin resistance; Igf-1 — insulin like growth factor-1; FBG — fasting blood glucose; FBI — fasting blood insulin; GE — glandular epithelial; ST — stromal; EC — endometrial cancer; PTH — phosphatase and tensin homolog; KLF — Krüppel-like factor 9; Erα — estrogen receptor α; PGR — progesterone receptor; BC — breast cancer; IGFBP-1 — insulin-like growth factor binding protein 1; IGFBP-7 — insulin-like growth factor binding protein 7; TKIs — tyrosine kinase inhibitors; EGFR — epidermal growth factor receptor; bid — twice daily; PFS — progression-free survival; NSNSC — non-squamous, non-small cell; CT — chemotherapy; IR — insulin resistant; sig — significant; NP — neutropenia; Met — metastatic; OS — overall survival; RR — response rate; QOL — quality of life; HR — hazard ratio; PSA DT — prostatic specific antigen doubling time; CNCRPS — chemotherapy-naive castration-resistant prostate cancer; DLTs — dose-limiting toxicities; AEs — adverse events; AMPK — adenosine mono-phosphate activated protein kinase; *Breast; Prostate; Colorectal; Lung; Lymphoma; Gastro-esophageal; Nasopharyngeal; Brain; Pancreas; Unknown primary; Appendiceal; Cholangiocarcinoma; Myeloma; Liver; Ovarian; Renal. Lt — letrozole; ER — estrogen receptor

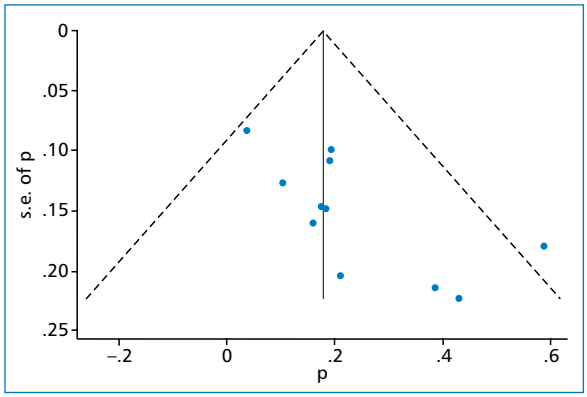

Figure 2. Funnel plot

cells. Therefore, metformin is used as a therapeutic agent in other clinical settings for all subtypes of breast cancer [16].

Secondly, patients with breast cancer, especially those suffering from less intense anti-cancer treatments can be treated with extreme diabetes regimens since usually they have more inconsistencies with chemotherapy, surgery, and other treatments [17]. Any metabolic disorder can adversely effect on cancer treatment response [18]. However, some studies have noted that metformin use in diabetics has survival advantages compared with non-diabetic patients or diabetics on other anti-diabetic medications. The high mortality rate amongst patients that are not taking metformin may be partially due to non-cancerous factors, such old age and low immunity [20] in spite of the positive effect of metformin on breast cancer, we had one mortality case out of 1,681 in our meta-analysis.

Our meta-analysis of qualitative research has shown that addition of metformin to routine treatment for non-diabetic patients with breast cancer compared to their counterparts, who did not receive metformin, is associated with reduced risks of all-cause and cancer-specific mortality. The risk of all-causes mortality in patients receiving metformin was lower than for patients who did not take metformin in adaptation studies for age, BMI stage, menopausal status, types of chemotherapy and hormonal receptor expression. Besides, taking metformin after diagnosis of breast cancer continues to prolong overall survival. These observations are unable to clarify the troubling variables, publication bias or unfair control from a single study.

To our knowledge, our meta-analysis is the first exclusive study of the association between metformin use and breast cancer outcome in non-diabetic population, though this topic has been investigated by many individual studies. Our results are not in accordance with a previous meta-analysis of mortality in diabetic patients with cancer by Yin et al. [7] WHO found that metformin use has been linked with a decreased risk of mortality for all cancers (HR: 0.66; 95% CI: 0.55–0.79) but not directly in breast cancer (HR: 0.64; 95% CI: 0.37–1.12).

Table 2. Pooled hazard ratios of all-cause mortality in non-diabetic breast cancer patients with and without metformin

Type of estimate	Studies (estimates), no.	Metformin	Non metformin	Pooled HR (95% CI)	I2,%	P value
All studies	11 (8)	841	840	0.6 (0.52–0.71)[a]	78.9	.001
Estimates adjusted for age 50–70 years	9 (7)	792	787	0.53 (0.39–0.71)[a]	80.3	.001
Estimates adjusted for duration > 48 weeks	2 (7)	110	118	0.43 (0.34–0.55)[b]	0	.771
Estimates adjusted for dose ≥ 2000 mg	1 (7)	59	67	0.40 (0.30–0.54)[b]	32.4	.170
Estimates adjusted for hormone receptors and metabolic effect	6 (7)	571	589	0.35 (0.15–0.84)[a]	60.2	.057
Estimates adjusted for Ki67	6 (7)	378	399	0.48 (0.23–1.00)[b]	9.1	.033
Estimates adjusted for PFS	2 (7)	81	85	0.66 (0.48–0.91)[a]	81.3	.001
Estimates adjusted for HOMAI	6 (7)	547	571	0.49 (0.27–0.87)[a]	84.0	.001
All estimates for TUNEL	1 (7)	45	42	0.87 (0.67–1.13)[a]	76.5	.39

BMI — body mass index; CI — confidence interval; DM — diabetes mellitus; HOMA-IR — homeostatic model assessment of insulin resistance; HR — hazard ratio; [a]Estimates calculated with use of random-effects model; [b]Estimates calculated with use of a fixed-effects model

