



제 2형 당뇨병 환자의 유방암 발생 위험 및 사망률에 대한 메트포민의 영향: 체계적 문헌고찰 및 메타분석

천부순*

인제대학교 약학대학
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Effects of Metformin on Breast Cancer Risk and Mortality in Type 2 Diabetes Mellitus: A Systematic Review and Meta-analysis

Pusoon Chun*

College of Pharmacy, Inje University, Gimhae 621-749, South Korea
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ABSTRACT

Background: The protective effect of metformin against breast cancer is inconclusive. **Objective:** To evaluate the effect of metformin on breast cancer risk and mortality in patients with type 2 diabetes. **Method:** A comprehensive literature search was performed for pertinent articles published prior to June 30, 2014, using PubMed and EMBASE. Study heterogeneity was estimated with I^2 statistic. The data from the included studies were pooled and weighted by random-effects model. The quality of each included study was assessed on the basis of the 9-star Newcastle-Ottawa Scale and publication bias was evaluated by visual inspection of a funnel plot. **Results:** Ten studies were included in the meta-analysis of the association of metformin and breast cancer risk. By synthesizing the data from the studies, the pooled odds ratio (OR) was 0.72 (95% CI: 0.59, 0.87) ($p = 0.0005$). Three cohort studies were included for meta-analysis of the association between metformin and breast cancer-related mortality. Metformin was associated with a significant decrease in mortality (Risk ratio: 0.68; 95% CI: 0.51, 0.90, $p = 0.007$). **Conclusion:** The present meta-analysis suggests that metformin appears to be associated with a lower risk of breast cancer incidence and mortality in patients with type 2 diabetes.

KEY WORDS: breast cancer, breast neoplasm, metformin, biguanide, diabetes mellitus

Introduction

Diabetes is a disease in which the body either has a shortage of insulin, a decreased ability to use insulin, or both. Type 2 diabetes accounts for 90-95% of all diabetes cases and is usually associated with older age, obesity and physical inactivity, family history of type 2 diabetes, or a personal history of gestational diabetes. Chronic hyperglycemia in patients with type 2 diabetes develops insulin resistance in fat and muscle tissues and leads to an inadequate, compensatory increased production of insulin.¹⁾

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females, accounting for

23% of the total cancer cases and 14% of the cancer deaths.²⁾ The risk of breast cancer is strongly related to age and menopausal status.^{3,4)} Other factors that increase a risk of developing breast cancer include obesity, having dense breasts, and inherited changes in certain genes.⁵⁻⁷⁾

Type 2 diabetes and breast cancer share several risk factors such as old age and obesity.^{8,9)} There is an evidence for increased risk of breast cancer incidence and mortality in diabetic individuals compared with individuals who do not have diabetes.^{10,11)} The exact mechanisms are yet to be explored, but insulin resistance with secondary hyperinsulinemia is the most frequently proposed hypothesis. Firstly, insulin resistance may

*Correspondence to: Pusoon Chun, College of Pharmacy, Inje University, 197 Inje-ro, Gimhae, Gyeongnam 621-749, South Korea
Tel: +82-55-320-3886, Fax: +82-55-320-3940
E-mail: pusoon@inje.ac.kr

enhance the bioactivity of insulin-like growth factor 1 (IGF-1), which may contribute to the carcinogenesis in hyperinsulinemic patients. Secondly, IGF-1 might increase the risk of cancer through its anti-apoptotic activity. Finally, insulin activity may affect the mitogenic pathways that include an overactivation of the mammalian target of rapamycin (mTOR) enzyme, an important positive regulator of translation initiation and cell proliferation. Therefore, the drugs that decrease insulin resistance and act as growth inhibitors by reducing mTOR activity, including metformin, are thought to lower the risk of developing cancer.^{12,13)}

