

Electronic cigarette use after smoking cessation and lung cancer risk

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This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
Dear Editor,

Thank you for the opportunity to review the manuscript entitled “Risk of Lung Cancer Associated with Electronic Cigarette Use After Smoking Cessation: A Nationwide Cohort Study” by Kim et al. This manuscript reports a prospective cohort analysis using data from the National Health Screening Program in South Korea. Self-reported information on smoking status (including pack-years) and e-cigarette use (including days per week) was collected in 2014–2016 and 2018. Participants who self-reported as ever-smokers and had available data on pack-years, e-cigarette use, and other study variables were included in the analysis (total $n = 4,524,895$). At the analysis baseline (2018), participants were categorized into five groups: 1) Current smokers (individuals who continued smoking through 2018); 2) Short-term quitters with e-cigarette use (current smokers in the first period who had quit smoking before 2018 and reported e-cigarette use in 2018); 3) Short-term quitters without e-cigarette use (current smokers in the first period who had quit smoking before 2018 and reported no e-cigarette use in 2018); 4) Long-term quitters with e-cigarette use (individuals who had maintained smoking cessation through 2018 and reported e-cigarette use in 2018); and 5) Long-term quitters without e-cigarette use (individuals who had maintained smoking cessation through 2018 and reported no e-cigarette use in 2018). Participants were followed through 2023. Using Cox regression models, the authors found that, compared with ex-smokers who did not use e-cigarettes, ex-smokers who used e-cigarettes after quitting had a significantly increased risk of lung cancer ($aHR=1.56$, 95% $CI=1.24–1.97$) and lung cancer-specific death ($aHR=2.00$, 95% $CI=1.28–3.15$). In contrast, compared with current smokers, ex-smokers without e-cigarette use had a significantly reduced risk of lung cancer ($aHR=0.56$, 95% $CI=0.55–0.57$) and lung cancer-specific death ($aHR=0.42$, 95% $CI=0.40–0.43$), with greater risk reduction observed with longer duration of smoking cessation. However, this risk reduction was not observed among ex-smokers who used e-cigarettes. The authors concluded that switching to e-cigarettes after quitting conventional smoking was associated with a higher risk of lung cancer and lung cancer-specific mortality, compared with no e-cigarette use, and diminished the benefits of smoking cessation.

I would like to congratulate the authors on performing this important and timely study. I found the manuscript to be very well written, the analyses are strong, the results are well presented, and the discussion and conclusion are supported by the findings.

I only have the following comments to be addressed by the authors:

1. The adjustment model described in the statistical analysis section of the Methods states that “the final multivariable models were adjusted for age, sex, body mass index (BMI), income (categorical; in quintiles), alcohol consumption, CCI, underlying COPD, and underlying IPF.” However, in the footnotes of the main tables and figures, the authors state that the models were “adjusted for age, sex, smoking pack-years, body mass index, household income, alcohol consumption, physical activity, CCI, underlying COPD or IPF.” In the text, smoking pack-years is not mentioned as a covariate in the adjusted model, whereas it is included in the tables and figures. Please harmonize the text, tables, and figures to accurately reflect the adjusted model. I assume the models were adjusted for pack-years, as this is an important confounder. If so, please correct the corresponding text.

2. In the last paragraph of the Results section, the authors mention a dose-dependent relationship between duration of smoking cessation and lung cancer risk. Please clarify in the Methods and Results how this relationship was assessed. An

appropriate statistical method, such as calculating and reporting the p-value for trend, should be used for assessing the dose-response relationship.

3. The manuscript does not clarify the inclusion of dual cigarette and e-cigarette users in the current smoking group. Please indicate whether current smokers also include dual users. If so, I suggest adding an analysis comparing lung cancer risk among dual users versus cigarette-only smokers.

4. How did the authors account for smoking relapse in their analysis? Specifically, how were participants treated who reported being ex-smokers in the first survey but then reported current smoking in the second survey?

5. While the overall sample size is very large, the number of events in the groups of quitters with e-cigarette use is limited. For some analyses, such as lung cancer-specific death, the number of events was only 17 and 2 for short-term and long-term quitters with e-cigarette use, respectively. Although the authors have done the best they could with the available data, this limitation should be mentioned in the final paragraph of the Discussion, along with other study limitations. The impact and implications of the limited number of events in the e-cigarette-exposed groups should also be discussed, and the need for future studies with larger exposed sample sizes should be emphasized.

6. I recommend that, when referring to the association between e-cigarette use and lung cancer, the authors use the term incidence rather than development. For example, "...increased risk of lung cancer incidence" rather than "...increased risk of lung cancer development."

Reviewer #2

(Remarks to the Author)

The manuscript closely resembles a previous publication by this team https://www.atsjournals.org/doi/10.1164/ajrccm-conference.2024.209.1_MeetingAbstracts.A3051 widely cited as showing that vaping causes lung cancer.

In a large data set from South Korea, people who were smokers or ex-smokers in 2012, 2014 and 2018 were followed up, to 2021 in the previous report and to 2023 in this one. In 2018, a question about use of e-cigarettes (EC) was included and people who said they were vaping nearly every day in the month of the survey were classified as having substantial EC use (vapers). Vapers had a risk of lung cancer that was non-significantly lower than that of current smokers (HR 0.89; 0.70 – 1.14), and greater than that of ex-smokers who did not vape (HR 1.56; 1.24 – 1.97).

The authors interpret these findings as suggesting that vaping causes lung cancer, an interpretation that seems somewhat tendentious. The cancers that were observed were likely the result of decades of smoking and the finding, if genuine, would more likely suggest that vaping was reducing the benefits of stopping smoking. There is a high probability though that the results are an artefact of several methodological issues.

Here is the main one. The by far the most important determinant of the reduction in cancer risk after stopping smoking is the duration of abstinence. As vaping is a relatively new development, duration of abstinence can be expected to differ substantially between vapers and non-vapers. The control for this was inadequate. Ex-smokers were divided into groups abstinent for <5 years and >5 years. It is a certainty that among >5 years quitters, vapers had quit much more recently; but this would be the case among <5-year-quitters too, as the popularity of vaping was increasing during that time. The results may be just showing that risk reduction is proportional to duration of abstinence and have nothing to do with vaping.

Apart from this key problem, there are several other issues.

The current findings could be in part due to reverse causality. Smokers with prodromal symptoms of lung cancer could have been more motivated to switch to vaping. A previous publication by some of the current authors using the same data set (<https://doi.org/10.1001/jamanetworkopen.2023.54958>) found that recent quitters had not just no reduction, but in fact an increase in risk of lung cancer compared to continuing smokers. They interpreted the finding as due to smokers with incipient cancer being more likely to stop smoking. This is not mentioned in the current manuscript where it would be highly relevant given that vapers were bound to be more recent quitters than non-vapers.

The data set used in this manuscript contains a very large number of variables and it is not clear how were those that were being controlled for selected. In unadjusted data, vapers had much lower incidence of cancer than non-vapers. This would be due to age differences and controlling for age was necessary. Apart from this, vapers and non-vapers probably differed in dozens of variables. Controlling for different covariates can lead to different and even opposite results. Some suspicions are raised by the fact that the manuscript copies closely a paper by a different team using the same data set to look at effects of vaping on CVD (<https://doi.org/10.1161/CIRCULATIONAHA.121.054967>) but it includes different covariates (and does not use propensity matching).

Regarding the questions of how short-term vaping could cause lung cancer, the uncertain duration of vaping adds to the problem. Vapers vaped regularly over one month in 2018, but there are no data on how long they were vaping for or whether they continued to vape or returned to smoking after 2018. It is possible that smokers who managed to quit unaided were more likely to maintain their abstinence than those who needed vapes.

Regarding some other more minor issues,

Data are missing on dual users (people who both smoke and vape). These results would be of obvious interest. It is in fact not clear whether dual users were included among current smokers or excluded.

An explanation is needed for why 2012, 2014 and 2018 surveys were used but not 2016.

It is also not clear how were the 2012 and 2014 data combined; and why are there two baseline surveys rather than one. How were people whose smoking status changed between 2012 and 2014 handled?

The number of recent quitters in Table 1 suggest an unusually high quit rate (some 40%). There are also discrepancies in lung cancer counts between this and the previous report (a 33% reduction in cases despite 67% increase in follow-up duration).

Presenting both lung cancer incidence and lung cancer deaths seems superfluous, lung cancer deaths are already included in the incidence.

No information is provided on age at smoking initiation. If the groups differed in this, controlling for the variable would be important as this is a major risk-factor for lung cancer independent of pack-years (<https://doi.org/10.1097/00001648-199309000-00010>).

There are some incorrect claims, possibly due to language issues – the authors did not conduct the nationwide study, just used its data; it is not true that vapers had higher risk of lung cancer than continuing smokers.

Reviewer #3

(Remarks to the Author)

The study is a population-based cohort study that examined individuals with a history of conventional smoking in South Korea to determine the risk of lung cancer incidence and related mortality (LCSD) associated with substantial electronic cigarette (e-cigarette) use following smoking cessation. Using multivariate Cox proportional hazard regression analyses, the study found that ex-smokers who switched to substantial e-cigarette use after quitting conventional cigarettes showed a significantly increased risk of developing lung cancer (adjusted HR [aHR]=1.56) and LCSD (aHR=2.00) compared to ex-smokers who did not use e-cigarettes. While complete cessation without e-cigarette use significantly reduced the risk of lung cancer and LCSD compared to continuous smoking, this risk reduction benefit was diminished or not observed in both short-term and long-term smoking quitters who used e-cigarettes. Ultimately, the manuscript concludes that switching to e-cigarette use after quitting conventional smoking is associated with a higher risk of lung cancer and related mortality, indicating that the potential harmful effects of alternative e-cigarette use must be considered when implementing smoking cessation interventions.

The paper requires clarification in several parts to be fully comprehensible.

First, the abstract is not clear at all. A concept like “substantial e-cigarette use”, which later appears in the main body of the manuscript, is unclear. The explanation of the groups into which the sample is classified is also unclear and should be improved. Also, the indication of “PY” is incomprehensible. The results mentioned in the Abstract do not indicate whether there is “substantial e-cigarette use” or not. Overall, the Abstract is very unclear.

Second, in the introduction (and throughout the text), the concept of “pack-years” (PY) is not explained. What does it mean at least 20 PY? Is this intensive smoking or not? Is this cut-off based on what evidence? As I understand it, 20 PY can imply, for example, smoking 1 pack per day for 20 years or 2 packs per day for 10 years. How do you differentiate between those cases?

Third, e-cigarettes are quite diverse in their form, content, formula, potential damage, etc. You acknowledge this in the limitations. However, more information is needed on the e-cigarettes that are most commonly used in Korea. A brief description of the market could inform the readers about this.

Fourth, the size of the final sample is quite smaller than the total number of observations. I understand why some individuals are not considered (eg, not smokers), but I have doubts about how the non-inclusion of others can affect results. For instance, are people with missing smoking cessation duration, e-cigarette use- smoking PY, etc, a missing completely at random sub-sample? If they are not, you may be biasing your results by considering them like that and simply dismissing them. Please elaborate on this and, if possible, correct your estimates.

Fifth, in the definition of groups, you say that current smokers are those who smoke at least until 2018. That is misleading, as “current” may be interpreted as those who smoke until the end of the study period (2023). I would suggest changing the name of this group for clarity. Also, please be consistent. In some parts you refer to them as “current” and in others as “continuous”.

Sixth, there are results described in the text that do not appear to be in the tables. For instance, you say “... compared with continuous smokers, e-cigarette users after smoking cessation demonstrated a significantly reduced risk of all-cause mortality (aHR=0.77 ...)” Where is that? In which Table? It is not a good idea to make the reader search for the results. Please refer to the results in the tables.

Seventh, there are some analyses that rely on a tiny number of events. For instance, in Table 2 there are groups with 7 or 2 events (affecting long-term smoking quitters with substantial e-cigarette use). That is quite unacceptable in statistical terms. The same applies to Table 3 (and several other tables in the Supplement). What are the implications of these small

numbers? How can you draw any statistical conclusion from 2 events? This is very unclear. Could you please explain in greater detail these figures?

Overall, the manuscript requires significant revision, particularly in the description of variables, method, and results. In its current form, it is unclear.

Reviewer #4

(Remarks to the Author)

The manuscript presents evidence that challenges a prevailing narrative that electronic cigarettes are a safer alternative for former smokers. Collecting data from over 4.3 million individuals in South Korea with a history of conventional smoking, the authors demonstrate a statistically significant increase in lung cancer incidence and mortality among ex-smokers who transitioned to e-cigarette use, compared to those who quit entirely.

This study is particularly timely given the global rise in e-cigarette use and the ongoing debate over their role in smoking cessation. Prior research has focused on short-term cessation outcomes or toxicological profiles of e-cigarette aerosols. However, the authors provide the first large-scale epidemiological evidence linking post-cessation e-cigarette use to long-term cancer outcomes.

Summary of Key Results

- Data from over 4.3 million individuals in South Korea with a history of conventional smoking were used to demonstrate a statistically significant increase in lung cancer incidence (53,354) and mortality (6,351) among ex-smokers who transitioned to e-cigarette use, compared to those who quit entirely.
 - Ex-smokers who used e-cigarettes after quitting had significantly higher risks of lung cancer and lung cancer-specific death compared to those who quit and did not use e-cigarettes.
- For ex-smokers ≥ 5 years since quitting, e-cigarette use was associated with a 2.69-fold increase in lung cancer-specific death (aHR=2.69, 95% CI=1.12–6.46).
- For ex-smokers < 5 years since quitting, e-cigarette use increased lung cancer incidence (aHR=1.23, 95% CI=1.09–1.39) and mortality (aHR=1.71, 95% CI=1.10–2.66).
- High-risk individuals (aged 50–80, ≥ 20 pack-years) showed even stronger associations.

Originality and Significance

- The first large-scale population-based study to directly assess lung cancer risk associated with e-cigarette use after smoking cessation.
- Prior studies have focused on e-cigarette toxicity or cessation efficacy, but not long-term cancer outcomes. This study fills a critical gap in public health knowledge.

Data and Methodology: Validity of Approach, Quality of Data, Quality of Presentation

- The data were sourced from the National Health Screening Program in South Korea, covering the years 2012–2014 and 2018, with follow-up through 2021.
- The sample size of 4,329,288 individuals is huge and representative.
- The study design is a cohort study with stratification by smoking history and e-cigarette use.
- Cox proportional hazards models with adjustments were used to enhance credibility, and a stratified analysis for high-risk groups was added to highlight clinical relevance.
- The categorization of groups and outcomes is clearly stated.

Appropriate Use of Statistics and Treatment of Uncertainties

- Adjusted hazard ratios (aHR) and 95% confidence intervals are appropriately applied.
- While stratification and multivariate adjustments reduce bias, potential residual confounding (e.g., unmeasured lifestyle factors) remains a limitation.
- Additional sensitivity analyses or competing risk models could strengthen robustness.

Conclusions: Robustness, Validity, Reliability

- The conclusions are well supported by data and statistical analysis.
- The sample size and national scope of the data increase the reliability of the findings. Still, causality cannot be definitively established due to the observational design.

Suggested improvements: experiments, data for possible revision

- Mechanistic experimental studies can be considered to explore causality and biological pathways.
- Evaluating biomarkers of exposure (e.g., cotinine levels) can assess frequency and duration of e-cigarette use, and controlling for environmental exposures and socioeconomic factors can enhance the current data for further analysis.
- Was vaping intensity after quitting considered for subgroup or sensitivity analyses to test robustness?
- Were “ex-smokers” defined by the duration of time since quitting?
- Were dual users (still smoking occasionally + vaping) excluded or analyzed separately?
- Include details of frequency, duration, type of device, and nicotine strength of the e-cigarette.
- Consider adding information on the changes in the vaping status of participants during follow-up.
- Explore the possibility of using cumulative incidence curves or survival plots by exposure groups to aid data interpretation.
- Given lung cancer’s long latency, consider addressing whether the follow-up duration is adequate to capture incidence.

- Ensure that key terms (e.g., pack-years [PY], adjusted hazard ratio [aHR], LCSD) are clearly defined at first mention.
- The abstract should reflect some study limitations alongside the main findings to avoid overstating the findings.
- While the rationale for focusing on ex-smokers who vape is strong, please clarify why you exclude current smokers and dual users.
- Interpret results cautiously, emphasizing that residual risk may stem from prior smoking, not necessarily e-cigarette use.
- Discuss the limitations of short follow-up relative to lung cancer's latency.
- Address possible misclassification bias (self-reported vaping/smoking).
- Consider comparing the results with those of prior cohorts or mechanistic studies.
- Suggest areas for future research (longer follow-up, biomarker validation, never-smoker comparison groups)
- The 24,182,543.0 person-years combine both cohorts. Could you clarify somewhere in the paper that the PYs were for roughly 10-year and 5-year follow-up periods?

References: Appropriate Credit to Previous Work

- The study cites some literature on e-cigarette toxicity and lung cancer screening guidelines. However, more references to mechanistic studies on e-cigarette constituents (e.g., carbonyl compounds, metals) would strengthen the discussion. Is there a link between any specific e-cigarette constituents that may be driving the incidence and mortality? Providing information on the fluid flavors used by participants will generate valuable data for the research community.

Clarity and context: lucidity of abstract/summary, appropriateness of abstract, introduction, and conclusions

- The abstract is concise and informative.
- The introduction is contextualized within the public health debate on e-cigarettes.
- Appropriate emphasis on the need for caution in recommending e-cigarettes as cessation tools is made.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

The authors have done an excellent job addressing all of my comments, as well as those from the other reviewers. I very much enjoyed reading the manuscript for a second time and have no further comments.

Reviewer #2

(Remarks to the Author)

As per my initial review, the finding is likely an artefact of EC users quitting more recently than non-users. Some non-users quit smoking 40+ years before the 2018 baseline, EC users could have quit only since about 2007 but more likely several years later when EC use in Korea became more widespread. Following a note from another reviewer, the paper now in fact acknowledges that duration of abstinence is a significant determinant of lung cancer risk in this cohort (as in all others).

The authors' response, if I understand it correctly, includes two points. One is that EC entered Korea several years before the cohort was established, but that does not address the problem that people who quit before EC arrival would be only present in the sample of non-users and so on average, EC users must have quit more recently than non-users. (Indeed, EC users comprise 3% of short-term quitters but only 0.4% of long-term quitters).