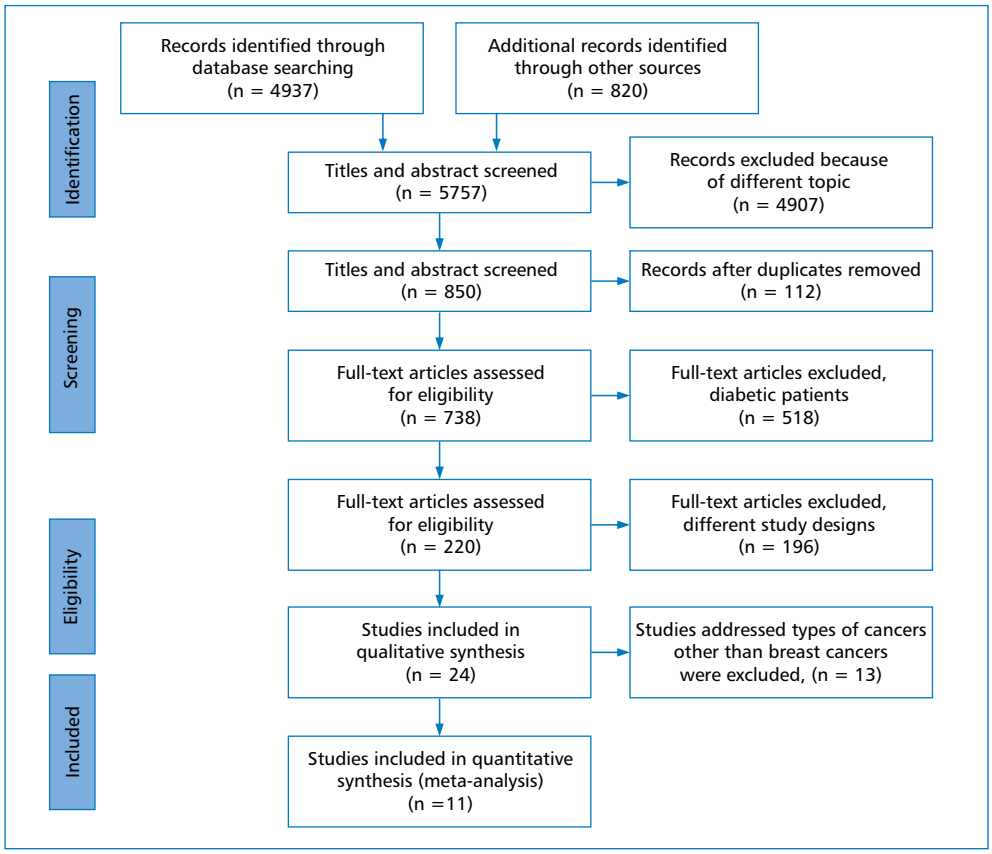

Figure 3. PRISMA diagram, based on [26] with permission

In addition, breast cancer-specific survival has been miscalculated by adoption recurrence-free survival as cancer-specific survival study by Bayraktar et al. [19]. For another analysis of metformin and cancer survival, metformin use has been linked with good survival of breast cancer in a subgroup (HR: 0.70; 95% CI 0.55–0.88) [2]. Yet the same number of patients was twice determined, that could overestimate the value of take metformin. These two experiments were both non diabetic in non-metformin category cases. Diabetes is defined as deficient prognostic factor for breast cancer. Thus, this inclusion is problematic because it would underestimate the survival benefit.

In the current larger-scale meta-analysis, we conducted post hoc power calculations and found that our study had 98.6% power in demonstrating the association between metformin use and overall cancer deaths. Such findings supported the assumption that the previous studies were having inconsistent findings because they were done on small numbers of patients.

The strengths of this study include an exhaustive examination for the multidisciplinary literature including ontological and epidemiological experts, with each article two people reviewed. We employed a broad search strategy and criteria for the inclusion of as much information from the literature as much as possible, including information of the kind of publication and language. While there are two related articles that were excluded from our meta-analysis due to lack of information, in general, the findings of these articles were on the risk estimates according to those in pooled meta-analysis. There were some shortcomings in the literature and consequently in our meta-analysis [7, 8].

We studied the population and confounding adaptation variables which could have given rise to overestimations and underestimated risks. Residual or unknown confounding factors remains possible after adjusting for most relevant confounding factors. The association may also not necessarily be causal, particularly regarding observation result [21].

The second drawback was that some of the publications were not reporting the types of anticancer treatments and their impact on outcomes. That's important since studies found that such treatments (such as surgery, and adjuvant chemotherapy) have a more beneficial impact on cancer than others; in addition, cancer is a chronic illness, and hence its origin, develop-

ment and treatment can have various prognostic consequences which can affect the final outcome [22, 23].

Finally, significant number of publications appeared to have literature bias as suggested by Eggers test. Nonetheless, this could be more of a small study influence than a true publication biases, in particular in the case between studies heterogeneity [24]. We tried to make our quantitative changes by including the missing studies. Trim and fill method is a statistical method which can be used in meta-analysis to underestimate the true positive effect in the absence of publication bias or less partial estimates can be given when bias is present in publication [25]. Using the conservative process, we found that metformin is linked to increased free survival rates. There are various potential explanations for the observed association of metformin use with improved survival time in non-diabetic patients with breast cancer.

Conclusion

The core results of our meta-analysis of RCTs show that metformin use is linked significantly to positive results for breast cancer prognosis in non-diabetic patients. Then, treatment with metformin in breast cancer might prolong the overall survival. Our results suggests the need for performing more prospective studies confirming metformin use as a predictive factor, and assess the scope for anti-diabetic regimens in dealing with breast cancer.

Conflict of interest

The authors declare no conflict of interest.

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