Reduced Risk of Lung Cancer With Metformin Therapy in Diabetic Patients: A Systematic Review and Meta-Analysis

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Initially submitted September 23, 2013; accepted for publication April 17, 2014.

Emerging evidence from epidemiologic studies and basic science suggests an inverse association between metformin use and cancer risk in diabetic patients. However, the association with lung cancer is not consistent. We summarized the evidence currently available (2009–2013) and explored sources of heterogeneity. Metformin therapy was associated with significantly lower risks of cancers of the lung (4 studies; pooled relative risk = 0.71, 95% confidence interval (CI): 0.55, 0.95; \( P = 0.02 \)) and respiratory system (6 studies; pooled relative risk = 0.85, 95% CI: 0.75, 0.96; \( P = 0.01 \)). There was evidence of moderate heterogeneity (\( I^2 > 50\% \)). The major sources of heterogeneity were smoking adjustment status and cancer site. The relative risk from studies that adjusted for smoking was 1.16-fold (95% CI: 1.00, 1.35) closer to the null than that from studies not adjusting for smoking. The relative risk of respiratory cancer was 1.23-fold (95% CI: 1.02, 1.49) closer to the null than that for lung cancer. In conclusion, metformin use appears to be associated with lower risks of lung and respiratory cancer in diabetic patients. However, caution regarding overestimation is needed, since adjustment for smoking attenuates the association.

Chemoprevention; diabetes; lung cancer; metformin; smoking

Abbreviation: CI, confidence interval.

Lung cancer is one of the most common malignant tumors. It is a major cause of cancer-related death, largely because in the majority of patients it is at an advanced stage when diagnosed (1). In light of the emerging evidence linking lung cancer to air pollution (2, 3) and the failure of agents previously recommended for lung cancer chemoprevention (4–7), it is necessary to identify new chemopreventive agents that are effective in reducing the risk of lung cancer. Metformin is a first-line drug for the management of type 2 diabetes. Some epidemiologic studies suggest a potential antitumor role of metformin in diabetic patients (8, 15). Basic research suggests that metformin inhibits lung-cancer cell growth and induces apoptosis (16, 17). Two experiments in mice showed a delay in the growth of grafted lung cancer with administration of metformin (16, 18). Moreover, a mouse experiment showed that metformin prevented lung tumorigenesis induced by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a tobacco carcinogen (19). Several epidemiologic studies (12–15), but not all (20, 21), have shown a significantly lower risk of lung cancer associated with metformin use. Accordingly, we performed a meta-analysis to summarize the evidence currently available and explore the sources of heterogeneity.

METHODS

Study selection

Relevant studies were identified by searching the PubMed, EMBASE, and SciVerse Scopus databases for all articles published through December 31, 2013. Keywords used for searching included “metformin,” “biguanides,” “cancer,” “neoplasms,” and “lung cancer.” The search was further restricted to English-language articles and human subjects. Additional studies were retrieved through a hand search of references from original reports and review articles. Studies were considered eligible if data on the relationship between metformin therapy and risk of lung cancer were available. We also included studies that investigated the association between metformin and respiratory cancer in diabetic patients. If there were multiple publications from the same study, the papers with the most complete data were given precedence.
Data extraction and statistical analyses

Two of the authors (Z.-J.Z. and G.Z.) independently reviewed each eligible article and extracted relevant data using a structured table. Each study was evaluated with regard to the STROBE statement (22) for ascertainment of data quality. Data extracted included name of the first author, year of publication, study design, region of study, source population, number of participants, length of follow-up (if applicable), and confounding factors controlled for. The term “relative risk” reflects both odds ratios and risk ratios in the present analysis. Forest plots were used to compare results across studies. For those studies consisting of multiple pairwise comparisons, we pooled the effect estimates with an inverse variance weight and used the combined estimate. We performed sensitivity analysis by including one comparison at a time when recalculating the summary relative risk. We derived the pooled relative risk by averaging per-study natural logarithmic relative risks weighted by the inverses of the variances. We used DerSimonian and Laird random-effects models (23) to incorporate between-study variance and to calculate the pooled relative risk.