The other point the authors make is that duration of smoking is a stronger risk factor than duration of abstinence, but this does not address the problem either. Time since quitting affects lung cancer risk independently of duration of smoking.

The authors are correct that this would be less of an issue for quitters for <5 years. In fact, a significant effect is clearly visible only in >5 year quitters. In <5 years quitters an effect was only borderline significant for cancer incidence (CI=1.00-1.71), but not significant for cancer death (CI=0.88-2.51), all-cause mortality (CI=0.92-1.28) or 'competing risk analysis' (CI=0.87-2.48).

The issue of confounding by duration of abstinence and the lack of clear effect in <5 years quitters are not presented in the Abstract or discussed. Similarly, results showing that dual use is associated with lower cancer risk than smoking alone – which does not align with the main conclusion – are omitted from the abstract and interpretation of the results.

My original review also noted that a paper using the same survey (overlapping years) reported that quitting smoking within the past 5 years was associated with an increased risk of lung cancer compared to continuing smoking. (I was wrong thinking the current authors were involved in that publication, apologies for that). The paper suggested that this could be due to smokers with prodromal symptoms trying to quit. If that was the case, a handful (see the N issue below) of worried smokers unable to quit unaided and switching to vaping would explain the borderline finding in <5 years quitters.

The present authors argue that the fact that Table 1 shows EC users to be healthier than non-users at baseline excludes this possibility. However, EC users were also much younger and they may have been less healthy if age were controlled for. The authors also argue that excluding events 1 year after baseline addresses the problem. However, prodromal symptoms can appear years before lung cancer is diagnosed; and whatever the explanation of the phenomenon may be, the increase in lung cancer risk persisted for 7 years post-cessation, peaking at about 5 years, so excluding 1-year data does not address the issue.

Some other points were answered by additional analyses, but also not acknowledged in the Discussion and conclusions. The study has a serious problem in not knowing the actual smoking status post 2018 of most participants. It is possible that quitters who needed EC to quit were more likely to relapse than those able to quit unaided. The authors looked at a subsample with updated smoking status (over an unclear time period, possibly also not up to the final census) and found that the link to lung cancer was not significant anymore. They interpret this as confirming the main result because there remained 'a trend' but this is a dubious interpretation and the point is again not acknowledged in the discussion or interpretation of the results. The results for <5 years and >5 years quitters are not shown for this analysis.

Regarding age of initiation of smoking, this is a known independent risk factor for lung cancer which can double or quadruple the risk (see <https://doi.org/10.1097/00001648-199309000-00010>). Korean smokers who use EC started to smoke earlier than other smokers ($p < 0.001$, see <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0274311>). The authors argue that the cohort is 'contemporary' and the legal age of purchasing cigarettes is 19, but the age restriction was implemented only in 1995 and the cohort includes people >80 years old. The problem has not been addressed and it remains another plausible explanation of the study findings.

There are also some additional issues that have emerged. The previous concerns about the study rigor were reinforced when it turned out that in the initial NM submission, over half of quitters for <5 years were misclassified. The finding that abstainers >5 years who vaped had a higher incidence of lung cancer death is based on 5 deaths in this group. The authors now also report changing lung cancer outcome definition from what they used in their previous report, i.e. a post-hoc modification of the primary outcome.

Alarming, I now also noted that the Korean NHIS questionnaire does not differentiate between heated tobacco products (HTP) and EC! The earlier study using the same data set that served as a model for this one (<https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.121.054967>) says: "the self-reported questionnaire on NNTP (noncombustible nicotine or tobacco product) use does not explicitly differentiate between HTPs (heated tobacco products) and NVPs (nicotine vapor products), but rather inquires on the frequency of NNTP use in general." HTP were used by 4.4% of Korean adult population in 2018 (<https://pmc.ncbi.nlm.nih.gov/articles/PMC7425751/>) and it had a much higher market share than e-cigarettes ([https://nosmk.khepi.or.kr/ntcc/eng/subIndex/547.do#:~:text=2017 E%2DCigarettes 0.6/Heated,Tobacco Products 17.1/ Cigarettes 82.4](https://nosmk.khepi.or.kr/ntcc/eng/subIndex/547.do#:~:text=2017%20Cigarettes%200.6/Heated,Tobacco%20Products%2017.1/Cigarettes%2082.4)). The study thus cannot be presented as a study of EC use.

Reviewer #4

(Remarks to the Author)
No further comments.

Version 2:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
Thank you for the opportunity to review the rebuttal letter. I have carefully considered the comments raised by Reviewers, as well as the authors' detailed responses to each point. I am fully convinced by their replies and believe that all concerns have been appropriately and satisfactorily addressed.

Reviewer #2

(Remarks to the Author)
I appreciate the authors' efforts to address the points raised, but the key issues remain.

There is no doubt that EC users quit smoking more recently than non-users (see the previous reviews for the explanation) and because time since quitting is a major predictor of lung cancer risk, this must have contributed to the findings. The issue also remains that Korean smokers who vape have been shown to initiate smoking earlier than non-vapers and earlier initiation of smoking dramatically increases lung cancer risk - after controlling for pack years (<https://doi.org/10.1097/00001648-199309000-00010>). Given several other issues, including the possibility of reverse causation, doubts remain whether the conclusions reliably reflect the data.

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Manuscript title: **Risk of Lung Cancer Associated with Electronic Cigarette Use After Smoking Cessation: A Nationwide Cohort Study**

Dear Editors:

We thank the editors and reviewers for their time reviewing our manuscript and deeply appreciate the comments which have helped us considerably in improving the quality of our manuscript. We have addressed the editor's and reviewer's comments and summarized these changes in our point-by-point responses. We hope that these modifications meet with your satisfaction.

Reviewers' Comments:

Reviewer #1 (Remarks to the Author):

Dear Editor,

Thank you for the opportunity to review the manuscript entitled "Risk of Lung Cancer Associated with Electronic Cigarette Use After Smoking Cessation: A Nationwide Cohort Study" by Kim et al. This manuscript reports a prospective cohort analysis using data from the National Health Screening Program in South Korea. Self-reported information on smoking status (including pack-years) and e-cigarette use (including days per week) was collected in 2014–2016 and 2018. Participants who self-reported as ever-smokers and had available data on pack-years, e-cigarette use, and other study variables were included in the analysis (total n = 4,524,895). At the analysis baseline (2018), participants were categorized into five groups: 1) Current smokers (individuals who continued smoking through 2018); 2) Short-term quitters with e-cigarette use (current smokers in the first period who had quit smoking before 2018 and reported e-cigarette use in 2018); 3) Short-term quitters without e-cigarette use (current smokers in the first period who had quit

smoking before 2018 and reported no e-cigarette use in 2018); 4) Long-term quitters with e-cigarette use (individuals who had maintained smoking cessation through 2018 and reported e-cigarette use in 2018); and 5) Long-term quitters without e-cigarette use (individuals who had maintained smoking cessation through 2018 and reported no e-cigarette use in 2018). Participants were followed through 2023. Using Cox regression models, the authors found that, compared with ex-smokers who did not use e-cigarettes, ex-smokers who used e-cigarettes after quitting had a significantly increased risk of lung cancer (aHR=1.56, 95% CI=1.24–1.97) and lung cancer-specific death (aHR=2.00, 95% CI=1.28–3.15). In contrast, compared with current smokers, ex-smokers without e-cigarette use had a significantly reduced risk of lung cancer (aHR=0.56, 95% CI=0.55–0.57) and lung cancer-specific death (aHR=0.42, 95% CI=0.40–0.43), with greater risk reduction observed with longer duration of smoking cessation. However, this risk reduction was not observed among ex-smokers who used e-cigarettes. The authors concluded that switching to e-cigarettes after quitting conventional smoking was associated with a higher risk of lung cancer and lung cancer-specific mortality, compared with no e-cigarette use, and diminished the benefits of smoking cessation.

I would like to congratulate the authors on performing this important and timely study. I found the manuscript to be very well written, the analyses are strong, the results are well presented, and the discussion and conclusion are supported by the findings.

Response. We thank the reviewer for their time spent reviewing our manuscript and appreciate the positive feedbacks and interest in our work.

I only have the following comments to be addressed by the authors:

1. The adjustment model described in the statistical analysis section of the Methods states that “the final multivariable models were adjusted for age, sex, body mass index (BMI), income (categorical; in quintiles), alcohol consumption, CCI, underlying COPD, and underlying IPF.” However, in the footnotes of the main tables and figures, the authors

state that the models were “adjusted for age, sex, smoking pack-years, body mass index, household income, alcohol consumption, physical activity, CCI, underlying COPD or IPF.”

In the text, smoking pack-years is not mentioned as a covariate in the adjusted model, whereas it is included in the tables and figures. Please harmonize the text, tables, and figures to accurately reflect the adjusted model. I assume the models were adjusted for pack-years, as this is an important confounder. If so, please correct the corresponding text.

Response. We thank the reviewer for these thoughtful comments and for pointing out the typographical errors we had missed. We confirm that smoking pack-years were predefined to be included as a covariate in all multivariable models. We have revised the text to correct these errors and ensure that all results are harmonized to reflect the adjusted multivariable model. For clarification, all final models were adjusted for age, sex, smoking pack-years, body mass index, income, alcohol consumption, physical activity, Charlson Comorbidity Index (CCI), underlying COPD, and underlying IPF. These points have been clarified in the revised Methods section.

Revised text in the Methods section (Page 19, Paragraph 2):

“Covariates for multivariable adjustment were pre-defined based on clinical relevance and previous literature to include known factors associated with lung cancer risk (age, sex, smoking intensity in PYs, underlying chronic obstructive pulmonary disease [COPD], and underlying idiopathic pulmonary fibrosis [IPF]). Additional demographic variables with $p < 0.2$ in univariable analyses were considered for inclusion, with exclusion of variables showing multicollinearity. Accordingly, the final multivariable models were adjusted for age, sex, smoking PYs, body mass index (BMI), income (categorical; in quintiles), alcohol consumption, physical activity, CCI, underlying COPD, and underlying IPF.”

2. In the last paragraph of the Results section, the authors mention a dose-dependent relationship between duration of smoking cessation and lung cancer risk. Please clarify

in the Methods and Results how this relationship was assessed. An appropriate statistical method, such as calculating and reporting the p-value for trend, should be used for assessing the dose-response relationship.

Response. We thank the reviewer for this insightful comment and agree that providing the appropriate statistical methods, including the p-value for trend would be relevant. To evaluate the trend across smoking cessation duration, we assigned ordinal values to the three categories (current smokers, short-term quitters, and long-term quitters) and included this variable as a continuous term in the Cox proportional hazards model. The p-value for trend was derived from the Wald test of this term and was statistically significant (<0.001). This finding was consistent with the pattern of nonoverlapping adjusted hazard ratios and 95% confidence intervals reported in Table 1. These methodological details have been added to the revised Methods section, and the corresponding trend results are explicitly described in the Results section.

Revised text in the Methods section (Page 19, Paragraph 2)

“To assess the dose-response trend across cessation-duration categories (current smokers at baseline, short-term quitters, and long-term quitters), an ordinal variable representing these categories was tested for linear trends.”

Revised text in the Results section (Page 8, Paragraph 2)

“Table 2 presents the results after further stratifying ex-smokers by duration of smoking cessation. Overall, a clear dose-response trend was observed with respect to cessation duration, with risk decreasing significantly across current smokers, short-term quitters, and long-term quitters (p for trend <0.001 for both lung cancer incidence and LCSD), regardless of e-cigarette use.”

3. The manuscript does not clarify the inclusion of dual cigarette and e-cigarette users in the current smoking group. Please indicate whether current smokers also include dual

users. If so, I suggest adding an analysis comparing lung cancer risk among dual users versus cigarette-only smokers.

Response. We thank the reviewer for these insightful comments. We confirm that dual users of conventional cigarettes and e-cigarettes were included in the current smoking group in our primary analyses. This classification aligns with our study aim, in which the primary exposure of interest was e-cigarette use specifically among former smokers after smoking cessation. Among current smokers, since conventional cigarette smoking remains the predominant driver of lung cancer risk, cigarette-only current smokers and dual users of conventional cigarettes and e-cigarettes were grouped together from an exposure-classification perspective. This clarification has been added to the revised Methods section. We fully agree that comparing lung cancer risk between dual users and cigarette-only smokers would be of interest. In response to the reviewer's valuable suggestion, we conducted an additional analysis examining this comparison. The results showed that the risk of lung cancer among dual users was lower than that of cigarette-only smokers in the overall population (presented in Page 8, Paragraph 2), and comparable among participants aged 50–80 years with a smoking history of more than 20 pack-years (presented in Page 9, Paragraph 2). These findings suggest that, among individuals who continue to smoke conventional cigarettes, dual use of e-cigarettes can be associated with reduced cigarette smoking intensity. Consequently, although e-cigarettes contain potentially carcinogenic substances, dual use may nevertheless be associated with lower overall exposure to toxicants compared with exclusive conventional cigarette smoking. However, these findings do not alter our primary results addressing the main research question regarding the association between e-cigarette use after smoking cessation and lung cancer. We have described these findings in the revised Results section.

Revised text in the Methods section (Page 18, Paragraph 1 and Page 20, Paragraph 2):

“By stratifying ex-smokers according to e-cigarette use after smoking cessation, the study population was classified into five groups at baseline (Figure S1): current smokers (including dual e-cigarette users), short-term smoking quitters with e-cigarette use after smoking cessation, short-term smoking quitters without e-cigarette use, long-term smoking quitters with e-cigarette use after smoking cessation, and long-term smoking quitters without e-cigarette use.”

“As sensitivity analyses, risks were additionally compared between cigarette-only current smokers and dual users of conventional cigarettes and e-cigarettes at baseline, by treating dual users as a separate exposure group.”

Revised text in the Results section (Page 8, Paragraph 2 and Page 9, Paragraph 2):

“Analysis of dual users as a separate exposure group revealed that these individuals had lower risks of lung cancer ($aHR=0.78$, 95% $CI=0.72-0.85$), LCSD ($aHR=0.66$, 95% $CI=0.55-0.79$), and all-cause mortality ($aHR=0.74$, 95% $CI = 0.71-0.78$) than current smokers at baseline who used only conventional cigarettes (Table S2)”

“When dual users were analyzed as a separate exposure group, no significant difference in lung cancer risk was observed compared with cigarette-only smokers ($aHR=0.94$, 95% $CI=0.83-1.07$); however, dual users exhibited a significantly lower risk of all-cause mortality ($aHR=0.72$, 95% $CI=0.72-0.80$, Table S5).”

4. How did the authors account for smoking relapse in their analysis? Specifically, how were participants treated who reported being ex-smokers in the first survey but then reported current smoking in the second survey?

Response. We thank the reviewer for this question and the opportunity to clarify our classification of smoking history. Because the baseline (time of cohort entry) was defined as the date of the 2018 health examination, smoking status (current or former) for all participants was determined based on the information reported at that time. Accordingly, individuals who reported being ex-smokers in the 2012–2014 survey and reported current smoking in 2018 were classified as current smokers at baseline. This approach is consistent with major epidemiologic and lung cancer risk prediction studies, in which baseline smoking status (current or former) and cumulative exposure (e.g., pack-years) are the principal determinants of future lung cancer risk.¹⁻³ Since cumulative smoking exposure was comprehensively captured in the 2018 survey,

which served as the baseline for cohort entry, we believe that classifying smoking relapse cases as current smokers aligns with established cohort methodology and provides a clear and interpretable framework for risk estimation. We have clarified this classification in the revised Methods section.

Revised text in the Methods section (Page 16, Paragraph 2):

“This study initially included 11,550,680 individuals who participated in the national health screening program in 2018 (baseline time of cohort entry), with prior screening records available from 2012-2014. This structure enabled assessment of smoking behaviors across the two time points and classification of participants according to their baseline cigarette smoking status into: current smokers (individuals who reported current cigarette smoking in 2018 regardless of past status, including continuous smokers or those who relapsed after reporting former smoking in 2012-2014), short-term smoking quitters (individuals who reported current smoking in 2012-2014 and former smoking in 2018), and long-term smoking quitters (individuals who reported former smoking at both time points).”

References

1. National Lung Screening Trial Research Team, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* **365**, 395–409 (2011).
2. Tammemagi, MC, *et al.* Selection criteria for lung-cancer screening. *N Engl J Med* **368**, 728–736 (2013)
3. Bach PB, et al. Variations in lung cancer risk among smokers. *J Natl Cancer Inst* **95**, 470–478. (2003)

5. While the overall sample size is very large, the number of events in the groups of quitters with e-cigarette use is limited. For some analyses, such as lung cancer-specific death, the number of events was only 17 and 2 for short-term and long-term quitters with

e-cigarette use, respectively. Although the authors have done the best they could with the available data, this limitation should be mentioned in the final paragraph of the Discussion, along with other study limitations. The impact and implications of the limited number of events in the e-cigarette–exposed groups should also be discussed, and the need for future studies with larger exposed sample sizes should be emphasized.

Response. We thank the reviewer for this excellent suggestion, and agree that the small number of lung cancer specific-death events among e-cigarette users after smoking cessation limits the statistical power to draw definitive conclusions in certain subgroup analyses. As suggested, we have explicitly acknowledged this limitation in the final paragraph of the revised Discussion section, highlighting that findings in subgroups with small event numbers should be interpreted with caution. We have additionally emphasized the need for future studies with larger numbers of e-cigarette-exposed former smokers and longer follow-up durations to validate and expand these early observations.

Revised text in the Discussion section (Page 15, Paragraph 1)

“In addition, some subgroup analyses were based on a small number of events among e-cigarette users after smoking cessation, which limited statistical power and warrants cautious interpretation. Future longitudinal studies with larger numbers of exposed former smokers and extended follow-up are needed to validate and expand these findings.”

6. I recommend that, when referring to the association between e-cigarette use and lung cancer, the authors use the term incidence rather than development. For example, “... increased risk of lung cancer incidence” rather than “...increased risk of lung cancer development.”

Response. We thank the reviewer for this insightful comment and the suggestion to use more accurate terminology regarding the nature of our study. As recommended, we have revised the terminology throughout the manuscript to refer to lung cancer “*incidence*” rather than “*development*” when describing risk estimates.

