Reviewer's report

Title: The Effect of Metformin and Thiazolidinedione use on Lung Cancer in Diabetics

Version: 3 Date: 9 August 2012

Reviewer: Tom Kristian K Grimsrud

Reviewer's report:

The authors have responded adequately to the comments, and the manuscript has improved materially. I found the added data on year of diagnosis of lung cancer and the period of electronic patient data very interesting. These data do, however, rise some new questions that should be given attention in the Discussion section (see below).

Major Compulsory Revisions

None

Minor Essential Revisions

1) The diagnoses of lung cancer span a period of more than 30 years (1978–2010). During this period there have been secular trends in the U.S. of the histological types of lung cancer (increasing rate of adenocarcinomas, and decreasing rate of squamous cell carcinomas, described e.g. by Wahbah M & al in Ann Diagn Pathol. 2007;11(2):89-96). This might influence the distribution of histological types among the lung cancer cases included in the present study, as the antidiabetic medication was introduced late in this period (in or after 1995) and possibly became more and more widespread after 1995. The potential effect on the distribution of histological types of lung cancer should be addressed in the discussion, or (perhaps even better) it could be addressed by restricting the cases included in table 3 to those diagnosed after 1995, or after a later year when peroral medication was considered to have become common.

2) The authors state in the discussion (page 14, para 2, line 7) that “The greatest remaining potential for error is the presence of a confounding variable.” I believe there is another potential bias that may deserve to be discussed: a possible selection in the form of choice of medication with oral antidiabetics according to the patients symptoms. A lung disease thought to increase the risk of lactic acidosis, seem to be a contraindication of metformin medication. Some thiazolidinediones, on the other hand, have been suspected of increasing the risk of coronary heart disease and heart attacks. This means that co-morbidity, symptoms, or a perceived increased risk of lung or heart disease may have influenced the doctor’s choice of medication. Additionally, there is a link between respiratory symptoms, cardiovascular mortality, and lung cancer that seems to be independent of smoking. It has been reported that respiratory symptoms
increases the risk of cardiovascular death and increases the risk of lung cancer, even under adjustment for smoking habits.

I believe it is important to beware that the present study is observational, and far from a randomised trial, and that the data and disease histories have developed, and may have been individually influenced by clinical judgement and decisions, opening for a selection that can mimic an effect of any intervention such as medication. If the doctor avoids oral antidiabetics in patients with respiratoory symptoms, which are linked to a higher risk of lung cancer, a preventive effect may be (falsely) ascribed to medication given to the patients with no respiratory symptoms, who have an ‘a priori’ better prognosis as regards lung cancer. This effect may exist despite similarities in (and matching according to) smoking habits.

It may be out of the reach for the present study to clarify these questions, but the discussion would improve the quality of the article.

Discretionary Revisions

1) In the abstract, the abbreviation DM should be introduced in the first line of the Methods part: “Patients with diabetes mellitus (DM) were ...”.

2) In the Results part of the Abstract, page 3, line 1, the phrasing “those who received neither of metformin and/or a TZD” seems unclear and may need attention.

3) The naming of the categories of antidiabetic medication could also profit of clarification, see page 5, line 2 from below, starting “metformin and/or a TZD”, where the “or a TZD” group might be taken to overlap with the category “TZD without metformin”. I assume this is a matter of wording, and that there is no real overlap.

4) When OR is introduced on page 9, line 1 from below, it should be probably be introduced as “odds ratio (OR)”.

5) On page 10, para 2, line 4, the word “trend” could preferably be changed with “suggestion”, as “trends” in an epidemiological context often is used for time trends.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.