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Two effects, suppression of hepatic gluconeogenesis and improvement of insulin sensitivity in skeletal muscle and adipose tissue, have been implicated as major contributors to glucose-lowering efficacy.¹⁴⁾ In addition to the antidiabetic effect, importantly, metformin has been shown to exert protective effects against cancer.¹⁵⁾ The potential anticancer activity of metformin is believed to be mediated mainly by adenosine monophosphate-activated protein kinase (AMPK). AMPK is a major metabolic sensor involved in regulating cellular energy homeostasis. By activating AMPK, metformin inhibits mTOR and protein synthesis and induces cell cycle arrest in cancer cells. The activation of AMPK is mediated by other proteins including Liver Kinase B1 (LKB1), a tumor suppressor protein kinase which mediates the action of metformin on AMPK activity. The absence or decreased expression of LKB1 in human breast carcinomas is associated with poor prognosis. Additionally, metformin decreases circulating insulin levels, inhibits angiogenesis, and exerts a toxic effect on cancer stem cells.¹⁶⁾

Although, a growing volume of evidence has been reported to show a potential protective action of metformin against cancer, the beneficial effects of metformin on the risk of breast cancer and mortality are controversial.^{17,18)}

A systematic review was conducted to examine relationship between metformin and breast cancer incidence and mortality in patients with type 2 diabetes.

Methods

Data sources and searches

A systematic literature search was conducted to identify publications addressing the association between metformin and

breast cancer incidence and/or mortality in patients with type 2 diabetes. The published studies from inception to June 30, 2014, were searched using PubMed and EMBASE by two independent investigators (MSK and JHP). The following keywords were used: (“breast cancer” OR “breast neoplasm”) AND (“metformin” OR “biguanide” OR “glucose-lowering drug” OR “diabetes mellitus.”). The reference lists of the identified studies, reviews, and meta-analyses on metformin and breast cancer risk/mortality were also scrutinized to find additional pertinent studies.

Study selection

Two investigators (MSK and JHP) independently identified potential studies and extracted detailed information from each included article. Discrepancies were resolved through a consensus discussion with a third investigator (PC).

Any study that met all of the following criteria was included: (1) evaluated the impact of metformin compared with non-metformin on breast cancer incidence or mortality; (2) involved treatment of patients with type 2 diabetes; (3) utilized appropriate methods of data collection.

Studies were excluded in accordance with the following criteria: (1) animal or cell model studies; (2) reviews, comment, editorial, conference abstract or paper, letter, and note; (3) studies without the number of cases and controls or clear grouping number; (4) cases of unclear diagnostic criteria; (5) analysis of individual cases

Data extraction and quality assessment

From each identified article, two researchers (MSK and JHP) independently extracted the data using predefined data extraction forms: the first author's name, study's year, country in which the study population lived, study design, comparator, age of participants, treatment or follow-up duration, numbers of events and total participants in each group, and the covariate-adjusted hazard ratio (HR)/ odds ratio (OR) estimates for breast cancer risk corresponding 95% confidence intervals (CIs). The quality of each included study was assessed on the basis of the 9-star Newcastle-Ottawa Scale (NOS).¹⁹⁾ The NOS assigns up to a maximum of 9 points for the least risk of bias: 4 for selection, 2 for comparability, and 3 for assessment of outcomes (for cohort study) or exposures (for case-control study). Studies with points of 0-3, 4-6, 7-9 were considered as low, moderate and high quality, respectively.²⁰⁾ Two raters (MSK and JHP) independently assessed the quality of the studies. Any disagreements were resolved by discussion and consensus with a third rater (PC).

Data synthesis and analysis

The present meta-analysis was performed using the Review Manager software (RevMan Version 5.2). The data from the included studies were pooled and weighted by random-effects model. Pooled OR and 95% CIs were used to measure the association between metformin and breast cancer incidence or mortality. Study heterogeneity was estimated with I^2 statistic, with values of 25%, 50%, and 75% representing low, moderate, and high degrees of heterogeneity. Two-sided P values less than 0.05 were considered statistically significant. Publication bias was evaluated by visual inspection of a funnel plot.