Reviewer #2 (Remarks to the Author):

The manuscript closely resembles a previous publication by this team https://www.atsjournals.org/doi/10.1164/ajrccm-conference.2024.209.1_MeetingAbstracts.A3051 widely cited as showing that vaping causes lung cancer.

In a large data set from South Korea, people who were smokers or ex-smokers in 2012, 2014 and 2018 were followed up, to 2021 in the previous report and to 2023 in this one. In 2018, a question about use of e-cigarettes (EC) was included and people who said they were vaping nearly every day in the month of the survey were classified as having substantial EC use (vapers). Vapers had a risk of lung cancer that was non-significantly lower than that of current smokers (HR 0.89; 0.70 – 1.14), and greater than that of ex-smokers who did not vape (HR 1.56; 1.24 – 1.97).

The authors interpret these findings as suggesting that vaping causes lung cancer, an interpretation that seems somewhat tendentious. The cancers that were observed were likely the result of decades of smoking and the finding, if genuine, would more likely suggest that vaping was reducing the benefits of stopping smoking. There is a high probability though that the results are an artefact of several methodological issues.

Response. We thank the reviewer for reviewing our manuscript and for the constructive comments. We agree that drawing a conclusion that e-cigarette use causes lung cancer would go beyond the scope of what our observational study can establish. We also would like to clarify that such causality was not our intended interpretation, and we have further ensured that causal language is avoided throughout the revised manuscript. As the reviewer correctly noted, our findings are more appropriately interpreted as suggesting that, in terms of lung cancer incidence and mortality, e-cigarette use may attenuate the benefits of smoking cessation. At the same time, because cigarette smoking remains the predominant risk factor for lung cancer and the primary determinant for defining high-risk populations in screening programs, we believe that our observation of reduced benefit among e-cigarette users after quitting has important public health implications. Considering that e-cigarettes are increasingly promoted as a less harmful option than traditional smoking, these findings may hold meaningful implications for lung

cancer prevention and screening strategies. In response to the reviewer's feedback, we have revised the manuscript to avoid causal language, enhance methodological rigor and transparency, and refine the interpretation of our findings throughout. We believe that these revisions have improved the scientific clarity and strengthened the methodological foundation of our study, and we hope the manuscript will merit further consideration.

Revised text in the Discussion (Page 15, Paragraph 2)

“In conclusion, substantial e-cigarette use after conventional smoking cessation was associated with a higher risk of lung cancer and related mortality compared with complete smoking cessation without e-cigarette use, with attenuated risk reduction when with current smokers at baseline”

Here is the main one. The by far the most important determinant of the reduction in cancer risk after stopping smoking is the duration of abstinence. As vaping is a relatively new development, duration of abstinence can be expected to differ substantially between vapers and non-vapers. The control for this was inadequate. Ex-smokers were divided into groups abstinent for <5 years and >5 years. It is a certainty that among >5 years quitters, vapers had quit much more recently; but this would be the case among <5-year-quitters too, as the popularity of vaping was increasing during that time. The results may be just showing that risk reduction is proportional to duration of abstinence and have nothing to do with vaping.

Response. We sincerely appreciate the reviewer's comment and valuable insights. We understand the concern that if e-cigarette was introduced more recently, the use might act as a surrogate for more recent cessation of conventional cigarette smoking, which could confound the observed associations. However, we would like to respectfully ask for reconsideration of the timing of e-cigarette introduction in the context of our cohort design, and clarify that both our study design and analytic approach were structured to minimize this potential bias. In addition, we believe that our findings further support the validity of our approach.

First, although e-cigarettes are a relatively new development compared with conventional

cigarettes, legal approval and widespread introduction of e-cigarettes in Korea began in 2007–2008,¹ which was approximately ten years before the baseline of our study cohort (2018) and five years prior to the first smoking-status assessment period (2012–2014). Therefore, we respectfully note that the assumption that e-cigarette users would necessarily have shorter durations of smoking cessation would not apply to our study setting, given that our cohort was established well after e-cigarette products had been introduced and widely available. To clarify this point and in accordance with suggestions from other reviewers, we have added details regarding the timing of introduction, types, and devices of e-cigarettes available in Korea in the Discussion section.

Second, we would like to respectfully clarify that the assumption that e-cigarette users among long-term smoking quitters must have quit much more recently is not necessarily supported. By definition, individuals in this group are confirmed to be abstinent from smoking for many years, and multiple epidemiologic studies, including the Framingham Heart Study,² have demonstrated that this duration of cessation is associated with a substantially reduced risk of lung cancer. In addition, previous evidence indicates that among former smokers, smoking intensity (measured in pack-years) is a stronger predictor of lung cancer risk than duration of abstinence. Accordingly, the most recent American Cancer Society (ACS) 2023 and National Comprehensive Cancer Network (NCCN) guidelines no longer include duration of cessation in determining the high-risk group eligible for lung cancer screening.^{3,4} Regarding short-term quitters, we also find the reviewer's concern less applicable, since in this group, quitting duration contributes minimally to future lung cancer risk compared with cumulative smoking exposure (pack-years), which remains the dominant determinant.

Importantly, our findings also indicate that the risk of all-cause mortality was consistently lower among individuals who used e-cigarettes after smoking cessation than among continuous smokers, suggesting that e-cigarettes use after smoking cessation is not devoid of health benefits. Taken together, our results imply that while e-cigarette use after quitting smoking may attenuate benefits of cessation specific to lung cancer, it does not eliminate the broader health advantages of quitting conventional cigarettes. We have also clarified this interpretation in the revised Discussion section.

Revised text in the Discussion section (Page 11, Paragraph 2 and Page 14, Paragraph 1)

“In South Korea, e-cigarettes were introduced in 2008 and rapidly expanded in use.²⁸ The current market includes refillable tank-type devices, pod-based systems, and disposable e-cigarettes, with commercially available e-liquids containing nicotine concentrations up to approximately 20mg/ml. Aside from a minimum legal purchase age of 19 years, regulatory restrictions are limited, resulting in high accessibility and widespread availability”

“However, it is noteworthy that the risk of all-cause mortality remained significantly lower among ex-smokers who used e-cigarettes after smoking cessation compared with continuous smokers. Additionally, among high-risk individuals aged 50–80 years with ≥ 20 PYs, all-cause mortality did not differ significantly between those with and without e-cigarette use after cessation. Taken together, our results suggest that while e-cigarette use after quitting smoking may attenuate the lung cancer-specific benefits of cessation, the broader health benefits of quitting conventional cigarettes are not eliminated.”

References

1. Lee K-H, Cho H-J, et al. *Public Health Challenges of Electronic Cigarettes in South Korea*. J Prev Med Public Health. **44**, 235–242 (2011).
2. Tindle, H.A., et al. Lifetime Smoking History and Risk of Lung Cancer: Results From the Framingham Heart Study. *J Natl Cancer Inst* **110**, 1201–1207 (2018).
3. Wolf, A.M.D., et al. Screening for lung cancer: 2023 guideline update from the American Cancer Society. *CA Cancer J Clin* **74**, 50–81 (2024).
4. National Comprehensive Cancer Network. NCCN Guidelines Version 1.2026 Lung Cancer Screening (2025)

Apart from this key problem, there are several other issues.

The current findings could be in part due to reverse causality. Smokers with prodromal symptoms of lung cancer could have been more motivated to switch to vaping. A previous

publication by some of the current authors using the same data set (<https://doi.org/10.1001/jamanetworkopen.2023.54958>) found that recent quitters had not just no reduction, but in fact an increase in risk of lung cancer compared to continuing smokers. They interpreted the finding as due to smokers with incipient cancer being more likely to stop smoking. This is not mentioned in the current manuscript where it would be highly relevant given that vapers were bound to be more recent quitters than non-vapers.

Response. We thank the reviewer for this comment and the opportunity to clarify our approach to addressing potential reverse causality. First, we would like to respectfully note that none of the authors of the present study were involved in the aforementioned publication. The NHIS database serves as a national administrative registry from which many independent cohorts can be constructed. Accordingly, the study question, cohort design, exposure definitions, and sample structure in our study are fully distinct from those in the referenced publication.

Regarding the concern about potential reverse causality, we believe that this mechanism is unlikely to be logically applicable in the context of our study and does not adequately explain our findings. If individuals experienced prodromal symptoms of lung cancer, it is more plausible that they would be motivated to completely cease smoking rather than switch to e-cigarettes, given that e-cigarette use is also associated with respiratory symptoms and airway inflammation as shown in previous studies.^{1,2} In fact, our baseline characteristics (Table 1) showed that e-cigarette users had lower comorbidity burden and a lower prevalence of COPD compared with complete quitters, suggesting that symptomatic individuals were less likely to use e-cigarettes after smoking cessation. Furthermore, if reverse causation were a possible explanation, one would expect that individuals who used e-cigarettes because of prodromal symptoms would have a higher risk of lung cancer compared with continuous smokers. However, our results did not demonstrate an increased risk in e-cigarette users relative to continuous smokers, but rather a higher risk compared with complete quitters, which contradicts the expected direction of a reverse causation bias. Nonetheless, to address any remaining concerns, we additionally conducted sensitivity analyses excluding incident lung cancer cases diagnosed within the first year of follow-up. The results remained materially unchanged, supporting the robustness of our conclusions. We have incorporated these details into the revised Methods and Results sections.

Revised text in the Methods section (Page 20, Paragraph 2)

“To address potential reverse causation, sensitivity analyses excluding cases that occurred within the first year of follow-up were conducted.”

Revised text in the Results section (Page 10, Paragraph 1)

“In sensitivity analyses excluding events that occurred during the first year of follow-up from baseline (Tables S6–S9), the associations between e-cigarette use after smoking cessation and the risks of lung cancer incidence and LCSD remained materially unchanged.”

References

1. Gotts, J.E., Jordt, S.E., McConnell, R. & Tarran, R. What are the respiratory effects of e-cigarettes? *BMJ* **366**, 15275 (2019).
2. Alqahtani et al. E-cigarette use and respiratory symptoms in adults: A systematic review and meta-analysis. *Tob Induc Dis* **21**, 168 (2023)

The data set used in this manuscript contains a very large number of variables and it is not clear how were those that were being controlled for selected. In unadjusted data, vapers had much lower incidence of cancer than non-vapers. This would be due to age differences and controlling for age was necessary. Apart from this, vapers and non-vapers probably differed in dozens of variables. Controlling for different covariates can lead to different and even opposite results. Some suspicions are raised by the fact that the manuscript copies closely a paper by a different team using the same data set to look at effects of vaping on CVD (<https://doi.org/10.1161/CIRCULATIONAHA.121.054967>) but it includes different covariates (and does not use propensity matching).

Response. We thank the reviewer for this comment and the opportunity to clarify our approach to covariate adjustment. In our study, covariates were pre-defined based on clinical relevance and previous literature, focusing on factors known to be associated with lung cancer risk (age,

sex, smoking intensity in pack-years, underlying COPD, and underlying IPF). In addition, demographic variables that demonstrated potential associations in univariable analyses were considered to be included in the final model, with pre-specified exclusion of variables showing multicollinearity. Regarding the aforementioned article, we respectfully note that the appropriate confounders should differ depending on the outcome of interest. As our study focused on lung cancer risk, we clarify that the variables included in the adjusted models were not selected arbitrarily but were identified based on theoretical rationale, clinical relevance, and prior epidemiologic evidence. Regarding propensity matching, we would like to note that our primary analyses involved at least 3 (up to 5) exposure groups within a single cohort. Implementing pairwise propensity score matching would require different matched samples for each contrast, resulting in substantial loss of participants and non-comparable target populations across comparisons. Moreover, limited covariate overlap for some exposure categories would necessitate extensive trimming or weighting, which could introduce selection bias and reduce precision.

To address the concerns on inclusion of covariates and validate the consistency of our results, we have performed additional analyses adjusting for the most basic and critical known factors to define future lung cancer risk integrated to lung cancer screening guidelines (age, sex, and smoking PYs) and checked whether the results differs between models adjusted for the three essential variables (Model 1) and the models with additional adjustments per pre-defined study design (Model 2). The results showed that when age, sex, and smoking PYs were adjusted for, the associations on both lung cancer incidence and mortality remained stable and consistent, regardless of the inclusion of other covariates. This indicates that our main findings are not sensitive to model specification and remain robust across different levels of adjustment. We have clarified this rationale and supporting results in the revised Methods and Results sections.

Revised text in the Methods section (Page 19, Paragraph 2)

“Covariates for multivariable adjustment were pre-defined based on clinical relevance and previous literature to include known factors associated with lung cancer risk (age, sex, smoking intensity in PYs, underlying chronic obstructive pulmonary disease [COPD], and underlying idiopathic pulmonary fibrosis [IPF]).⁹ Additional demographic variables with $p < 0.2$ in univariable analyses were considered for inclusion, with exclusion of variables showing

multicollinearity. Accordingly, the final multivariable models were adjusted for age, sex, smoking PYs, body mass index (BMI), income (categorical; in quintiles), alcohol consumption, physical activity, CCI, underlying COPD, and underlying IPF. To assess robustness, we compared estimates from a minimally adjusted model including fundamental determinants (age, sex, smoking PYs; Model 1) with the fully adjusted model (Model 2)."

Revised text in the Results section (Page 8, Paragraph 2)

"Overall, Analyses using minimal adjustment (Model 1) and full adjustment (Model 2) produced similar results, indicating that when age, sex, and smoking PYs were adjusted for, the associations on both lung cancer incidence and LCSD remained consistent, regardless of the inclusion of other covariates (Table S1 and S2)."

Regarding the questions of how short-term vaping could cause lung cancer, the uncertain duration of vaping adds to the problem. Vapers vaped regularly over one month in 2018, but there are no data on how long they were vaping for or whether they continued to vape or returned to smoking after 2018. It is possible that smokers who managed to quit unaided were more likely to maintain their abstinence than those who needed vapes.

Response. We appreciate this insightful comment. As acknowledged in the Discussion, the total amount or intensity of vaping could not be quantified because validated tools or standardized metrics for measuring cumulative e-cigarette exposure are not available in national health databases. Nevertheless, within the constraints of currently feasible measurement, we defined the main exposure (e-cigarette use after smoking cessation) based on "daily use during the prior month", which reflects a population with relatively high and sustained vaping exposure. To test the robustness of this exposure definition, we additionally conducted analyses using an alternative classification of "any e-cigarette use", and observed consistent results, suggesting that the association is not driven solely by exposure categorization.

We appreciate the reviewer's point that vaping and smoking status may change after the 2018 baseline. Ideally, a time-varying analysis for the full study population would be the most appropriate approach to address this concern. However, post-baseline exposure information

was available only for a subset of participants who underwent additional health examinations, and for others, outcome events could occur before any subsequent screening. This raises concerns regarding potential selection bias and immortal-time bias. To address the reviewer's concern while minimizing bias, we conducted an additional sensitivity analysis in a subpopulation of individuals who underwent additional health screening during 2019–2020 with updated information on cigarette smoking and e-cigarette use. Specifically, we applied a time-varying Cox proportional hazards model, treating smoking status and e-cigarette use status as time-dependent covariates updated at the subsequent health screening. In the time-varying exposure analysis, precision was reduced and confidence intervals widened, likely reflecting the reduced sample size and number of events. Nevertheless, the direction and trend toward a higher risk of lung cancer incidence among individuals who used e-cigarettes after smoking cessation remained consistent with our main analysis, thereby further supporting our primary findings. We have added these details to the Methods and Results section.

Revised text in the Methods section (Page 20, Paragraph 2)

“To account for changes in smoking status and e-cigarette use after baseline, an additional sensitivity analysis was conducted in a subpopulation of participants who underwent additional health screening during 2019–2020 with updated information on smoking and e-cigarette use. Using this exploratory subpopulation (n=3,465,275), time-varying Cox proportional hazards models were fitted, treating smoking status and e-cigarette use status as time-dependent covariates updated at the date of follow-up health screening. Multivariable models were fitted to estimate aHRs using the same covariate adjustment strategy as in the primary analysis.”

Revised text in the Results section (Page 10, Paragraph 1)

“In time-varying exposure analyses restricted to participants with updated smoking and e-cigarette use information, precision was reduced and confidence intervals widened, likely reflecting the reduced sample size and number of events. Nevertheless, the direction and trend toward a higher risk of lung cancer incidence among individuals who used e-cigarettes after smoking cessation were consistent (aHR=1.38, 95% CI=0.98–1.98, Tables S10–S11). Results

from analyses defining the exposure of interest as any e-cigarette use are presented in Tables S12–S19 and show similar directional trends, including in the time-varying analyses (Tables S20–S21).”

Regarding some other more minor issues,

Data are missing on dual users (people who both smoke and vape). These results would be of obvious interest. It is in fact not clear whether dual users were included among current smokers or excluded.

Response. We thank the reviewer for this invaluable comment. We confirm that dual users of conventional cigarettes and e-cigarettes were included in the current smoking group, as our primary exposure of interest was e-cigarette use among former smokers. We have clarified this in the revised Methods section. We also agree that an additional analysis comparing dual users with cigarette-only smokers would be of great interest and therefore conducted an additional analysis to explore this comparison. The results showed that the risk of lung cancer among dual users was lower than that of cigarette-only smokers in the overall population (presented in Page 8, Paragraph 2), and comparable among participants aged 50–80 years with a smoking history of more than 20 pack-years (presented in Page 9, Paragraph 2). This finding suggests that, among continuous cigarette smokers, dual use of e-cigarettes can be associated with reduced conventional cigarette smoking intensity. Consequently, although e-cigarettes contain potentially carcinogenic substances, dual use may nevertheless be associated with lower overall exposure to toxicants compared with exclusive conventional cigarette smoking. However, these findings do not alter our primary results addressing the main research question regarding the association between e-cigarette use after smoking cessation and lung cancer. We have described these findings in the revised Results section.

Revised text in the Methods section (Page 18, Paragraph 1 and Page 20, Paragraph 2):

“By stratifying ex-smokers according to e-cigarette use after smoking cessation, the study population was classified into five groups at baseline (Figure S1): current smokers (including dual e-cigarette users), short-term smoking quitters with e-cigarette use after smoking

cessation, short-term smoking quitters without e-cigarette use, long-term smoking quitters with e-cigarette use after smoking cessation, and long-term smoking quitters without e-cigarette use.”