To visually examine and assess the estimates of relative risk and corresponding 95% confidence intervals across studies, we generated forest plots. To assess the heterogeneity of relative risks across studies, we calculated Cochran’s $Q$ statistic with a significance level of $P < 0.10$ (24). We also calculated the $I^2$ statistic, which reflects between-study heterogeneity. $I^2$ values less than 25%, 50%, and 75% indicate low, medium, and high heterogeneity, respectively (25). Sources of heterogeneity were explored by fitting prespecified covariates (i.e., study design: cohort vs. case-control; region: Europe vs. United States; cancer site: lung vs. other respiratory system; smoking: adjustment vs. no adjustment) in a random-effects meta-regression model. Subgroup analyses were performed for the covariates that were statistically significant in the meta-regression model. Finally, we assessed evidence of publication bias by visually examining Begg’s funnel plot and performing Begg’s adjusted rank correlation test and Egger’s regression asymmetry test.

All analyses were performed using Stata, version 10.0 (StataCorp LP, College Station, Texas). A 2-tailed $P$ value less than 0.05 was considered significant in statistical tests.

RESULTS

We retrieved 6 relevant studies, including 4 cohort studies (12, 14, 15, 21) and 2 case-control studies (13, 20), comprising a total of 566,435 diabetic patients. The study selection process is depicted in Web Figure 1 (available at http://aje.oxfordjournals.org/). Information on first author name, publication year, study type, region, source population, reference group, and confounding adjustment is presented in Web Table 1. Two studies were based in the United States (13, 21), 2 in the United Kingdom (15, 20), 1 in the Netherlands (12), and 1 in China (14). Four studies investigated the association between metformin therapy and lung cancer (13–15, 20), and the other two investigated the association with all cancers of the respiratory system (12, 21). Four studies controlled for smoking (13, 15, 20, 21), and the other two did not (12, 14). Only 1 study adjusted for obesity (15). No investigators described the pathological subtypes of lung cancer.

We pooled data from the 4 studies on metformin therapy and lung cancer (13–15, 20). Metformin was associated with a significantly lower risk of lung cancer (pooled relative risk = 0.71, 95% confidence interval (CI): 0.55, 0.95; $P = 0.02$) (Figure 1, Table 1). There was evidence for the presence of moderate heterogeneity ($Q = 7.0, P = 0.07; I^2 = 57\%$). There was no evidence of publication bias from funnel plot examination or from Begg’s test ($P = 0.31$) or Egger’s test ($P = 0.12$). The pooled relative risk did not change materially after we omitted one comparison at a time when recalculating the summary relative risk (data not shown).

We included the 2 additional studies that investigated all cancers of the respiratory system (12, 21). Metformin was associated with a significantly lower risk of cancers of the respiratory system (pooled relative risk = 0.85, 95% CI: 0.75, 0.96; $P = 0.01$) (Figure 1, Table 1). There was evidence for the presence of moderate heterogeneity ($Q = 11.4, P = 0.04; I^2 = 56\%$). There was no evidence of publication bias from funnel plot examination (Web Figure 2) or from Begg’s test ($P = 0.13$) or Egger’s test ($P = 0.45$).