Results

The process of identifying reports for inclusion is outlined in Fig. 1. The initial search yielded 1,363 articles. After review of the titles and abstracts, a total of 36 articles were chosen for further review. Three articles were identified through the reference lists and included in this study. Among the 39 articles, 4 articles were excluded because they were cellular model. Fifteen of these articles were excluded because they did not study the impact of metformin on breast cancer risk or mortality. Two articles were excluded because of lack of reported HR or OR,

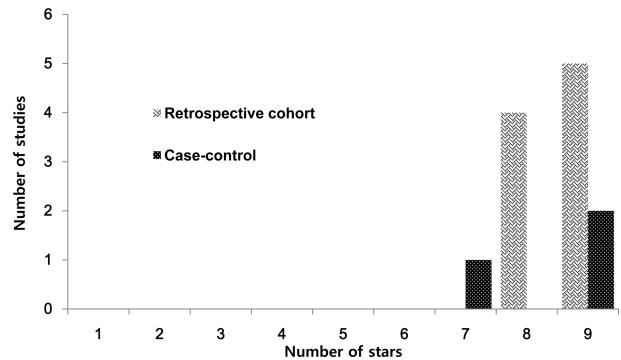


Fig. 2. Newcastle-Ottawa-Scale. The number of studies based on the number of the "stars" assigned in the retrospective cohort and case-control studies.

and 6 were excluded because they did not report the number of the patients, breast cancer events, or breast cancer-related deaths in each group. After these exclusions, 12 retrospectively designed studies were included: 9 retrospective cohort, 1 case-control, and 2 nested case-control studies. When assessing quality of the studies, all the included studies received between 7 and 9 stars and met the criteria of high quality based on NOS (Fig. 2).

The effect of metformin therapy on breast cancer risk

Ten studies with a total of 14,715 cases of breast cancer were

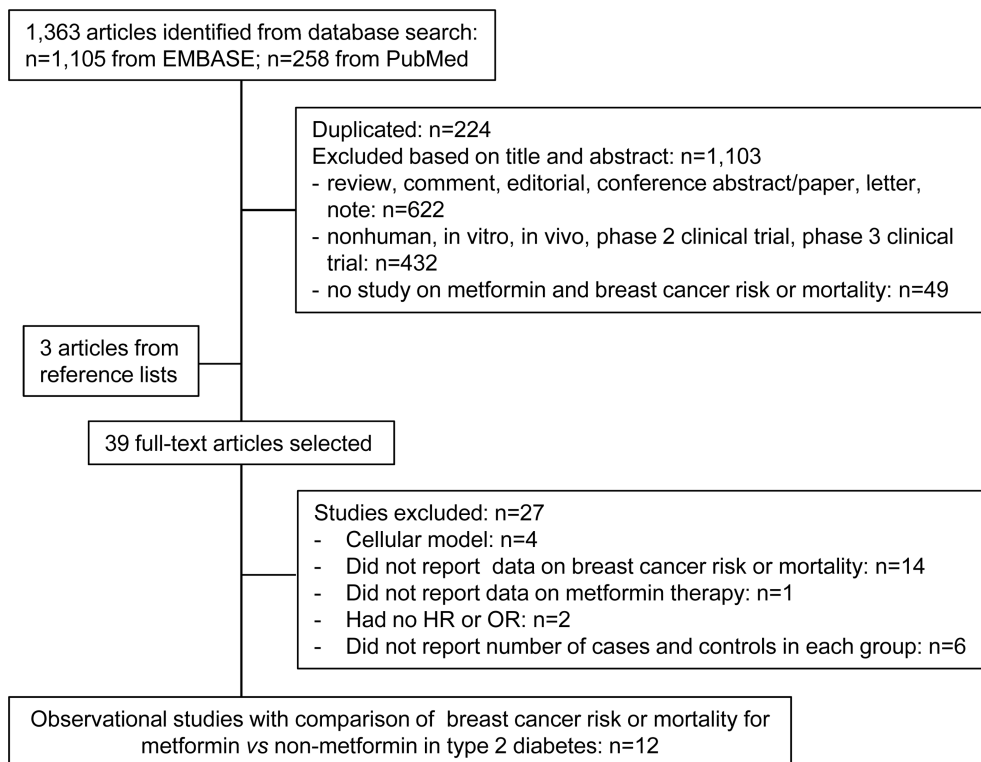


Fig. 1. Literature search and study selection process.