“As sensitivity analyses, risks were additionally compared between cigarette-only current smokers and dual users of conventional cigarettes and e-cigarettes at baseline, by treating dual users as a separate exposure group.”

Revised text in the Results section (Page 8, Paragraph 2 and Page 9, Paragraph 2):

Analysis of dual users as a separate exposure group revealed that these individuals had lower risks of lung cancer (aHR=0.78, 95% CI=0.72–0.85), LCSD (aHR=0.66, 95% CI=0.55–0.79), and all-cause mortality (aHR=0.74, 95% CI = 0.71–0.78) than current smokers at baseline who used only conventional cigarettes (Table S2)

“When dual users were analyzed as a separate exposure group, no significant difference in lung cancer risk was observed compared with cigarette-only smokers (aHR=0.94, 95% CI=0.83–1.07); however, dual users exhibited a significantly lower risk of all-cause mortality (aHR=0.72, 95% CI=0.72–0.80, Table S5).”

An explanation is needed for why 2012, 2014 and 2018 surveys were used but not 2016. It is also not clear how were the 2012 and 2014 data combined; and why are there two baseline surveys rather than one. How were people whose smoking status changed between 2012 and 2014 handled?

Response. We thank the reviewer for this valuable comment and the opportunity to clarify the rationale of our study design and the collection of baseline characteristics. We designed the study to assess smoking status and history at baseline (2018) and to validate and stratify the duration of smoking cessation using data from the previous health examination period (2012–

2014), which occurred approximately five years before the baseline survey. The 2012–2014 period was selected because approximately five years of smoking cessation is generally required to observe a meaningful reduction in lung cancer risk. Health screening data from 2012 to 2014 were treated as a single “past period” since the national health screening program is biennial and participants undergo examinations at different years within the same cycle. Individuals whose smoking status changed during 2012–2014 were assigned the smoking status reported at their most recent examination within that period. Accordingly, individuals who were ex-smokers during the 2012–2014 period and remained ex-smokers in 2018 were classified as long-term quitters, whereas those who reported current smoking in 2012–2014 but were ex-smokers in 2018 were classified as short-term quitters. This approach allowed us to validate smoking cessation status and to stratify participants by cessation duration with sufficient temporal separation. We have added a detailed description of the smoking history stratification method and how multiple examinations were handled in the revised Methods section.

Revised text in the Methods section (Page 16, Paragraph 2):

This study initially included 11,550,680 individuals who participated in the national health screening program in 2018 (baseline time of cohort entry), with prior screening records available from 2012–2014. This structure enabled assessment of smoking behaviors across the two time points and classification of participants according to their baseline cigarette smoking status into: current smokers (individuals who reported current cigarette smoking in 2018 regardless of past status, including continuous smokers or those who relapsed after reporting former smoking in 2012–2014), short-term smoking quitters (individuals who reported current smoking in 2012–2014 and former smoking in 2018), and long-term smoking quitters (individuals who reported former smoking at both time points). This stratification was based on evidence that lung cancer risk decreases substantially within approximately five years after smoking cessation.^{42,54} Individuals whose smoking status changed during 2012–2014 were assigned the smoking status (current or former smoking) reported at their most recent examination within that period.

The number of recent quitters in Table 1 suggest an unusually high quit rate (some 40%). There are also discrepancies in lung cancer counts between this and the previous report (a 33% reduction in cases despite 67% increase in follow-up duration).

Response. We thank the reviewer for this comment and for drawing our attention to the distribution of the smoking cessation subgroups. Upon re-evaluation of our baseline classification, we identified a misclassification whereby a proportion of long-term quitters (with or without e-cigarette use) had been incorrectly categorized as short-term quitters. We have corrected this error and repeated all analyses appropriately stratified by duration of smoking cessation. After correction, the proportion of recent quitters in Table 1 is 17.4%, resolving the concern regarding the unusually high quit rate. The corrected classification also affected the accumulation of lung cancer cases across subgroups. All results presented in the revised manuscript reflect the corrected classification and re-analyses, yielding more accurate and precise estimates of the associations between e-cigarette use after smoking cessation and lung cancer outcomes, particularly among long-term quitters.

We also appreciate the reviewer's reference to our previous abstract presented at the American Thoracic Society International Conference. Since the presentation of those preliminary findings, we have substantially strengthened the study in two key aspects. First, we obtained longer follow-up data through updated linkage with the National Health Insurance system. Second, we adopted a stricter definition of lung cancer diagnosis, which in the preliminary analysis was based solely on ICD-10 codes. In the updated analysis, lung cancer diagnosis was identified using registered diagnosis codes (ICD-10, C33 and C34) in combination with a specific Support for Serious Illness (SSI) program code for lung cancer (V193 or V194), thereby improving the validity of cancer case ascertainment. This definition has been clarified in the Methods section.

Revised text in the Methods section (Page 18, Paragraph 1):

"The primary outcomes were lung cancer incidence and LCSD. Lung cancer incidence was identified using the registered lung cancer diagnosis codes (ICD-10; C33 and C34), with a specific insurance code (Support for Serious Illness Program code) for lung cancer (V193 or V194). In South Korea, once a patient receives the V193 or V194 code, they are registered in the National Cancer Registry with a specific code indicating that the patient would receive

special insurance benefits owing to cancer diagnosis. Once a patient receives a V-code, it is documented in their medical records and used in subsequent claims. Therefore, lung cancer diagnosis based on claims are considered highly reliable.”

Presenting both lung cancer incidence and lung cancer deaths seems superfluous, lung cancer deaths are already included in the incidence.

Response. We thank the reviewer for this comment. We understand the point that presenting both lung cancer incidence and lung cancer-specific deaths may appear overlapping, as the latter is inherently derived from incident lung cancer cases. However, we believe that reporting lung cancer-specific mortality provides additional value, as it represents a major health outcome of interest in the context of lung cancer management and screening at a population level and allows meaningful comparison with all-cause mortality. Furthermore, the additional competing risk analysis offers complementary insights beyond incidence data, providing a distinct clinical perspective on cause-specific mortality patterns. Nevertheless, we fully respect the reviewer’s and editors’ preferences; if the inclusion of lung cancer-specific death results is considered redundant, we are happy to remove these findings or move them to the Supplementary Materials as appropriate.

No information is provided on age at smoking initiation. If the groups differed in this, controlling for the variable would be important as this is a major risk-factor for lung cancer independent of pack-years (<https://doi.org/10.1097/00001648-199309000-00010>).

Response. We thank the reviewer for this valuable comment and for highlighting the potential importance of age at smoking initiation. Unfortunately, direct self-reported information on age at smoking initiation was not available in our cohort. We carefully reviewed the referenced study, which reported an elevated risk of lung cancer among men who initiated smoking before the age of 19, based on cohorts with a mean initiation age of approximately 16.5–17.7 years. These findings support the concept that early exposure to tobacco during critical developmental periods may increase susceptibility to tobacco-related carcinogenesis. In contrast, our cohort represents a more contemporary adult population in South Korea, where the minimum legal

age for purchasing cigarettes is strictly regulated at 19 years. Given this regulatory context and the demographic differences between the study populations, additional adjustment for age at smoking initiation would be less likely to materially affect our findings. Nevertheless, because age at smoking initiation was not directly measured, residual confounding cannot be completely excluded. We have therefore acknowledged this limitation in the revised Discussion section.

Revised text in the Discussion section (Page 14, Paragraph 2):

“Second, while all analyses were comprehensively adjusted for available important covariates, residual confounding from unmeasured exposures (e.g., age at smoking initiation, emerging inhaled toxicants, environmental exposures, and socioeconomic influences) may persist and remains an inherent limitation.”

There are some incorrect claims, possibly due to language issues – the authors did not conduct the nationwide study, just used its data; it is not true that vapers had higher risk of lung cancer than continuing smokers.

Response. We thank the reviewer for this helpful comment and pointing out the language issues. To address this, we have revised the sentence in the Introduction to more accurately reflect our study design and analytical scope.

Revised text in the Introduction section (Page 6, Paragraph 2):

“Therefore, we performed an analysis of a nationwide, population-based cohort to examine the association between e-cigarette use after smoking cessation and subsequent lung cancer risk and related mortality.”

For the second comment, we have carefully reviewed both the original and revised versions of

our manuscript and confirmed that there are no data or statements indicating that e-cigarette users have a higher risk of lung cancer than continuing smokers. Rather, our findings consistently show that e-cigarette use after smoking cessation is associated with a higher risk of lung cancer compared with complete quitters, suggesting that the risk-reduction benefits of smoking cessation may be attenuated among individuals who use e-cigarettes after quitting.

Reviewer #3 (Remarks to the Author):

The study is a population-based cohort study that examined individuals with a history of conventional smoking in South Korea to determine the risk of lung cancer incidence and related mortality (LCSD) associated with substantial electronic cigarette (e-cigarette) use following smoking cessation. Using multivariate Cox proportional hazard regression analyses, the study found that ex-smokers who switched to substantial e-cigarette use after quitting conventional cigarettes showed a significantly increased risk of developing lung cancer (adjusted HR [aHR]=1.56) and LCSD (aHR=2.00) compared to ex-smokers who did not use e-cigarettes. While complete cessation without e-cigarette use significantly reduced the risk of lung cancer and LCSD compared to continuous smoking, this risk reduction benefit was diminished or not observed in both short-term and long-term smoking quitters who used e-cigarettes. Ultimately, the manuscript concludes that switching to e-cigarette use after quitting conventional smoking is associated with a higher risk of lung cancer and related mortality, indicating that the potential harmful effects of alternative e-cigarette use must be considered when implementing smoking cessation interventions.

The paper requires clarification in several parts to be fully comprehensible.

Response. We thank the reviewer for the time and effort dedicated to evaluating our manuscript. We appreciate the thoughtful comments and constructive feedback, which have strengthened the clarity and rigor of our study. We have carefully revised the manuscript to address all points raised and hope that the changes meet with your satisfaction.

First, the abstract is not clear at all. A concept like “substantial e-cigarette use”, which later appears in the main body of the manuscript, is unclear. The explanation of the groups into which the sample is classified is also unclear and should be improved. Also, the indication of “PY” is incomprehensible. The results mentioned in the Abstract do not indicate whether there is “substantial e-cigarette use” or not. Overall, the Abstract is very unclear.

Response. We thank the reviewer for this valuable comment and the opportunity to improve

the clarity of our Abstract. We have thoroughly revised the Abstract to (1) clearly define the exposure of interest (daily e-cigarette use at baseline), (2) more explicitly describe how the study population was classified according to smoking history and exposure status after smoking cessation, and (3) clarify the meaning of “PY” (pack-years). To enhance transparency and avoid wordiness, we have removed the term “substantial” and unified the terminology describing the exposure group as “e-cigarette users” throughout the manuscript, after clearly defining this term in the Methods section of the Abstract. We have also shortened the Abstract to focus on the key findings and ensure alignment with the journal’s word limit. We believe these revisions have improved the overall clarity and readability. In addition, we included supplementary analyses based on an alternative definition of e-cigarette use (any e-cigarette use at baseline) and the corresponding classification in the Supplementary Materials.

Revised Methods in the Abstract (Page 3, Paragraph 1):

“We evaluated 4,524,895 adults with a conventional smoking history who participated in the National Health Screening Program in South Korea in 2018 (baseline), with prior records from 2012–2014. Participants were classified as current smokers at baseline, short-term quitters (smoked in 2012–2014 but quit before 2018), or long-term quitters (ex-smokers at both time points), and followed up until December 2023. Smoking intensity was quantified in pack-years (PYs). Daily e-cigarette use at baseline was defined as the exposure of interest and was used to classify participants as e-cigarette users after smoking cessation. Risks of lung cancer incidence and lung cancer-specific death (LCSD) were assessed using multivariable Cox models. Stratified analysis was performed for high-risk individuals aged 50–80 years with ≥ 20 PYs smoking history.”

Second, in the introduction (and throughout the text), the concept of “pack-years” (PY) is not explained. What does it mean at least 20 PY? Is this intensive smoking or not? Is this cut-off based on what evidence? As I understand it, 20 PY can imply, for example, smoking 1 pack per day for 20 years or 2 packs per day for 10 years. How do you differentiate between those cases?

Response. We thank the reviewer for this valuable comment and the opportunity to clarify how smoking exposure intensity was measured in this study. We agree that a clear explanation of the pack-years (PYs) metric and the rationale for applying a ≥ 20 PY cutoff is necessary. Smoking pack-years are calculated as the average number of cigarette packs smoked per day multiplied by the total number of years of smoking (e.g., 1 pack/day for 20 years or 2 packs/day for 10 years = 20 PY), which represents the most widely validated and commonly used measure to quantify cumulative lifetime smoking exposure and estimate lung cancer risk in clinical research. Accordingly, individuals with the same cumulative exposure (20 PY) were treated equivalently in the analyses. We used ≥ 20 PY as the cutoff to define high-risk smokers in accordance with eligibility criteria established by the American Cancer Society (ACS) and the US preventive Services Task Force (USPSTF), which recommend annual low-dose computed tomography (LDCT) screening for high-risk individuals aged 50–80 years with a smoking history of at least 20 PYs. This threshold is supported by epidemiologic evidence demonstrating a markedly increased lung cancer risk above this cumulative exposure level. These clarifications regarding the PY definition and the rationale for this cutoff have been added to the revised Introduction and Methods sections.

Revised text in the Introduction (Page 5, Paragraph 1):

“The risk of lung cancer increases with cumulative exposure to cigarette smoking, with a higher risk in current smokers than in ex-smokers.⁴ Cumulative exposure is typically quantified in pack-years (PYs; calculated as packs smoked per day multiplied by the total years of smoking) and is widely used to identify high-risk individuals that can benefit from low-dose computed tomography (LDCT)-based lung cancer screening (LCS) to reduce lung cancer-related mortality.⁵⁻⁷ Currently, based on epidemiologic evidence demonstrating a markedly increased risk above this threshold, the 2021 US Preventive Services Task Force (USPSTF) and the 2023 American Cancer Society (ACS) guidelines recommend LCS for individuals aged 50–80 years with a smoking history ≥ 20 PYs with or without consideration of years since quitting smoking (YSQ).^{8,9}”

Revised text in the Method (Page 17, Paragraph 2):

“In addition to smoking status classification, baseline smoking exposure intensity (in PYs) and e-cigarette use were assessed using health screening results from 2018.”

Third, e-cigarettes are quite diverse in their form, content, formula, potential damage, etc. You acknowledge this in the limitations. However, more information is needed on the e-cigarettes that are most commonly used in Korea. A brief description of the market could inform the readers about this.

Response. We thank the reviewer for this important comment. We agree that the considerable diversity of e-cigarette devices and liquids warrants further contextual information to aid interpretation of our findings. To this end, we have added a brief overview of the Korean e-cigarette market in the revised manuscript. Specifically, we have described the types of products most commonly used in Korea, prevailing formulations, and regulatory features which may influence exposure and potential harm. We believe this addition enhances readers’ understanding of how our results may apply in the Korean context.

Revised text in the Discussion section (Page 11, Paragraph 2)

“In South Korea, e-cigarettes were introduced in 2008 and rapidly expanded in use.²⁸ The current market includes refillable tank-type devices, pod-based systems, and disposable e-cigarettes, with commercially available e-liquids containing nicotine concentrations up to approximately 20mg/ml. Aside from a minimum legal purchase age of 19 years, regulatory restrictions are limited, resulting in high accessibility and widespread availability”

Fourth, the size of the final sample is quite smaller than the total number of observations. I understand why some individuals are not considered (eg, not smokers), but I have doubts about how the non-inclusion of others can affect results. For instance, are people with missing smoking cessation duration, e-cigarette use- smoking PY, etc, a missing completely at random sub-sample? If they are not, you may be biasing your results by considering them like that and simply dismissing them. Please elaborate on this and, if

possible, correct your estimates.

Response. We appreciate this valuable comment regarding handling of missing data. As the reviewer also have acknowledge, exclusion of persons with no smoking history and those with history of lung cancer was pre-defined by study design to specify the target population. To assess whether the exclusion of participants with unclassifiable or missing data could introduce bias, we examined patterns of missingness across covariates using the Little's test and confirmed that the missing data occurred completely at random (MACR). Given MACR of the missing data and that the overall proportion of missing data was very small ($< 0.5\%$), we applied listwise deletion. We have now included additional clarification in the Methods section. We believe this additional clarification appropriately addresses the reviewer's concern and ensures the transparency of our data-handling process.

Revised text in the Methods (Page 17, Paragraph 1):

“Additionally, individuals with missing values for e-cigarette use, smoking PYs, or other covariates were excluded listwise after confirming missingness was completely at random (MCAR) based on Little's MCAR test, with less than 0.5% of data missing overall.”

Fifth, in the definition of groups, you say that current smokers are those who smoke at least until 2018. That is misleading, as “current” may be interpreted as those who smoke until the end of the study period (2023). I would suggest changing the name of this group for clarity. Also, please be consistent. In some parts you refer to them as “current” and in others as “continuous”.

Response. We thank the reviewer for this helpful comment. To avoid potential misinterpretation and improve clarity and consistency, we have revised the terminology to “current smokers at baseline”, defined as individuals who reported current smoking cigarettes at the time of the 2018 baseline screening. This clarification has been incorporated to the Methods, and all corresponding references in the Results, Figures, and Tables have been updated to ensure consistent use of the term throughout the manuscript.

Sixth, there are results described in the text that do not appear to be in the tables. For instance, you say "... compared with continuous smokers, e-cigarette users after smoking cessation demonstrated a significantly reduced risk of all-cause mortality (aHR=0.77 ...". Where is that? In which Table? It is not a good idea to make the reader search for the results. Please refer to the results in the tables.

Response. We thank the reviewer for noting this point. The mentioned result (aHR = 0.77 for all-cause mortality among e-cigarette users after smoking cessation compared with continuous smokers) was presented in Figure 1, which summarizes the adjusted hazard ratios for lung cancer incidence (Figure 1A), lung cancer-specific death (Figure 1B), and all-cause mortality (Figure 1C) across smoking status groups. To improve clarity for readers, we have revised the Results section to explicitly reference the corresponding Figure. We have also double-checked the entire manuscript to ensure that all numerical results described in the text are clearly referenced to their corresponding Figures or Tables (including supplementary data).

