Peer Review Report

Review Report on Effect of annual influenza vaccination on the risk of lung cancer in patients with hypertension–A population-based cohort study in Taiwan

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EVALUATION

Q 1 — **Please summarize the main findings of the study.**

The researchers examined whether the influenza vaccine increased lung cancer incidence in an analysis of individuals with hypertension in health insurance data from Taiwan.

Q 2 — **Please highlight the limitations and strengths.**

Limitations: The exclusion criteria could be better described to allow readers to think about possible selection bias. It is not always clear what exactly was analyzed.

Strengths: The propensity score analysis is appropriate for this question.

Q 3 — **Please provide your detailed review report to the authors. The editors prefer to receive your review structured in major and minor comments. Please consider in your review the methods (statistical methods valid and correctly applied (e.g. sample size, choice of test), is the study replicable based on the method description?), results, data interpretation and references. If there are any objective errors, or if the conclusions are not supported, you should detail your concerns.**

Generally, it would be useful to have an overview of what could be possible pathways could be that make the influenza vaccine contribute to lung cancer incidence. Is 1 dose of the influenza vaccine really enough to increase lung cancer risk?

Incidence of lung cancer should be defined in more detail. Is time 0 defined as the time of the first influenza vaccine? Does the lunch cancer diagnosis need to be strictly after that, or is any timepoint acceptable here?

I have seen other works discussing the necessity for lung cancer patients to get the flu vaccine. Is it possible that that is what is happening in this dataset? If not, why not?

It would also be useful to put the research on lung cancer in Taiwan into context, especially if it is quite different from other countries.

Regarding the exclusion criteria:
– Subjects younger than 55 were excluding even though the flu vaccine was recommended for high risk adults 50+. Could you justify the use of 55+?
– Diagnosis of hypertension prior to 2001 could possibly exclude many older subjects who have lived decades with hypertension. This is likely a strong source of selection bias (for example, only 16% of the analysis population is 75+). What is the justification for that?
– what is the rationale for excluded subjects with previous cancer diagnoses?

In looking at this paper, I tried to reconstruct a cross-tabulation of vaccination status and lung cancer by age group. It would be very useful for readers if such a table was included.

Regarding the suggested dose-response relationship: Please give some numbers for how many subjects got how many doses of the flu vaccine? If a subject got 4 doses, does that many they had the flu shot in 4 of the possible 12 years?

The sensitivity analysis is not really a sensitivity analysis, as it does not explore other possible assumptions (for example, other exclusion criteria). Is it possible you mean a "subgroup analysis"?

Table 1 should not contain p-values and any discussion of it should focus on the magnitude of differences observed. Many p-values here will be significant because of the sample size, even if the differences are relatively small.

How is season defined in Table 2? Why is this related to lung cancer incidence? Table 2 would have been interested if CCI was also included.

Tables 1 and 2 should not contain significance stars.

PLEASE COMMENT

Q 4 **Is the title appropriate, concise, attractive?**

The title is fine.

Q 5 **Are the keywords appropriate?**

The keywords are ok. However, it's not discussed in the paper what the resulting "public health policy" changes could be.

Q 6 **Is the English language of sufficient quality?**

Yes.

Q 7 **Is the quality of the figures and tables satisfactory?**

No.

Q 8 **Does the reference list cover the relevant literature adequately and in an unbiased manner?)**

No answer given.

QUALITY ASSESSMENT

Q 9 **Originality**

Q 10 **Rigor**

Q 11 **Significance to the field**

Q 12 **Interest to a general audience**

Q 13 **Quality of the writing**

Q 14 **Overall scientific quality of the study**

REVISION LEVEL

Q 15 **Please make a recommendation based on your comments:**

Major revisions.