Table 1. Characteristics of the included studies and events of breast cancer among patients with type 2 diabetes after exposure to meiformin compared with non-meiformin.

Study	Country	Study design	Control	Age (year)		Treatment duration (year)		Meiformin group (n)		Control group (n)	
				meiformin	Control	meiformin	Control	events	total	events	total
Libby et al., 2009	Scotland	Retrospective cohort	Meiformin nonuser	≥ 35	≥ 35	3.5 (median)	2.6 (median)	24	4085	41	4085
Bodmer et al., 2010	UK	Nested case-control	Other antidiabetics	30-79	30-79	> 5	> 5	17	62	120	260
Bosco et al., 2011	Denmark	Nested case-control	Other antidiabetics	≥ 50	≥ 50	≥ 1	≥ 1	96	1154	297	2776
Ruifer et al., 2012	Netherlands	case-control	Sulfonylurea	61.8 ± 13.4 (mean)	65.6 ± 13.8 (mean)	2.3	2.9	207	32714	217	32591
Bayraktar et al., 2012	USA	Retrospective cohort	Meiformin nonuser	30-67	35-80	0.08-14.7	0.08-14.7	24	63	29	67
Hsieh et al., 2012	Taiwan	Retrospective cohort	Meiformin nonuser	61.4 ± 13.2 (mean)	61.4 ± 13.2 (mean)	8	8	19	2048	53	3142
Qiu et al., 2012	UK	Retrospective cohort	Sulfonylurea	60.5 ± 10.7 (mean)	64.2 ± 10.4 (mean)	3.35 ± 2.5 (mean)	5.02 ± 3.02 (mean)	616	39070	517	16904
Redantel et al., 2012	UK	Retrospective cohort	Sulfonylurea	≥ 35	≥ 35	≥ 0.5	≥ 0.5	151	7523	93	4815
Tsilidis et al., 2014	UK	Retrospective cohort	Sulfonylurea	35-90	35-90	2.9-8.1	2.9-8.1	307	51484	153	26428
Tseng et al., 2014	USA	Retrospective cohort	Meiformin never-user	54.93 (mean)	56.54 (mean)	7	7	2412	191195 (cases)	9322	443847 (cases)

Table 2. Events of all-cause and breast cancer-specific deaths among patients with type 2 diabetes and breast cancer after exposure to meiformin compared with non-meiformin.

Study	Country	Study design	Control	Age (year)		Follow-up (year)		Meiformin group (n)		Control group (n)	
				meiformin	control	Control	Meiformin	events	total	events	total
Bayraktar et al., 2012	USA	Retrospective cohort	Meiformin nonuser	30-67	35-80	Meiformin nonuser	0.08-14.7	20	63	23	67
Lega et al., 2013	Canada	Retrospective cohort	Meiformin nonuser	≥ 66	≥ 66	Meiformin nonuser	3.7 ± 2.8	126	1094	260	1267
Peeters et al., 2013	Netherlands	Retrospective cohort	Meiformin nonuser	68 (median)	76 (median)	Meiformin nonuser	1	51	508	75	550