Revised text in the Results (Page 7, Paragraph 2):

"Figure 1 and Table S1 depict the comparisons on risk of lung cancer incidence and LCSD in current smokers at baseline, ex-smokers without e-cigarette use, and ex-smokers who used e-cigarette after smoking cessation. Compared with ex-smokers without e-cigarette use, ex-smokers with e-cigarette use revealed a significantly increased risk of lung cancer incidence (adjusted hazard ratio [aHR]=1.56, 95% confidence interval [CI]=1.24–1.97, Figure 1A) and LCSD (aHR=2.00, 95% CI=1.28–3.15, Figure 1B). Compared with current smokers at baseline, ex-smokers without e-cigarette use had a significantly lower risk of lung cancer (aHR=0.56, 95% CI=0.55–0.57) and LCSD (aHR=0.42, 95% CI=0.40–0.43). However, the risk reduction observed among ex-smokers was not significant in those who used e-cigarettes after quitting smoking. In addition, ex-smokers with e-cigarette use had a significantly increased risk of all-cause mortality (aHR=1.22, 95% CI=1.05–1.41) compared with ex-smokers without e-cigarette use. Nevertheless, compared with current smokers at baseline, e-cigarette users after smoking cessation demonstrated a significantly lower risk of all-cause mortality (aHR=0.77, 95% CI=0.66–0.89, Figure 1C). Overall, the adjusted subdistribution hazard ratios (aSHRs) for LCSD, accounting for competing risks, were consistent with the results from the Cox models (Figure 1D)."

Seventh, there are some analyses that rely on a tiny number of events. For instance, in Table 2 there are groups with 7 or 2 events (affecting long-term smoking quitters with substantial e-cigarette use). That is quite unacceptable in statistical terms. The same applies to Table 3 (and several other tables in the Supplement). What are the implications of these small numbers? How can you draw any statistical conclusion from 2 events? This is very unclear. Could you please explain in greater detail these figures?

Response. We thank the reviewer for this important comment. We fully agree that the small number of lung cancer specific-death events among e-cigarette users after smoking cessation in certain subgroups limits statistical power and precludes drawing definitive conclusions for these subgroup analyses. Consistent with this limitation, the corresponding estimates did not reach statistical significance in some subgroups. To address this concern, the Results section was revised to clearly indicate which findings were limited in statistical power owing to the small numbers of events and to avoid conclusive or causal wording for these subgroups. We have also acknowledged this issue in the final paragraph of the Discussion, emphasizing that results derived from subgroups with sparse events should be interpreted with caution. Furthermore, we have highlighted the need for future studies with larger numbers of e-cigarette–exposed former smokers and longer follow-up durations to validate and more reliably estimate these associations.

Revised text in the Results (Page 8, Paragraph 2 and Page 9, Paragraph 2):

“E-cigarette use after smoking cessation was significantly associated with higher risk of lung cancer incidence among both long-term quitters (aHR=1.74, 95% CI=1.07–2.84) and short-term quitters (aHR=1.31, 95% CI=1.00–1.71). For those who used e-cigarettes after quitting, the risk reduction associated with smoking cessation (relative to current smokers at baseline) appeared attenuated (Table 2). Although long-term quitters with e-cigarette use showed significantly higher risk of LCSD than complete quitters (aHR=2.57, 95% CI=1.07–6.19), stratification resulted in a small number of LCSD events among e-cigarette users within each subgroup, limiting the overall statistical power.”

“E-cigarette use after smoking cessation was significantly associated with higher risk of lung cancer among both long-term (aHR=2.51, 95% CI=1.42–4.42) and short-term (aHR=1.49, 95% CI=1.08–2.06) quitters. Although a similar pattern was observed for LCSD, the association

did not reach statistical significance, likely due to the limited number of events (Table 3). ”

Revised text in the Discussion (Page 15, Paragraph 1):

“In addition, some subgroup analyses were based on a small number of events among e-cigarette users after smoking cessation, which limited statistical power and warrants cautious interpretation. Future longitudinal studies with larger numbers of exposed former smokers and extended follow-up are needed to validate and expand these findings.”

Overall, the manuscript requires significant revision, particularly in the description of variables, method, and results. In its current form, it is unclear.

Response. We sincerely thank the reviewer for the thorough evaluation and constructive feedback. In accordance with these recommendations, we have made substantial revisions to improve the clarity of variable definitions, strengthen methodological descriptions, and refine the presentation and interpretation of our findings. We believe that these revisions have meaningfully enhanced the clarity of the manuscript.

Reviewer #4 (Remarks to the Author):

The manuscript presents evidence that challenges a prevailing narrative that electronic cigarettes are a safer alternative for former smokers. Collecting data from over 4.3 million individuals in South Korea with a history of conventional smoking, the authors demonstrate a statistically significant increase in lung cancer incidence and mortality among ex-smokers who transitioned to e-cigarette use, compared to those who quit entirely.

This study is particularly timely given the global rise in e-cigarette use and the ongoing debate over their role in smoking cessation. Prior research has focused on short-term cessation outcomes or toxicological profiles of e-cigarette aerosols. However, the authors provide the first large-scale epidemiological evidence linking post-cessation e-cigarette use to long-term cancer outcomes.

Summary of Key Results

- Data from over 4.3 million individuals in South Korea with a history of conventional smoking were used to demonstrate a statistically significant increase in lung cancer incidence (53,354) and mortality (6,351) among ex-smokers who transitioned to e-cigarette use, compared to those who quit entirely.**
- Ex-smokers who used e-cigarettes after quitting had significantly higher risks of lung cancer and lung cancer-specific death compared to those who quit and did not use e-cigarettes.**

For ex-smokers ≥ 5 years since quitting, e-cigarette use was associated with a 2.69-fold increase in lung cancer-specific death (aHR=2.69, 95% CI=1.12–6.46).

For ex-smokers < 5 years since quitting, e-cigarette use increased lung cancer incidence (aHR=1.23, 95% CI=1.09–1.39) and mortality (aHR=1.71, 95% CI=1.10–2.66).

High-risk individuals (aged 50–80, ≥ 20 pack-years) showed even stronger associations.

Originality and Significance

- The first large-scale population-based study to directly assess lung cancer risk associated with e-cigarette use after smoking cessation.
- Prior studies have focused on e-cigarette toxicity or cessation efficacy, but not long-term cancer outcomes. This study fills a critical gap in public health knowledge.

Response. We sincerely thank the reviewer for this comprehensive review and for the positive feedback on the originality and relevance of our study.

Data and Methodology: Validity of Approach, Quality of Data, Quality of Presentation

- The data were sourced from the National Health Screening Program in South Korea, covering the years 2012–2014 and 2018, with follow-up through 2021.
- The sample size of 4,329,288 individuals is huge and representative.
- The study design is a cohort study with stratification by smoking history and e-cigarette use.
- Cox proportional hazards models with adjustments were used to enhance credibility, and a stratified analysis for high-risk groups was added to highlight clinical relevance.
- The categorization of groups and outcomes is clearly stated.

Response. We thank the reviewer for the comprehensive review on our Methodology and positive feedbacks.

Appropriate Use of Statistics and Treatment of Uncertainties

- Adjusted hazard ratios (aHR) and 95% confidence intervals are appropriately applied.
- While stratification and multivariate adjustments reduce bias, potential residual confounding (e.g., unmeasured lifestyle factors) remains a limitation.
- Additional sensitivity analyses or competing risk models could strengthen robustness.

Response. We thank the reviewer for the thoughtful evaluation and positive feedback. We fully agree that, as with any large-scale cohort study, potential residual confounding from unmeasured factors should be acknowledged as an inherent limitation. Although we carefully adjusted for all clinically relevant covariates available in our dataset, residual confounding may still exist. We have explicitly emphasized this limitation in the revised manuscript to clarify our recognition of this issue.

Revised text in the Discussion (Page 14, Paragraph 2):

“Second, while all analyses were comprehensively adjusted for available important covariates, residual confounding from unmeasured exposures (e.g., age at smoking initiation, emerging inhaled toxicants, environmental exposures, and socioeconomic influences) may persist and remains an inherent limitation.”

In response to this comment and suggestions from other reviewers, we have performed additional sensitivity and competing risk analyses to strengthen the robustness of our findings as follows:

1. Reverse causation sensitivity analysis: To address potential reverse causation, sensitivity analyses excluding cases that occurred within the first year of follow-up were conducted. The results remained consistent with the main analysis.
2. Subgroup sensitivity analysis (post-2018 data): Among participants with available health screening during data during 2019–2020 with updated information on cigarette smoking and e-cigarette use, we additionally performed time-varying analyses for the major exposures. These sensitivity analyses showed similar trends in the associations between e-cigarette use after smoking cessation and subsequent lung cancer risk, supporting the stability and robustness of our main findings.
3. Competing risk analysis: We additionally applied Fine–Gray models to account for competing risks of death from causes other than lung cancer. The results were materially unchanged, supporting the robustness of our main Cox regression findings.

We have incorporated descriptions of these additional analyses into the Methods and Results

sections, and the detailed results are presented in the revised Tables and the Supplementary Materials.

Revised text in the Methods (Page 19, Paragraph 2 and Page 20, Paragraph 2):

“In addition, risk of all-cause mortality was evaluated as a secondary outcome. LCSD was further evaluated using Fine–Gray models accounting for death from other causes as a competing event, with aSHRs reported.”

“To address potential reverse causation, sensitivity analyses excluding cases that occurred within the first year of follow-up were conducted. To account for changes in smoking status and e-cigarette use after baseline, an additional sensitivity analysis was conducted in a subpopulation of participants who underwent additional health screening during 2019–2020 with updated information on smoking and e-cigarette use. Using this exploratory subpopulation (n=3,465,275), time-varying Cox proportional hazards models were fitted, treating smoking status and e-cigarette use status as time-dependent covariates updated at the date of follow-up health screening. Multivariable models were fitted to estimate aHRs using the same covariate adjustment strategy as in the primary analysis.”

Revised text in the Results (Page 10, Paragraph 1):

“In sensitivity analyses excluding events that occurred during the first year of follow-up from baseline (Tables S6–S9), the associations between e-cigarette use after smoking cessation and the risks of lung cancer incidence and LCSD remained materially unchanged. In time-varying exposure analyses restricted to participants with updated smoking and e-cigarette use information, precision was reduced and confidence intervals widened, likely reflecting the reduced sample size and number of events. Nevertheless, the direction and trend toward a higher risk of lung cancer incidence among individuals who used e-cigarettes after smoking cessation were consistent (aHR=1.38, 95% CI=0.98–1.98, Tables S10–S11).”

Conclusions: Robustness, Validity, Reliability

- **The conclusions are well supported by data and statistical analysis,**
- **The sample size and national scope of the data increase the reliability of the findings.**

Still, causality cannot be definitively established due to the observational design.

Response. We thank the reviewer for these positive comments. We agree that definitive causality cannot be inferred from our observational design, and that our conclusions should emphasize associations rather than causal relationships. Accordingly, we have revised the wording throughout the Discussion section and Conclusions to clearly indicate that our findings reflect associations between e-cigarette use after smoking cessation and subsequent lung cancer risk and mortality, rather than causal effects. Specifically, we have replaced phrases such as “e-cigarette use after smoking cessation was associated with a higher risk” for any statements that could imply causation. We believe this revision appropriately aligns the interpretation of our results with the study design and improves the precision and validity of the conclusions.

Revised text in the Discussion (Page 15, Paragraph 2):

“In conclusion, e-cigarette use after conventional smoking cessation was associated with a higher risk of lung cancer and related mortality compared with complete smoking cessation without e-cigarette use, with attenuated risk reduction when compared with current smokers at baseline. Potential harms of alternative e-cigarettes must be considered when integrating interventions on smoking cessation and tobacco control to reduce the burden of lung cancer.”

Suggested improvements: experiments, data for possible revision

- **Mechanistic experimental studies can be considered to explore causality and biological pathways.**

Response. We thank the reviewer for this excellent suggestion. Some mechanistic experimental studies have elucidated the causal and biological pathways underlying the link between e-cigarette exposure and carcinogenesis in the lungs, and we believe that future experimental studies, in combination with large-scale epidemiologic evidence such as ours, will provide a

more comprehensive understanding of how e-cigarette exposure may influence lung carcinogenesis. We have revised the Discussion section to explicitly acknowledge the current experimental data exploring potential mechanisms and the need for future laboratory and translational studies.

Revised text in the Discussion (Page 12, Paragraph 1 and Page 15, Paragraph 1):

“The potential harms of e-cigarettes include acute pulmonary toxicity and lung carcinogenesis beyond the known effects of nicotine and its metabolites.^{17,30} Several studies have shown that e-cigarettes and heating elements contain carbonyl compounds (e.g. formaldehyde, acetaldehyde, acrolein, and diacetyl) and toxic metals (e.g. chromium, nickel, and lead) which are known to be carcinogenic and also present in conventional cigarettes.^{31,32} The carcinogenic potential of e-cigarette-derived compounds has been demonstrated in experimental models, including mouse studies showing DNA methylation modifications similar to those caused by conventional cigarettes.^{30,33} More recent mechanistic studies have further demonstrated epigenetic and molecular alterations induced by e-cigarette exposure that are directly linked to lung carcinogenesis.^{34,35}”

“While our study provides early population-based evidence suggesting a potentially harmful association between e-cigarette use after smoking cessation and lung cancer risk, definitive causality cannot be established from our observational design. Therefore, future mechanistic and experimental studies are needed to clarify potential causal pathways induced by e-cigarette exposure.”

- **Evaluating biomarkers of exposure (e.g., cotinine levels) can assess frequency and duration of e-cigarette use, and controlling for environmental exposures and socioeconomic factors can enhance the current data for further analysis.**

Response. We thank the reviewer for this comment. We agree that incorporating biomarkers of exposure and controlling for additional environmental and socioeconomic variables could

enhance the precision of exposure assessment. However, there are currently no available biomarkers within our cohort that can accurately quantify the intensity of e-cigarette exposure. Because our study population consisted of individuals with a history of conventional cigarette smoking, cotinine levels would likely be confounded by prior or concurrent nicotine exposure and therefore may not reliably distinguish e-cigarette use from residual effects of smoking. We have further elaborated on these limitations in the Discussion section, emphasizing both the potential for residual confounding and the need for future studies incorporating objective biomarkers and longitudinal exposure data to refine the assessment of e-cigarette use.

Revised text in the Discussion (Page 14, Paragraph 2):

“Efforts to develop validated measures of constituent-specific exposure, along with relevant questionnaires and biomarkers, are essential to improve our understanding of e-cigarette use and associated health outcomes. Second, while all analyses were comprehensively adjusted for available important covariates, residual confounding from unmeasured exposures (e.g., age at smoking initiation, emerging inhaled toxicants, environmental exposures, and socioeconomic influences) may persist and remains an inherent limitation.”⁴⁷

• **Was vaping intensity after quitting considered for subgroup or sensitivity analyses to test robustness?.**

Response. We thank the reviewer for this insightful comment. We have performed sensitivity analyses using alternative definitions of e-cigarette use according to vaping intensity. Specifically, we redefined exposure to include any e-cigarette use, in addition to the primary definition of the exposure of interest (daily use), and compared the outcomes accordingly. The results remained consistent with the main findings, although the effect sizes were smaller, as presented in the Supplementary Tables (Tables S12–S19).

Revised text in the Results (Page 10, Paragraph 1)

“Results from analyses defining the exposure of interest as any e-cigarette use are presented in Tables S12–S19 and show similar directional trends, including in the time-varying analyses (Tables S20–S21).”

- **Were “ex-smokers” defined by the duration of time since quitting?**

Response. We thank the reviewer for this comment and the opportunity to clarify the rationale our group definitions. We defined ex-smokers according to the duration of smoking cessation based on responses from two national health screening periods. Smoking status and history was assessed at baseline (health screening data in 2018) and validated and stratified by the duration of smoking cessation using data from a previous health examination period (2012–2014), which occurred approximately five years before the baseline survey. The 2012–2014 period was selected because approximately five years of smoking cessation is generally required to observe a meaningful reduction in lung cancer risk. Health screening data from 2012–2014 were treated as a single “past period” since the national health screening program is biennial and participants undergo examinations at different years within the same cycle. Accordingly, individuals who were ex-smokers during the 2012–2014 period and remained ex-smokers in 2018 were classified as long-term quitters, whereas those who reported current smoking in 2012–2014 but were ex-smokers in 2018 were classified as short-term quitters. This approach allowed us to validate smoking cessation status and to stratify participants by cessation duration with sufficient temporal separation. We have added a detailed description of the smoking history stratification method and how multiple examinations were handled in the revised Methods section.

Revised text in the Methods section (Page 16, Paragraph 2):

“This study initially included 11,550,680 individuals who participated in the national health screening program in 2018 (baseline time of cohort entry), with prior screening records

available from 2012-2014. This structure enabled assessment of smoking behaviors across the two time points and classification of participants according to their baseline cigarette smoking status into: current smokers (individuals who reported current cigarette smoking in 2018 regardless of past status, including continuous smokers or those who relapsed after reporting former smoking in 2012-2014), short-term smoking quitters (individuals who reported current smoking in 2012-2014 and former smoking in 2018), and long-term smoking quitters (individuals who reported former smoking at both time points). This stratification was based on knowledge that lung cancer risk decreases substantially within approximately five years after smoking cessation.^{42,54} Individuals whose smoking status changed during 2012–2014 were assigned the smoking status (current or former smoking) reported at their most recent examination within that period”

- **Were dual users (still smoking occasionally + vaping) excluded or analyzed separately?**

Response. We thank the reviewer for this comment. We confirm that dual users of conventional cigarettes and e-cigarettes were included in the current smoking group, as our primary exposure of interest was e-cigarette use among former smokers. This classification aligns with our study aim, in which the primary exposure of interest was e-cigarette use specifically among former smokers after smoking cessation. Among current smokers, since conventional cigarette smoking remains the predominant driver of lung cancer risk, current smokers with and without e-cigarette use were grouped together from an exposure-classification perspective. This clarification has been added to the revised Methods section.