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Figure 1. Pooled relative risk of cancers of the lung (A) and respiratory system (B) associated with metformin therapy among diabetic patients in 6 published studies, 2009–2013. The squares indicate the relative risk for each available study, and the horizontal lines represent the 95% confidence intervals. The size of each square is proportional to the weight of the corresponding study in the meta-analysis. The diamond indicates the pooled relative risk, and the diamond’s width represents the 95% confidence interval.
In the meta-regression model, region and study design were not major sources of heterogeneity. Two factors—cancer site and whether the investigators adjusted for smoking—modified the relative risk associated with metformin (Table 1). The relative risk from studies that adjusted for smoking was 1.16-fold (95% CI: 1.00, 1.35) higher than that from studies without adjustment for smoking (i.e., 1.16-fold closer to the null). The relative risk for all respiratory cancers was 1.23-fold (95% CI: 1.02, 1.49) higher than that for lung cancer alone (i.e., 1.23-fold closer to the null). Results of subgroup analyses based on smoking adjustment and cancer site are presented in Table 1.

**DISCUSSION**

In the present study, we summarized the evidence currently available to evaluate the potential role of metformin in chemoprevention for lung cancer. Metformin therapy was associated with estimated reductions of 29% in lung cancer and 15% in cancer of the respiratory system. The main sources of heterogeneity in this analysis were smoking adjustment status and cancer site. Lack of smoking adjustment led to overestimation of the potential benefit of metformin. In addition, the association of metformin with lung cancer was more prominent than that with other cancers of the respiratory system.

Caution is required, however, in interpreting these results. One major limitation of the present study is heterogeneity. Our findings suggested that lack of adjustment for smoking would lead to overestimation of the inverse association of metformin with lung cancer. This may indicate an influence of residual confounding by smoking, which is one of the most important risk factors for lung cancer. It remains unknown whether metformin has differential chemopreventive associations with lung cancer among smokers and nonsmokers. Indeed, in 1 mouse experiment, Memmott et al. (19) reported that metformin prevented tobacco-induced lung tumorigenesis. Future studies need to investigate whether smokers benefit more from metformin treatment than nonsmokers and whether pack-years of smoking have an impact on the association between metformin and lung cancer.

In addition, the present study showed that the association of metformin with lung cancer might be more prominent than the association with other cancers of the respiratory system. Experiments using animal models have shown that metformin inhibits tumor growth in the lung (16, 18, 19), but data on the association of metformin with other cancers of the respiratory system are sparse. Furthermore, there are 2 major subtypes of lung cancer: non-small-cell and small-cell. These 2 subtypes exhibit different biological process. Non-small-cell lung cancers are relatively insensitive to chemotherapy. It is unknown whether the association of metformin with lung cancer differs for these 2 subtypes. None of the studies included in our analysis differentiated between lung cancer subtypes.

Residual confounding is one of the major limitations inherent in observational studies. Only 1 study included in the present meta-analysis adjusted for obesity (15), though obesity-related epigenetic changes are enriched in antitumor genes and oncogenes (26). Factors that affect a physician’s decision to prescribe metformin, as opposed to other hypoglycemic agents, as well as factors that improve patients’ adherence to metformin regimens, may also be associated with lung cancer risk. Thus, the observed association for metformin may simply reflect the consequences of these unknown factors. In addition, other hypoglycemic agents may affect the risk of lung cancer, such as insulin and sulfonylureas (27–29). When metformin is compared with these agents, the observed inverse association could be overestimated. There are other limitations pertaining to study design. Time-related bias, particularly immortal time bias, is present in some previous studies, which results in an exaggerated beneficial effect. One study designed to avoid time-related bias showed a null association (20). Although latency period was accounted for, the possibility of reverse causation was not completely ruled out. Most of the studies included in our analysis ascertained cancer incidence by using administrative data or linking to cancer registries. Misclassification of lung cancer was possible in some studies. Finally, no dose-response data were available.

In conclusion, metformin therapy appears to be associated with a significantly lower risk of lung cancer in diabetic patients. However, caution regarding possible overestimation is needed. Besides immortal time bias, lack of smoking adjustment could also have led to overestimation of the inverse association. In addition, the inverse association with lung cancer might be more prominent than the association with other cancers of the respiratory system. Further investigation should take these factors into account.

**ACKNOWLEDGMENTS**

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Conflict of interest: none declared.

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