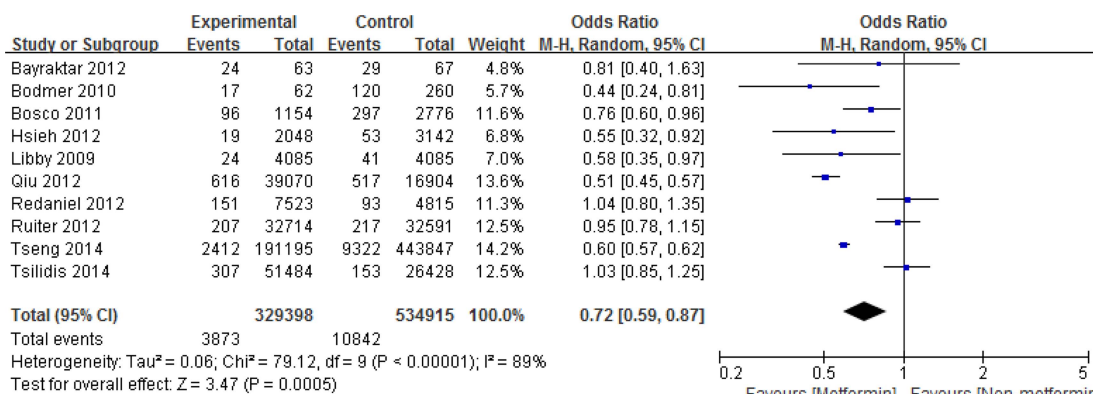


Fig. 3. Random-effects meta-analysis of breast cancer risk in type 2 diabetic patients exposed to metformin compared with non-metformin. Squares represent study-specific relative risk estimates; horizontal lines represent 95% CIs; diamond represents a summary relative risk estimate with corresponding 95% CI (0.62, 0.88).

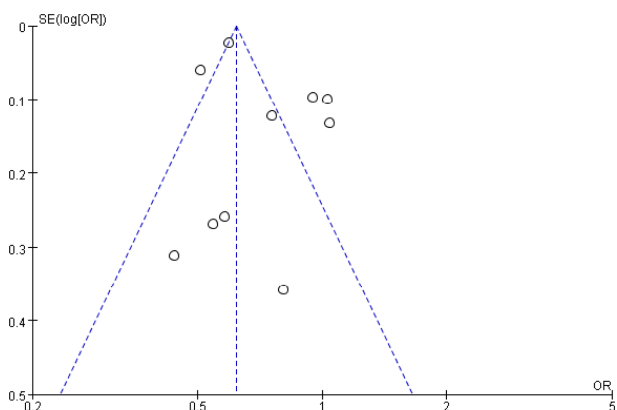


Fig. 4. Funnel plot for publication bias of the included studies in the meta-analysis of the effect of metformin on breast cancer risk.

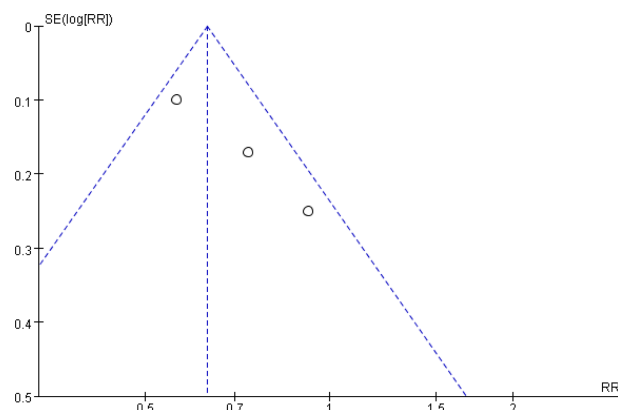


Fig. 6. Funnel plot for publication bias of the included studies in the meta-analysis of the effect of metformin on breast cancer mortality.

included in the present meta-analysis reviewing the association between metformin and breast cancer risk in patients with type 2 diabetes (Table 1). Of the studies, 5 studies showed the adjusted HR for comorbid conditions, such as age, sex, smoking, BMI, and HbA1C, and adjusted HR for breast cancer risk for metformin compared with non-metformin.^{21,24,28-30} By synthesizing the data from the 10 studies, the pooled OR was 0.72 (95% CI: 0.59, 0.87) (p = 0.0005) (Fig. 3). Visual inspection of a funnel plot suggested possible publication bias (Fig. 4).

The effect of metformin use on breast cancer-related mortality

The association between metformin and breast cancer-related mortality was reported in 3 cohort studies recruiting 555 breast cancer-related deaths (Table 2). Of the studies, 2 studies showed the adjusted HR for all potential confounders, such as other antidiabetic agents, age at breast cancer diagnosis, and duration of diabetes before breast cancer.^{31,32} With random-effects model analysis, metformin treatment was associated with a significant