Revised text in the Methods section (Page 18, Paragraph 1):

“By stratifying ex-smokers according to e-cigarette use after smoking cessation, the study population was classified into five groups at baseline (Figure S1): current smokers (including dual e-cigarette users), short-term smoking quitters with e-cigarette use after smoking cessation, short-term smoking quitters without e-cigarette use, long-term smoking quitters with e-cigarette use after smoking cessation, and long-term smoking quitters without e-cigarette use.”

- **Include details of frequency, duration, type of device, and nicotine strength of the e-cigarette.**

Response. We thank the reviewer for this comment. Unfortunately, detailed information on e-cigarette use on the specific device type and nicotine strength, was not available in our cohort. In response to the reviewer's suggestion, we have expanded the Discussion section to provide context on the characteristics of e-cigarette products commonly available in the Korean market during the study period. This addition aims to help readers interpret our findings in light of regional product availability and variability in nicotine content.

Revised text in the Discussion (Page11, Paragraph 2):

“In South Korea, e-cigarettes were introduced in 2008 and rapidly expanded in use.²⁸ The current market includes refillable tank-type devices, pod-based systems, and disposable e-cigarettes, with commercially available e-liquids containing nicotine concentrations up to approximately 20mg/ml. Aside from a minimum legal purchase age of 19 years, regulatory restrictions are limited, resulting in high accessibility and widespread availability.²⁹”

- **Consider adding information on the changes in the vaping status of participants during follow-up.**

Response. We thank the reviewer for this excellent suggestion. As noted above, we performed additional sensitivity analyses among participants with available follow-up data on e-cigarette use status in 2019–2020. Using this subpopulation, we evaluated updated e-cigarette use status and changes from baseline, and conducted time-varying Cox proportional hazards analyses incorporating these changes. In the time-varying exposure analysis, the direction and trend toward a higher risk of lung cancer incidence among individuals who used e-cigarettes after smoking cessation remained consistent with our main analysis, thereby further supporting our primary findings. We have added these details to the Methods and Results section.

Revised text in the Methods (Page 20, Paragraph 2):

“To account for changes in smoking status and e-cigarette use after baseline, an additional sensitivity analysis was conducted in a subpopulation of participants who underwent additional health screening during 2019–2020 with updated information on smoking and e-cigarette use. Using this exploratory subpopulation (n=3,465,275), time-varying Cox proportional hazards models were fitted, treating smoking status and e-cigarette use status as time-dependent covariates updated at the date of follow-up health screening. Multivariable models were fitted to estimate aHRs using the same covariate adjustment strategy as in the primary analysis.”

Revised text in the Results (Page 10, Paragraph 1):

In sensitivity analyses excluding events that occurred during the first year of follow-up from baseline (Tables S6–S9), the associations between e-cigarette use after smoking cessation and the risks of lung cancer incidence and LCSD remained materially unchanged. In time-varying exposure analyses restricted to participants with updated smoking and e-cigarette use information, precision was reduced and confidence intervals widened, likely reflecting the reduced sample size and number of events. Nevertheless, the direction and trend toward a higher risk of lung cancer incidence among individuals who used e-cigarettes after smoking cessation were consistent (aHR=1.38, 95% CI=0.98–1.98, Tables S10–S11).”

- **Explore the possibility of using cumulative incidence curves or survival plots by exposure groups to aid data interpretation.**

Response. We thank the reviewer for this valuable suggestion. As recommended, we explored the feasibility of generating adjusted cumulative incidence curves or survival plots. However, given the extremely large study population (over 4.5 million participants) and the complexity of multivariable modelling, generating such curves was not computationally feasible within the constraints of the designated analytic environment for the Korean National Health Insurance data, which does not allow access to high-performance computing resources. Accordingly, and

consistent with standard epidemiologic reporting for large-scale exposure-outcome analyses, we have presented standardized effect estimates using forest plots and structured tables. We believe these formats facilitate interpretation and clear comparisons of our results.

- **Given lung cancer's long latency, consider addressing whether the follow-up duration is adequate to capture incidence.**

Response. We thank the reviewer for this important comment. We agree that the long latency period of lung cancer warrants careful consideration of the follow-up duration. This is one of the main reasons we focused our study population on individuals already exposed to significant cigarette smoking, who represent the population at risk for lung cancer. In addition, we conducted subgroup analyses among participants aged 50–80 years with ≥ 20 pack-years of smoking history, consistent with the high-risk group recommended for lung cancer screening according to international guidelines. Notably, previous lung cancer risk prediction models derived from large cohort studies have commonly used a 5–6-year horizon.^{1,2} Therefore, we believe that our maximum follow-up period of up to 6 years (from Jan 2018 to Dec 2023) is comparable and sufficient to evaluate incident lung cancer in this at-risk population. To clarify this point, we have supplemented the Discussion section to emphasize the relevance of our follow-up duration in reporting some of the earliest population-based evidence on the associations between e-cigarette use after smoking cessation and lung cancer. In addition, we have also highlighted the need for future studies with longer follow-up durations to validate and more reliably estimate the revealed associations.

Revised text in the Discussion (Page 13, Paragraph 1):

“Regarding the long lag periods between carcinogenic exposure and cancer development, the current lack of epidemiologic evidence on e-cigarette use and lung cancer risk is predictable. Accordingly, the impact of e-cigarettes on lung cancer risk in the general population will not be apparent until a few decades. Therefore, evaluating associations related to exposure within a vulnerable population with established and quantifiable risk factors would provide more actionable evidence to guide interventional strategies regarding e-cigarette use in terms of

reducing lung cancer risk.¹⁷ In our population-based study, only current or former smokers with meaningful conventional cigarette exposure at baseline were included, who would have increased lung cancer risk by 15- to 30-fold compared with individuals who have never smoked.³⁹ Although extended follow-up is important, the maximum follow-up period of up to 6 years in our cohort, which is comparable to time horizons used in risk-prediction models,^{40,41} supports the validity of reporting early associations in this at-risk population.”

References

1. Tammemagi, MC, *et al.* Selection criteria for lung-cancer screening. *N Engl J Med* **368**, 728–736 (2013)
2. Cassidy, A., *et al.* The LLP risk model: an individual risk prediction model for lung cancer. *Br J Cancer* **98**, 270–276 (2008).

- **Ensure that key terms (e.g., pack-years [PY], adjusted hazard ratio [aHR], LCSD) are clearly defined at first mention.**

Response. Thank you for this valuable comment. We have carefully reviewed the entire manuscript to ensure that all key terms and abbreviations are clearly defined at their first mention throughout the text. Please note that the Methods sections has been moved to the end of the manuscript in accordance with the journal’s formatting guidelines.

- **The abstract should reflect some study limitations alongside the main findings to avoid overstating the findings.**

Response. We thank the reviewer for this comment and excellent suggestion. We have revised the abstract to include a concise statement of limitations, ensuring that the findings are presented in a balanced and cautious manner.

Revised text in the Abstract (Page 3, Paragraph 1):

“Although definitive causality cannot be established from this observational study, these findings suggest that potential health risks of e-cigarette use should be considered when implementing smoking cessation interventions aimed at reducing lung cancer risk.”

- **While the rationale for focusing on ex-smokers who vape is strong, please clarify why you exclude current smokers and dual users.**

Response. We thank the reviewer for this insightful comment and the opportunity to clarify our group definitions. We would like to clarify that current smokers and dual users were not excluded from the analysis. Both groups were included in the overall study population. As noted above, dual users of conventional cigarettes and e-cigarettes were included in the current smoking group, as our primary exposure of interest was e-cigarette use among former smokers. Including these participants allowed us to maintain a consistent source population and avoid potential bias arising from restricting the analysis solely to individuals who had quit smoking. We have clarified this point in the Methods section by explicitly describing our classification criteria. In addition, as a sensitivity analysis, we have conducted an additional analysis comparing lung cancer risk between dual users and cigarette-only smokers. The results showed that the risk of lung cancer among dual users was lower than that of cigarette-only smokers in the overall population (presented in Page 8, Paragraph 2), and comparable among participants aged 50–80 years with a smoking history of more than 20 pack-years (presented in Page 9, Paragraph 2).

Revised text in the Methods section (Page 18, Paragraph 1):

“By stratifying ex-smokers according to e-cigarette use after smoking cessation, the study population was classified into five groups at baseline (Figure S1): current smokers (including dual e-cigarette users), short-term smoking quitters with e-cigarette use after smoking cessation, short-term smoking quitters without e-cigarette use, long-term smoking quitters with e-cigarette use after smoking cessation, and long-term smoking quitters without e-cigarette

use.”

- **Interpret results cautiously, emphasizing that residual risk may stem from prior smoking, not necessarily e-cigarette use.**

Response. We thank the reviewer for this important suggestion. We agree that interpreting our findings as evidence that e-cigarette use directly causes lung cancer cannot be robustly supported by our study design and results. Such an evaluation would ideally require a non-smoking population with and without e-cigarette use, followed over several decades, given the relatively low incidence of lung cancer among non-smokers and the younger age of most e-cigarette users. We agree that our findings are more appropriately interpreted as suggesting that e-cigarette use may attenuate the benefits of smoking cessation in terms of lung cancer risk. At the same time, because cigarette smoking remains the predominant risk factor for lung cancer and the key determinant for defining high-risk populations in screening programs, we believe that our observation that e-cigarette use may reduce the benefits of quitting has important public health implications. In the revised manuscript, we have incorporated several changes in line with the reviewer’s suggestions and strengthened the clarity of our interpretation.

Revised text in the Discussion (Page 15, Paragraph 2):

“In conclusion, e-cigarette use after conventional smoking cessation was associated with a higher risk of lung cancer and related mortality compared with complete smoking cessation without e-cigarette use, with attenuated risk reduction when compared with current smokers at baseline. Potential harms of alternative e-cigarettes must be considered when integrating interventions on smoking cessation and tobacco control to reduce the burden of lung cancer.”

- **Discuss the limitations of short follow-up relative to lung cancer’s latency.**

Response. We thank the reviewer for this important suggestion. As recommended, we have

expanded the Discussion section to address the potential limitation of the relatively short follow-up period in relation to the long latency of lung cancer development, while emphasizing that this study was designed to focus on an at-risk population with prior cigarette exposure to provide some of the earliest population-based evidence on the associations between e-cigarette use and lung cancer.

Revised text in the Discussion (Page 15, Paragraph 1):

“Third, the relatively short follow-up duration may not sufficiently capture the long latency of lung cancer development and related outcomes, particularly among younger individuals with lower cumulative smoking exposure. This limitation was a major rationale for focusing our analyses on at-risk individuals. For the general population, including persons with no smoking history, future studies with longer follow-up and detailed assessments of other potential risk factors and biomarkers are required to determine the association between e-cigarette exposure and lung cancer risk.”

- **Address possible misclassification bias (self-reported vaping/smoking).**

Response. We thank the reviewer for this comment. In the revised Discussion, we have further addressed the possibility of misclassification bias as a limitation of our study, acknowledging that self-reported information on smoking e-cigarette may introduce recall or reporting bias.

Revised text in the Discussion (Page 14, Paragraph 2):

“Our study has limitations. First, we assessed e-cigarette use using available self-reported questionnaires, which may be subject to recall bias leading to potential misclassifications.”

- **Consider comparing the results with those of prior cohorts or mechanistic studies.**

Response. We thank the reviewer for this excellent suggestion. As suggested, we conducted additional literature searches for mechanistic and prior cohort studies related to e-cigarette use and lung cancer risk, and identified several mechanistic studies that support biologically plausible pathways consistent with our findings. We have incorporated these studies into the Discussion section. We also explicitly noted that, there remains no epidemiological evidence establishing whether e-cigarette use is associated with lung cancer among former smokers. Accordingly, we have emphasized how our large, population-based cohort contributes new and timely data to this emerging area and contextualized our findings within the existing body of evidence.

Revised text in the Discussion (Page 12, Paragraph 1):

“However, increasing evidence reveals that e-cigarettes are associated with adverse outcomes in lung health. The potential harms of e-cigarettes include acute pulmonary toxicity and lung carcinogenesis beyond the known effects of nicotine and its metabolites.^{17,30} Several studies have shown that e-cigarettes and heating elements contain carbonyl compounds (e.g. formaldehyde, acetaldehyde, acrolein, and diacetyl) and toxic metals (e.g. chromium, nickel, and lead) which are known to be carcinogenic and also present in conventional cigarettes.^{31,32} The carcinogenic potential of e-cigarette-derived compounds has been demonstrated in experimental models, including mouse studies showing DNA methylation modifications similar to those caused by conventional cigarettes.^{30,33} More recent mechanistic studies have further demonstrated epigenetic and molecular alterations induced by e-cigarette exposure that are directly linked to lung carcinogenesis.^{34,35} However, there is lacking epidemiological evidence either on the role of e-cigarettes in enhancing lung cancer risk or in their potential of reducing oncogenic process for those who previously smoked.^{25,36}”

- **Suggest areas for future research (longer follow-up, biomarker validation, never-smoker comparison groups)**

Response. We thank the reviewer for this valuable suggestion. As recommended, we have emphasized in the Discussion section the need for future studies including non-smokers with

longer follow-up durations and relevant biomarkers to better capture the long-term carcinogenic potential of e-cigarette use.

Revised text in the Discussion (Page 15, Paragraph 1):

“For the general population, including persons with no smoking history, future studies with longer follow-up and detailed assessments of other potential risk factors and biomarkers are required to determine the association between e-cigarette exposure and lung cancer risk.”

• The 24,182,543.0 person-years combine both cohorts. Could you clarify somewhere in the paper that the PYs were for roughly 10-year and 5-year follow-up periods?

Response. We thank the reviewer for this comment and the opportunity to clarify how follow-up duration was captured in our study. The total follow-up of 24,182,543 person-years represents the cumulative observation time from the baseline assessment in 2018 (cohort entry) to the end of the study (December 31, 2023). The 2012–2014 period was used to ascertain participants’ smoking status and classify the duration of smoking cessation prior to the 2018 assessment. To avoid any potential confusion, we have clarified this point in the Methods section.

Revised text in the Methods (Page 17, Paragraph 1):

“All participants were followed up from the baseline date (health screening date in 2018) to the date of documentation of the outcome of interest (lung cancer diagnosis and lung cancer-specific death (LSCD)), death from any other cause, or the end of the study period (December 31, 2023, the latest date with available data), whichever occurred first.”

References: Appropriate Credit to Previous Work

- The study cites some literature on e-cigarette toxicity and lung cancer screening guidelines. However, more references to mechanistic studies on e-cigarette constituents (e.g., carbonyl compounds, metals) would strengthen the discussion. Is there a link between any specific e-cigarette constituents that may be driving the incidence and mortality? Providing information on the fluid flavors used by participants will generate valuable data for the research community.

Response. We thank the reviewer for this helpful comment. In the revised manuscript, we have incorporated additional references to mechanistic studies that support similar biological pathways linking e-cigarette exposure to lung carcinogenesis. Specifically, we have included studies demonstrating that e-cigarette components (e.g., nicotine, metals, flavorings, and solvents) can induce DNA-damaging effects, oxidative stress, and chronic inflammation similar to conventional cigarettes in airway epithelial cells. These mechanistic findings provide biological plausibility supporting our observed epidemiologic associations between e-cigarette use after smoking cessation with lung cancer incidence and mortality. Unfortunately, information on the specific fluid flavors or e-liquid compositions used by participants was not available in our dataset. We have acknowledged this as a limitation and highlighted the importance of future efforts to develop validated measures on e-liquid constituents to better elucidate component-specific effects.

Revised text in the Discussion (Page 12, Paragraph 1 and Page 14, Paragraph 2):

“The carcinogenic potential of e-cigarette-derived compounds has been demonstrated in experimental models, including mouse studies showing DNA methylation modifications similar to those caused by conventional cigarettes.^{30,33} More recent mechanistic studies have further demonstrated epigenetic and molecular alterations induced by e-cigarette exposure that are directly linked to lung carcinogenesis.^{34,35}”

“In addition, the specific type of e-cigarette device, liquid characteristics including flavorings, and duration of e-cigarette use could not be explicitly differentiated among the e-cigarette users. However, unlike conventional smoking, there is currently no consensus on e-cigarette use intensity measures owing to product and user behavior heterogeneity.²⁶ Efforts to develop

validated measures of constituent-specific exposure, along with relevant questionnaires and biomarkers, are essential to improve our understanding of e-cigarette use and associated health outcomes.”

Clarity and context: lucidity of abstract/summary, appropriateness of abstract, introduction, and conclusions

- **The abstract is concise and informative.**
- **The introduction is contextualized within the public health debate on e-cigarettes.**
- **Appropriate emphasis on the need for caution in recommending e-cigarettes as cessation tools is made.**

Response. Thank you for your comprehensive review on the clarity and importance of our paper and positive feedbacks.

Reviewers' Comments:

Reviewer #1 (Remarks to the Author):

The authors have done an excellent job addressing all of my comments, as well as those from the other reviewers. I very much enjoyed reading the manuscript for a second time and have no further comments.

We thank the reviewer for the careful and comprehensive evaluation of our manuscript and for the positive feedback. We are pleased that the reviewer found our revisions satisfactory. In particular, we appreciate the reviewer's recognition that our clarifications regarding smoking status and cessation-duration classification, e-cigarette use patterns, and the sensitivity analyses addressing post-baseline changes are methodologically sound and scientifically rigorous.

Reviewer #2 (Remarks to the Author):

As per my initial review, the finding is likely an artefact of EC users quitting more recently than non-users. Some non-users quit smoking 40+ years before the 2018 baseline, EC users could have quit only since about 2007 but more likely several years later when EC use in Korea became more widespread. Following a note from another reviewer, the paper now in fact acknowledges that duration of abstinence is a significant determinant of lung cancer risk in this cohort (as in all others).

The authors' response, if I understand it correctly, includes two points. One is that EC entered Korea several years before the cohort was established, but that does not address the problem that people who quit before EC arrival would be only present in the sample of non-users and so on average, EC users must have quit more recently than non-users. (Indeed, EC users comprise 3% of short-term quitters but only 0.4% of long-term quitters).

The other point the authors make is that duration of smoking is a stronger risk factor than duration of abstinence, but this does not address the problem either. Time since quitting affects lung cancer risk independently of duration of smoking.

Response and rebuttal: We respectfully address Reviewer 2's persistent concern that our findings may reflect an "artifact". We believe there is a fundamental discordance between the reviewer's hypothetical assumption and the empirical evidence provided by our data. We would like to clarify the following points:

First, Reviewer 2 consistently asserts that our findings are an "artifact" based on the assumption that e-cigarette users must have quit more recently than non-users. However, this assertion cannot be verified in our dataset or substantiated by existing evidence, and it does not account for the analyses we implemented to address abstinence duration using the information available in this nationwide cohort. In particular, the descriptive observation that the proportion of e-cigarette users is higher among short-term quitters than among long-term quitters (3% vs. 0.4%) does not demonstrate that e-cigarette users, at the individual level, quit more recently than non-users. This comparison indicates how common e-cigarette use is within each abstinence-duration category, not how long ago e-cigarette users quit on average. Thus, it does not provide direct evidence for the reviewer's claim that e-cigarette users necessarily quit more recently than non-users. Beyond this conceptual issue, we also tested robustness to exposure specification by implementing a time-updated analysis in participants with follow-up screening records, allowing smoking and e-cigarette status to be updated during follow-up. The directionally consistent results under this time-varying framework provide further evidence that our findings are not readily explained by a baseline "artifact".

Second, we directly tested the reviewer's core hypothesis by conducting stratified analyses within abstinence-duration strata. The association between e-cigarette use after smoking cessation and increased lung cancer risk remained present in both short-term and long-term quitters after adjustment for major confounders. If the entire association were driven primarily by the proposed "recency-of-quitting artifact," we would expect the association to substantially attenuate or disappear when comparing e-cigarette users and non-users within the longer-abstinence stratum. This was not observed. For clarity, we respectfully note that our analytical framework is based on duration of abstinence categories, and "not" on the assumption that duration of smoking is a stronger determinant than duration of abstinence. We are concerned that Reviewer 2 continues to misinterpret both the direction of our analytical approach and the scope of our findings.

We fully acknowledge that residual confounding by more granular time since quitting cannot

be eliminated without adjusting exact quit-time information as a “continuous” measure, and we have explicitly stated this limitation. Nonetheless, using all available data in this nationwide cohort, we operationalized cessation status across defined timeframes to derive a meaningful proxy for smoking abstinence, thereby integrating duration of abstinence as a “categorical” factor. The totality of evidence from our prespecified stratified analyses and additional sensitivity analyses indicates that the observed association is not readily explained by Reviewer 2’s proposed mechanism. We therefore respectfully maintain that our data support the primary conclusion: **e-cigarette use after smoking cessation is associated with a higher risk of lung cancer outcomes compared with complete quitters** in this nationwide cohort, with appropriate caution regarding causal interpretation.

We also wish to note that Reviewer 1 and Reviewer 4 independently and consistently requested clarification and strengthening of the subgroup analyses, residual confounding considerations, and smoking history classification. We addressed these points thoroughly in the revision, and we understand that both reviewers found the resulting methodological rigor and interpretation to be appropriate. We respectfully ask the editors to consider whether the remaining concern reflects an untestable assumption rather than a methodological flaw that invalidates the study’s conclusions.

The authors are correct that this would be less of an issue for quitters for <5 years. In fact, a significant effect is clearly visible only in >5 year quitters. In <5 years quitters an effect was only borderline significant for cancer incidence (CI=1.00-1.71), but not significant for cancer death (CI=0.88-2.51), all-cause mortality (CI=0.92-1.28) or ‘competing risk analysis’ (CI=0.87-2.48).

Response and rebuttal: We respectfully note that the reviewer’s interpretation appears to place selective emphasis on results that support the reviewer’s position (particularly those near conventional significance thresholds) while overlooking the full pattern of results across prespecified analyses and relevant subgroups.

Contrary to the reviewer’s statement that the association in short-term quitters is “only borderline significant,” our prespecified analysis shows that, among short-term quitters, e-

cigarette use after smoking cessation is associated with a higher risk of lung cancer incidence with a meaningful effect size (**aHR=1.31, 95% CI=1.00–1.71; Table 2**). Importantly, this association is more clearly evident in the clinically relevant high-risk subgroup eligible for lung cancer screening (aged 50–80 years with ≥ 20 pack-years), where the estimate and statistical significance is more prominent (**aHR=1.49, 95% CI=1.08–2.06; Table 3**). In addition, the finding is robust to alternative exposure definitions. When defining exposure as any e-cigarette use (rather than daily use), the association with lung cancer incidence remains statistically significant in the overall cohort (**aHR=1.44, 95% CI=1.20–1.73; Table S14**) and also in the lung cancer screening–eligible subgroup under the same exposure definition (**aHR=1.58, 95% CI=1.25–1.99; Table S18**). Taken together, these results do not support the characterization that the association in short-term quitters is merely “borderline” or inconsistent.

Regarding the reviewer’s emphasis on non-significant mortality endpoints within the short-term quitter stratum, we note that the corresponding mortality analyses within the long-term quitter stratum were also not consistently statistically significant. As stated in the Results and in our response to other reviewers, this is most plausibly explained by limited statistical power due to the small number of lung cancer–specific deaths among e-cigarette users within each cessation-duration subgroup after stratification. Therefore, the absence of statistical significance for mortality outcomes in some subgroups should not be overinterpreted as evidence against the incidence findings.

Finally, we wish to clarify that Reviewer 2’s initial review questioned whether presenting both lung cancer incidence and lung cancer-specific death was necessary (“**Presenting both lung cancer incidence and lung cancer deaths seems superfluous, lung cancer deaths are already included in the incidence.**”). Consistent with that comment, we emphasize that the results on lung cancer incidence show a consistent and statistically significant association between e-cigarette use after smoking cessation and increased lung cancer risk across the main analysis and relevant subgroup and sensitivity analyses.

The issue of confounding by duration of abstinence and the lack of clear effect in <5 years quitters are not presented in the Abstract or discussed. Similarly, results showing that dual use is associated with lower cancer risk than smoking alone – which does not align with the main conclusion - are omitted from the abstract and interpretation of the results.

Response and rebuttal: We respectfully clarify the following points.

First, as noted above, we do not agree that there is a “lack of clear effect” among short-term quitters. In our prespecified stratified analyses, e-cigarette use after smoking cessation was associated with an increased risk of lung cancer incidence among short-term quitters (Table 2), and the association was statistically significant and more precisely estimated in the clinically relevant lung cancer screening-eligible subgroup (Table 3). We have strengthened the corresponding wording in the Results and Discussion to ensure this is clear to readers.

Second, the reviewer raises concern that findings for dual users appear inconsistent with the main conclusion. We respectfully note that our primary conclusion is explicitly limited to the main research question: **whether e-cigarette use after smoking cessation smoking quitters is associated with lung cancer outcomes**. In contrast, the dual-use analysis is a secondary comparison within **current smokers**, addressing a different exposure scenario and interpretation framework. The dual-use findings therefore do not contradict the main conclusion; rather, they provide additional context regarding heterogeneity among people who continue to smoke combustible cigarettes. To avoid any misunderstanding, in the revision letter, we have corrected the previous misinterpretation from the reviewer (“**The authors interpret these findings as suggesting that vaping causes lung cancer, an interpretation that seems somewhat tendentious. The cancers that were observed were likely the result of decades of smoking and the finding, if genuine, would more likely suggest that vaping was reducing the benefits of stopping smoking.**”), since our findings should be appropriately interpreted as suggesting that, in terms of lung cancer incidence and mortality, e-cigarette use may attenuate the benefits of smoking cessation. As requested by multiple referees (Reviewers 1, 2, and 4), we clarified the exposure classification and added the dual-use analyses in the revised manuscript. Specifically, dual users were included in the current smoking group in the primary analysis because the primary exposure of interest was e-cigarette use among former smokers after cessation. We additionally conducted a comparison between dual users and cigarette-only current smokers. In the overall population, dual use was associated with a lower

lung cancer risk than cigarette-only smoking (Page 8, Paragraph 2), whereas in the lung cancer screening–eligible subgroup the risk was comparable (Page 9, Paragraph 2). We have discussed plausible explanations (although e-cigarettes contain potentially carcinogenic substances, dual use may nevertheless be associated with lower overall exposure to toxicants compared with exclusive conventional cigarette smoking) and emphasized that these secondary findings do not alter our primary results addressing the main research question regarding the association between e-cigarette use after smoking cessation and lung cancer. If the editors consider it helpful to further elaborate on these secondary findings, we would be willing to add the following sentences to the Discussion:

“Sensitivity analyses comparing cigarette-only current smokers and dual users of conventional cigarettes and e-cigarettes at baseline suggest that, among individuals who continue to smoke conventional cigarettes, dual use of e-cigarettes can be associated with reduced cigarette smoking intensity. Consequently, although e-cigarettes contain potentially carcinogenic substances, dual use may nevertheless be associated with lower overall exposure to toxicants compared with exclusive conventional cigarette smoking.”

Third, regarding the Abstract, our intent was to keep it focused on the primary research question and its key results. However, if the editors consider it important for transparency and balance, we are willing to add a brief statement to the Abstract noting that the dual-use analysis was conducted as a secondary comparison among current smokers, with the results briefly summarized.

My original review also noted that a paper using the same survey (overlapping years) reported that quitting smoking within the past 5 years was associated with an increased risk of lung cancer compared to continuing smoking. (I was wrong thinking the current authors were involved in that publication, apologies for that). The paper suggested that this could be due to smokers with prodromal symptoms trying to quit. If that was the case, a handful (see the N issue below) of worried smokers unable to quit unaided and switching to vaping would explain the borderline finding in <5 years quitters.

Response and rebuttal: While we acknowledge the reviewer’s reference to the prior publication, we respectfully note that adjudicating the interpretation proposed in that study is

beyond the scope of our manuscript, which addresses a different research question and comparison framework. Our response therefore focus on what can be evaluated directly using our data and prespecified analyses.

As clarified in our revision letter, the reverse-causality mechanism proposed by the reviewer does not align with the comparisons or the empirical patterns observed in our study. Our primary research question and inference are **not** that e-cigarette use after cessation increases lung cancer risk relative to continuing smoking. Rather, our results consistently show that former smokers (regardless of e-cigarette use) have a lower lung cancer risk than current smokers, whereas e-cigarette use after cessation is associated with a higher risk compared with complete quitters, suggesting attenuation of the benefits of cessation. We have clarified this interpretation throughout the revised manuscript.

Importantly, even if prodromal symptoms led some smokers to attempt quitting (and thereby could influence comparisons of recent quitters versus continuing smokers in other settings), this would not readily explain our key finding: **within former smokers**, those who use e-cigarettes after cessation show an elevated risk compared with complete quitters. If reverse causation were the dominant explanation, one would more plausibly expect symptomatic individuals to be motivated toward complete cessation rather than switching to e-cigarettes, particularly given evidence that e-cigarette use can also be associated with respiratory symptoms and airway inflammation. Moreover, the reviewer's proposed scenario would primarily affect comparisons involving current smokers; it does not explain the consistent elevation observed within former smokers when comparing post-cessation e-cigarette users with complete quitters across multiple analyses.

We respectfully suggest that the reviewer's argument conflated two distinct comparisons: (1) former smokers versus current smokers and (2) e-cigarette users after smoking cessation versus complete quitters. Our data support the latter comparison as the basis for our primary conclusion, and they do not show that post-cessation e-cigarette users have a higher risk than continuing smokers. In light of this, we respectfully ask that our previous response on reverse causality, together with the additional sensitivity analyses described in the revision, be considered as directly addressing this concern.

The present authors argue that the fact that Table 1 shows EC users to be healthier than non-users at baseline excludes this possibility. However, EC users were also much younger and they may have been less healthy if age were controlled for. The authors also argue that excluding events 1 year after baseline addresses the problem. However, prodromal symptoms can appear years before lung cancer is diagnosed; and whatever the explanation of the phenomenon may be, the increase in lung cancer risk persisted for 7 years post-cessation, peaking at about 5 years, so excluding 1-year data does not address the issue.

Response and rebuttal: We respectfully disagree that the reviewer's proposed reverse-causality scenario adequately accounts for the empirical patterns observed in our study. Importantly, the reviewer's argument appears to be grounded in a comparison framework that differs from ours. Our primary inference is based on within-former-smoker comparisons, not on comparing recent quitters to continuing smokers. Our results consistently show that, across all subgroups, smoking quitters had a significantly lower risk of lung cancer compared with current smokers, with a clear dose-response relationship. **Neither our results nor our discussion suggests that post-cessation e-cigarette users have a higher risk of lung cancer than current smokers.**

If prodromal symptoms were the dominant driver of the observed association, the most direct expectation would be inflation of risk among those changing behavior due to symptoms in a way that would also tend to raise risk relative to continuing smokers. However, our results do not show an increased risk for e-cigarette users after smoking cessation relative to current smokers. Instead, the elevation is observed specifically relative to **complete quitters**, which is not the direction most consistent with the reviewer's proposed mechanism. Nonetheless, to address any remaining concerns, we conducted an additional analysis excluding lung cancer events diagnosed within the first year of follow-up. This approach of excluding early follow-up events is a commonly used in cancer epidemiology studies to reduce potential bias from preclinical disease and reverse causality.^{1,2} The results remained materially unchanged, which further supports that the main association is not readily explained by the reviewer's hypothesis.

Reference

1. Bosch de Basea M et al. Risk of hematological malignancies from CT radiation exposure in

children, adolescents and young adults. *Nat Med.* **29**, 3111–3119 (2023)

2. Yang J et al. Association of Dietary Fiber and Yogurt Consumption With Lung Cancer Risk
A Pooled Analysis. *JAMA Oncol.* **6**, e194107 (2020)

Some other points were answered by additional analyses, but also not acknowledged in the Discussion and conclusions. The study has a serious problem in not knowing the actual smoking status post 2018 of most participants. It is possible that quitters who needed EC to quit were more likely to relapse than those able to quit unaided. The authors looked at a subsample with updated smoking status (over an unclear time period, possibly also not up to the final census) and found that the link to lung cancer was not significant anymore. They interpret this as confirming the main result because there remained ‘a trend’ but this is a dubious interpretation and the point is again not acknowledged in the discussion or interpretation of the results. The results for <5 years and >5 years quitters are not shown for this analysis.

Response and rebuttal: We appreciate the reviewer’s concern that smoking status after the 2018 baseline was not repeatedly observed for a sizable proportion of participants. We agree this is a relevant limitation for causal interpretation in any cohort where post-baseline behavior is not continuously measured. That said, our primary study design is a standard baseline-exposure cohort framework widely used in cancer epidemiology and risk prediction research (e.g., established lung cancer risk models such as PLCOm2012 and LLP similarly rely on baseline information to predict future risk).^{1,2} Our main inference is therefore anchored to baseline exposure classification, with appropriate discussion of residual exposure misclassification over follow-up.

In response to comments from multiple referees (Reviewer 1, 2, and 4), we additionally performed a time-updated (time-varying) sensitivity analysis in the subset of participants who underwent subsequent health screening examinations, allowing smoking and e-cigarette use status to be updated during follow-up. We emphasize that this analysis is necessarily restricted to individuals with repeat examinations, and thus may be susceptible to selection bias and immortal time bias (e.g., participants must remain event-free and engaged in screening to have updated exposure information). For this reason, we treated the time-varying analysis as a

sensitivity check rather than as a replacement for the primary baseline analysis, and we described this explicitly in the Methods and Results. Regarding the reviewer’s statement that the association was “not significant anymore” in the time-varying analysis, the point estimate for lung cancer incidence remained elevated (**aHR=1.38, 95% CI=0.98–1.98**) and was directionally consistent with the primary findings; the wider confidence interval is most plausibly explained by reduced precision due to fewer events after restricting to the repeat-exam subset and applying time-updated exposure definitions. Importantly, when using an alternative exposure definition with greater event accrual (any e-cigarette use), the association in the time-varying analysis was statistically significant (**aHR=1.57, 95% CI=1.22–2.02**), supporting that the direction and magnitude are not inconsistent with the primary results. Accordingly, our interpretation does not hinge on “trend” language; it is based on the direction and magnitude of effect estimates, the associated uncertainty, and consistency across exposure specifications.

Finally, we note that stratifying the time-varying analysis by “<5 years” versus “≥5 years” cessation at baseline is not conceptually appropriate, because cessation status and e-cigarette use are updated over time in that framework. **Baseline cessation-duration categories do not remain fixed once post-baseline changes are modeled**, and subgroup definitions would become time-dependent. If the editors consider it important, we are willing to add clarifying text to the Discussion to more explicitly describe the time-varying findings and their interpretation and limitations.

References

1. Tammemagi, MC, *et al.* Selection criteria for lung-cancer screening. *N Engl J Med* **368**, 728–736 (2013)
2. Cassidy, A., *et al.* The LLP risk model: an individual risk prediction model for lung cancer. *Br J Cancer* **98**, 270–276 (2008).

Regarding age of initiation of smoking, this is a known independent risk factor for lung cancer which can double or quadruple the risk (see <https://doi.org/10.1097/00001648-199309000-00010>). Korean smokers who use EC started to smoke earlier than other smokers ($p < 0.001$, see <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0274311>). The authors argue that the cohort is ‘contemporary’ and the legal age of purchasing cigarettes is 19, but the age restriction was implemented only in 1995 and the cohort includes people > 80 years old. The problem has not been addressed and it remains another plausible explanation of the study findings.

Response and rebuttal: We appreciate the reviewer’s point that age at smoking initiation can be an independent predictor of lung cancer risk. We also acknowledge that our nationwide cohort does not include a direct measure of age at smoking initiation, and we have further emphasized this as a limitation (i.e., potential residual confounding by unmeasured smoking-history details) in the revised Discussion.

That said, we respectfully note that the reviewer’s proposed explanation is not readily consistent with the empirical structure of our cohort. The cited evidence regarding initiation age among Korean e-cigarette users is primarily derived from samples of current smokers, which differs from our primary analytic contrast focusing on former smokers. Importantly, our multivariable models adjust for key components of cumulative smoking exposure available in this dataset (including pack-years and other smoking-history measures). Because age at initiation is strongly correlated with smoking duration and cumulative exposure, adjustment for these exposure metrics is expected to account for a substantial portion of the risk variation attributable to earlier initiation. We also note that age at smoking initiation is not uniformly included as a required covariate in widely used lung cancer risk prediction frameworks when detailed smoking history variables are available. While we cannot exclude residual confounding due to unmeasured initiation age, we believe it is unlikely to fully account for the consistent association observed across prespecified analyses and sensitivity analyses.