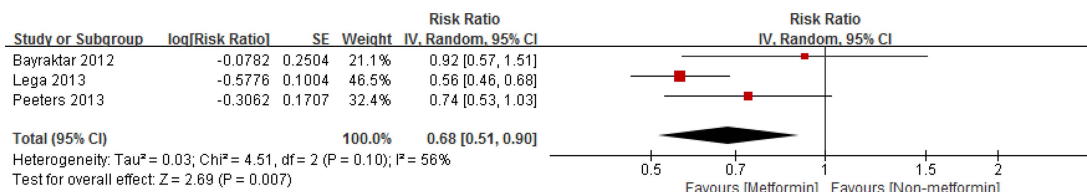


Fig. 5. Random-effects meta-analysis of breast cancer-related mortality in patients with type 2 diabetes and breast cancer after exposure to metformin compared with non-metformin. Squares represent study-specific relative risk estimates; horizontal lines represent 95% CIs; diamond represents a summary relative risk estimate with corresponding 95% CI (0.51, 0.90).

reduction in the risk of breast cancer-related mortality in patients with type 2 diabetes (RR: 0.68; 95% CI: 0.51, 0.90, $p = 0.007$) (Fig. 5). Visual inspection of a funnel plot suggested possible publication bias (Fig. 6).

Discussion

In this meta-analysis, metformin therapy was associated with a significantly decreased risk of breast cancer compared with non-metformin treatment in patients with type 2 diabetes. This supports the hypothesis that metformin may have an anticancer effect.^{33,34} In this study, metformin was associated with a 26% decrease in the incidence of breast cancer. This result is consistent with the finding of a previous study by Col et al. that reviewed seven studies^{21-24,36-38} (OR: 0.83; 95% CI: 0.71, 0.97).³⁵ Although the three studies³⁶⁻³⁸ were excluded from the present study due to unfulfilled inclusion criteria, no substantial difference in the overall effect of metformin on breast cancer risk was found between the previous study and the present meta-analysis. In addition, the study by DeCensi et al., which analyzed three observational studies,^{21,22,36} found a 30% decrease in overall summary RR (95% CI: 0.28, 1.77) in the metformin users compared with other antidiabetic drug users.³⁹ On the contrary, in the previous meta-analysis of 9 randomized controlled trials (RCTs), no beneficial effect of metformin was observed (RR: 0.99; 95% CI: 0.80, 1.24) in trials comparing metformin to other antidiabetic drugs.⁴⁰ This discordance may be partly explained by the fact that the previous meta-analysis of RCTs has fewer patients of follow-up and fewer cancer cases than those of the present study (398 vs. 14,715 for cancer cases).

In this meta-analysis, metformin use was associated with a significant risk reduction of breast cancer-related mortality compared to non-metformin use in patients with type 2 diabetes (OR: 0.72; 95% CI: 0.59, 0.87, $p = 0.007$). This finding is consistent with the result from the meta-analysis by Noto et al. that analyzed three observational studies^{21,42,43} and two RCTs.^{44,45} In that study, a significant reduction in mortality was observed in metformin users compared with other medication users (RR: 0.66; 95% CI: 0.49, 0.88; $p = 0.005$).⁴¹

There are some limitations in this meta-analysis. The findings from this study are based on the results derived from observational studies, which are inherently more susceptible to bias. In addition, most of the included studies did not analyze data on pathological type of breast cancer. In this study, the presence of publication bias cannot be ruled out. This publication bias may

be related to the exclusion of "grey literature" and of studies which do not report precise data on cases and controls in each group. Lastly, a high degree of heterogeneity was found in the analysis of breast cancer risk while the heterogeneity observed in the analysis of breast cancer related-mortality was moderate: $I^2 = 89\%$ for the analysis of breast cancer risk ($p < 0.00001$), $I^2 = 56\%$ for the analysis of breast cancer related-mortality. This can be partly explained by the differences in the treatment duration and age of the subjects among the included studies.

Despite of these limitations, this study has two strengths. First of all, this meta-analysis is mainly based on large population-based data originating from multiple nations. In addition, all the populations included in the present study were people with type 2 diabetes while non-diabetic populations were excluded because diabetes is emerging risk factor for breast cancer.

Conclusion

The present meta-analysis suggests that metformin appears to be associated with a lower risk of breast cancer incidence and mortality in patients with type 2 diabetes.

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