We respectfully submit that, in the context of a nationwide cohort with extensive adjustment for cumulative smoking exposure and consistent findings across analyses, the absence of initiation-age data should be viewed as an inherent limitation of the dataset rather than a flaw that undermines the primary inference.

There are also some additional issues that have emerged. The previous concerns about the study rigor were reinforced when it turned out that in the initial NM submission, over half of quitters for <5 years were misclassified. The finding that abstainers >5 years who vaped had a higher incidence of lung cancer death is based on 5 deaths in this group. The authors now also report changing lung cancer outcome definition from what they used in their previous report, i.e. a post-hoc modification of the primary outcome.

Response and rebuttal: We sincerely apologize for the misclassification identified in the initial submission regarding the stratification of quitters by duration of abstinence (short-term vs. long-term). We corrected this issue during the revision process and believe that transparently identifying and rectifying such errors is a central aim of revision. Importantly, this correction affected only the abstinence-duration stratification, and the primary association in the overall cohort remained materially unchanged (Figure 1). We have also ensured that the revised manuscript clearly reflects the corrected classification and corresponding results.

We also acknowledge the reviewer's concern regarding the small number of lung cancer-specific deaths among e-cigarette users after smoking cessation in subgroup analyses. This concern was also raised by Reviewer 1 and Reviewer 3. We agree that such small event counts limit statistical power and yield imprecise estimates; accordingly, we have explicitly stated in the revised Discussion that subgroup findings with sparse events should be interpreted with caution. We emphasize that lung cancer incidence is the primary and more statistically well-powered endpoint in this study, and the incidence results remain consistent across the main analysis and sensitivity analyses. This also aligns with Reviewer 2's initial comment: **"Presenting both lung cancer incidence and lung cancer deaths seems superfluous, lung cancer deaths are already included in the incidence."** We fully respect the editors' preferences; if the inclusion of lung cancer-specific death results is considered redundant, we are happy to remove these findings or move them to the Supplementary Materials, as appropriate.

Finally, regarding the comment that the lung cancer outcome definition was changed post hoc: none of the study definitions, methods, or results have been previously published as a full peer-reviewed journal article. Our earlier work on this topic was explicitly exploratory and was presented only as a conference abstract (ATS 2024). Following that preliminary presentation, we initiated a strengthened longitudinal study, including a renewed application for the NHIS

cohort data and additional follow-up time to accrue more follow-up length and improve precision. In parallel with this planned strengthening, we refined the lung cancer outcome definition by incorporating additional lung cancer–specific diagnostic codes to improve outcome validity and specificity. We respectfully submit that refining operational definitions when transitioning from exploratory analyses to a finalized nationwide longitudinal cohort study, is an appropriate practice in epidemiologic research. Importantly, the refined outcome definition was applied uniformly across the cohort and all analyses and was documented explicitly in the Methods. Accordingly, we respectfully disagree that this constitutes an ad hoc modification of the primary outcome; rather, it reflects a transparent refinement implemented as part of a prespecified strengthening of the study.

Alarming, I now also noted that the Korean NHIS questionnaire does not differentiate between heated tobacco products (HTP) and EC! The earlier study using the same data set that served as a model for this one (<https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.121.054967>) says: “the self-reported questionnaire on NNTP (noncombustible nicotine or tobacco product) use does not explicitly differentiate between HTPs (heated tobacco products) and NVPs (nicotine vapor products), but rather inquires on the frequency of NNTP use in general.” HTP were used by 4.4% of Korean adult population in 2018 (<https://pmc.ncbi.nlm.nih.gov/articles/PMC7425751/>) and it had a much higher market share than e-cigarettes (https://nosmk.khepi.or.kr/ntcc/eng/subIndex/547.do#:~:text=2017 E%2DCigarettes 0.6/Heated,Tobacco Products 17.1/ Cigarettes 82.4)). The study thus cannot be presented as a study of EC use.

Response and rebuttal: We respectfully disagree that our study “cannot be presented as a study of e-cigarette use.” The NHIS health screening questionnaire used at our 2018 baseline asked specifically about “**electronic cigarette**” use, and our exposure variable was defined directly from that item. Therefore, it is accurate to describe our exposure as **self-reported e-cigarette use as assessed by the NHIS questionnaire**.

While we respect prior NHIS-based publications, we do not consider it appropriate to adjudicate methodological choices from other studies within this rebuttal. We therefore focus

on the factual basis of our exposure definition in the NHIS instrument used for our cohort. We also note that, following the introduction of heated tobacco products (HTPs) in Korea beginning in 2017, the NHIS questionnaire later included a separate HTP-specific item from 2019 onward. Finally, it is consistent with prior NHIS-based cardiovascular publications to describe this questionnaire-derived exposure as “e-cigarette use.” For example, Kang et al. used nationwide NHIS data and reported outcomes associated with switching to e-cigarette use after percutaneous coronary intervention. If the editors consider it helpful for transparency, we are willing to include the original Korean wording of the NHIS questionnaire item in the Supplementary Materials.

Reference

Kang D et al. Prognosis after switching to electronic cigarettes following percutaneous coronary intervention: a Korean nationwide study. *Eur Heart J.* **46**, 84–95 (2025)

Reviewer #4 (Remarks to the Author):

No further comments.

We thank the reviewer for the careful and comprehensive evaluation of our manuscript and for their positive assessment. Reviewer 4’s comments were among the most detailed and constructive, and we incorporated many of their suggestions to strengthen the clarity of the methodology, the subgroup analyses, and the sensitivity analyses. We appreciate that, after these revisions, Reviewer 4 indicated that no further changes were required, which we interpret as support for the methodological rigor and scientific soundness of the revised manuscript.

Manuscript title: **Risk of Lung Cancer Associated with Electronic Cigarette Use After Smoking Cessation: A Nationwide Cohort Study**

Dear Editors:

We sincerely thank the Editors and reviewers for the time and effort devoted to the evaluation of our manuscript and for the opportunity to revise. We have addressed the Editors' and reviewers' comments and summarized these changes in our point-by-point responses. We hope that these modifications meet with your satisfaction.

Editors' Comments:

Dear Dr Kim,

Your revised Article, "Risk of Lung Cancer Associated with Electronic Cigarette Use After Smoking Cessation: A Nationwide Cohort Study" has now been seen by 2 referees. In light of their feedback, and provided that you can address their remaining concerns as well as our editorial points below, we would be happy to offer to publish your study in Nature Medicine once this next round of revision is completed.

While the adjudicating reviewer feels the study has improved, concerns remain. In your next revision, it is important that you provide context of the findings in light of the Circulation study and previous studies as well as highlight and explain in the limitations that the questionnaire is unable to distinguish between directly vaporising nicotine and heated tobacco products, as well as other technical concerns raised by reviewer 2.

Response. We thank the Editors and reviewers for the careful and comprehensive evaluation of our manuscript and for the constructive feedback. In response to the Editors' request, we have revised the Discussion to provide clearer context for our findings in relation to the Circulation study. We have also strengthened the limitations section to state explicitly that, although the 2018 NHIS questionnaire asked specifically about "electronic cigarette" use, it did not include a separate item to ascertain heated tobacco product (HTP) use in that year. We therefore acknowledge the possibility of residual misclassification between product types and discussed

that some NHIS-based publications have described the same questionnaire-derived exposure using broader umbrella terminology (e.g., noncombustible nicotine or tobacco product) rather than the direct “electronic cigarette” label. Finally, we have incorporated additional clarifying text to address other technical concerns raised by Reviewer 2 where appropriate and revised the manuscript accordingly.

Revised text in the Discussion (Page 13, Paragraph 2)

“Our study has limitations. First, we assessed e-cigarette use using available self-reported questionnaires, which may be subject to recall bias leading to potential misclassifications. Although our exposure definition is anchored to the exact wording of the 2018 NHIS questionnaire item that specifically asked about “electronic cigarette” use, the 2018 instrument did not include a separate item to ascertain heated tobacco product (HTP) use because of the very recent introduction of HTPs in Korea (commercial availability beginning in June 2017) and the absence of a standardized HTP-specific ascertainment item at that time. Accordingly, given the possibility of residual misclassification between product types, some publications appear to have described the same questionnaire-derived exposure using a broader umbrella term (e.g., noncombustible nicotine or tobacco product) rather than the direct label.⁴⁷”

Please also address the following formatting and editorial comments in your next revision:

- Please note that per Nature Medicine style, the abstract needs to be unstructured with a limit of no less than 200 words

Response. We have now condensed our abstract to be unstructured with the word count no less than 200.

- Please remove the Keywords from the title page

Response. We have removed the Keywords from the title page

- In the results, please have more concise subheadings. They must be non-declarative.

Response. We have revised our subheadings in the results to be non-declarative and more concise.

- Please remove editorialising terms/language throughout the manuscript when describing the study and findings- i.e. “first”, “novel”, “largest/most comprehensive”, “clearly”

Response. As suggested, we have editorialising terms/languages throughout the manuscript.

- Role of the funding source section must be merged with the Acknowledgements.

Response. We have merged role of the funding source within the Acknowledgements.

- Please move Figure S1 from the supplementary and relabel as “Extended Data Figure 1”. We do not allow figures in the supplementary.

Response: We thank the Editors for this instruction. Because this figure S1 directly supports the main message and we were within the allowed limit for main display items, we have moved it into the main text and relabeled it as Figure 1. We have renumbered subsequent figures accordingly and updated all in-text citations. In addition, we reviewed the remaining Supplementary materials and, where appropriate, moved tables that directly contribute to the main message into Extended Data display items, ensuring that the total number of main and Extended Data display items remains within the journal’s limits.

- Please fill out the STROBE checklist and include the relevant details.

Response. We have completed the STROBE checklist and included it with the revised submission. In the checklist, we indicate where each STROBE item is addressed in the manuscript (page numbers).

- Please provide a separate ethics section in the methods, including the consent provided by the participants, the ethics committee that approved the study and institutional review board numbers

Response: We have added a separate Ethics section at the end of the Methods, including statements on informed consent (waiver) and the approving ethics committees/Institutional Review Boards with their approval numbers.

- The current methods section is quite short. Please ensure that all of the methods are included and that there is enough detail for the readers to be able to reproduce the findings. Please provide details in the Methods section that adheres to STROBE guidelines.

Response: We thank the Editors for this request. We have expanded the Methods section (now up to 1,467 words) to include sufficient detail for readers to reproduce the analyses, and we have revised the text to align with STROBE recommendations. Key additions include clearer descriptions of the cohort selection, exposure and outcome definitions, covariates, statistical models, and sensitivity analyses.

- Any references cited only in the methods needs to be included in a separate methods-only references section and should be numbered contiguously to the main reference list (i.e. number starts at XX following on from the numbering of the main reference list, not 1).

Response: We thank the Editors for this instruction. We have added a separate Methods-only References section for citations that appear only in the Methods. These references are numbered contiguously, continuing from the last reference in the main reference.

- The Data Availability statement is very brief and not up to Nature medicine standards. Please justify why the NHIS dataset is not publicly available. You must provide more details and procedures regarding how researchers can apply for using the NHIS dataset, including timelines in which decisions will be granted upon application.

Response: We thank the Editors for this request. We have expanded the Data Availability statement to meet Nature Medicine standards by explaining why the NHIS dataset cannot be made publicly available (i.e., it contains sensitive individual-level health and claims information governed by NHIS data-use regulations and privacy protections). We also added clear instructions on how qualified researchers may apply for access through the NHIS data access process, including the required application materials, review/approval steps, and an

estimated timeline for decisions (as specified by NHIS).

Revised Data Availability statement:

“The data supporting the findings of this study are derived from the Korean National Health Insurance Service (NHIS) health screening and claims databases. Individual-level data are not publicly available because they contain sensitive personal health information and are protected under NHIS data governance and privacy regulations. For research purposes, de-identified data are accessible upon application through the NHIS Big Data Platform. Applicants are required to submit a research proposal (including study aims, cohort definition, and a data specification), documentation of Institutional Review Board approval, and other materials requested by NHIS. Applications undergo administrative and data-provision review, and access is granted only for approved variables and time periods. Approved users can analyze the data through NHIS-designated secure analysis environments. The review and approval timeline is determined by NHIS and may vary by the complexity of the requested dataset and operational demand. Decisions are typically issued after completion of the review process (often within several weeks, but potentially longer for customized datasets). Further information on eligibility, required documents, fees, and access procedures is available at: <https://nhiss.nhis.or.kr/>.”

- Please provide a code availability statement. We do not allow “code available upon request”. Please either deposit the code in a repository, such as GitHub and provide the appropriate details. Alternatively, please provide more information for readers on any restrictions to accessing the code and how the code can be accessed, including how the data can be accessed upon application, the contact details and timelines.

Response: We thank the Editors for this instruction. All analyses were performed using standard, built-in procedures in SAS and freely available open-source R packages. We did not use any proprietary/custom algorithms or non-public packages. We have added a Code Availability Statement specifying the software used and the key analytic scripts/packages, and cross-referenced the Data Availability Statement for details on how the underlying analytic datasets

can be accessed upon application and approval.

Revised Code Availability Statement:

“The statistical analyses in this paper were conducted using SAS version 9.4 with the built-in SAS/STAT procedure proc phreg. Figures were generated using R (version 4.3.3) with the open-source packages ggplot2 (version 3.5.1) and patchwork (version 1.2.0). No customized or non-public packages were used. De-identified NHIS analytic datasets are accessible upon application through the NHIS Big Data Platform, subject to NHIS approval and data extraction procedures, and can be analyzed within NHIS-designated secure analysis environments.”

- You will need to update the Reporting summary so that the Data and code availability statements match those provided in the manuscript

Response: We thank the Editors for this instruction. We have updated the Reporting Summary to ensure that the Data Availability and Code Availability statements are fully consistent with, and match exactly, the corresponding statements provided in the revised manuscript.

The article file must only contain these items in this order:

- Title
- Author List and affiliations
- Abstract
- Introduction
- Results (with Subheadings)
- Discussion
- Acknowledgements
- Author Contributions
- Competing Interests Statement
- References (for main text only)
- Figure legends (for main text only)
- Tables (note: tables should be pasted into Word files as editable tables, not as images)
- Methods

- **Data Availability Statement**
- **Code Availability Statement**
- **Methods-only References**

Response: We thank the Editors for this instruction. We have reformatted the manuscript so that the article file contains only the requested items, in the specified order (Title through Methods-only References), and we have ensured that tables are included as editable Word tables.

In addition to addressing the remaining points from the reviewers, please edit your manuscript to comply with our formatting guidelines for Articles, which are:

- * Abstract: 200 words, unreferenced.**
- * Main text: 4000 words with subheadings for the Introduction, Results and Discussion**
- * References: up to 60 in the main text + 20 methods-only references**
- * Display items: up to 6 main display items (inclusive of figures and tables) and up to 10 Extended Data display items (inclusive of figures and tables). Extended Data are an integral part of the paper and only data that directly contribute to the main message should be presented.**
- * Online Methods: no word limit; please provide the methods consolidated in a single section at the end of the main text document**

Response: We thank the Editors for this guidance. We have revised the manuscript to comply with Nature Medicine's Article formatting requirements, including an unreferenced Abstract within 200 words, a main text within 4,000 words with subheadings for the Introduction, Results, and Discussion, and reference limits (≤ 60 main-text references and ≤ 20 Methods-only references). We have also consolidated all methods into a single Online Methods section at the end of the document and adjusted the number of display items to meet the journal limits (≤ 6 main figures/tables and ≤ 10 Extended Data figures/tables), retaining only items that directly support the main message.

Response: We thank the Editors for this guidance. We have revised the manuscript to comply with Nature Medicine's Article formatting requirements. We have ensured that the word count and reference limits are met and have adjusted the number of display items to align with the journal's standards.

Reviewers' Comments:

Reviewer #1 (Remarks to the Author):

Thank you for the opportunity to review the rebuttal letter. I have carefully considered the comments raised by Reviewers, as well as the authors' detailed responses to each point. I am fully convinced by their replies and believe that all concerns have been appropriately and satisfactorily addressed.

Response. We thank the reviewer for the thorough evaluation of our manuscript and for the positive feedback. We are pleased that the reviewer found our revisions satisfactory. In particular, we appreciate the reviewer's recognition that our clarifications regarding smoking status and cessation-duration classification, e-cigarette use patterns, and the sensitivity analyses addressing post-baseline changes are methodologically sound and scientifically rigorous.

Reviewer #2 (Remarks to the Author):

I appreciate the authors' efforts to address the points raised, but the key issues remain.

There is no doubt that EC users quit smoking more recently than non-users (see the previous reviews for the explanation) and because time since quitting is a major predictor of lung cancer risk, this must have contributed to the findings. The issue also remains that Korean smokers who vape have been shown to initiate smoking earlier than non-vapers and earlier initiation of smoking dramatically increases lung cancer risk - after controlling for pack years (<https://doi.org/10.1097/00001648-199309000-00010>). Given several other issues, including the possibility of reverse causation, doubts remain whether the conclusions reliably reflect the data.

Response. We thank the reviewer for the careful and comprehensive evaluation of our manuscript. We regret that our additional analyses and clarifications did not fully address all of the reviewer's concerns. Nevertheless, we have made best efforts to respond within the constraints of the NHIS health screening data, and we have revised the manuscript to (i) strengthen analyses that are feasible with the available variables and (ii) explicitly acknowledge, as limitations, the residual sources of uncertainty that cannot be eliminated in this cohort. We

have also further tempered the language in the Discussion and Conclusions to avoid overstatement. Our conclusions are framed as an association and emphasize that post-cessation e-cigarette use may attenuate the benefits of complete smoking cessation with respect to lung cancer outcomes, while acknowledging the above limitations.

Revised text in the Discussion (Page 14, Paragraph 1):

“Second, while all analyses were comprehensively adjusted for available key covariates and included subgroup analyses by categorized duration of smoking cessation, residual confounding by unmeasured factors (e.g., exact quit-time information as a continuous measure, age at smoking initiation, emerging inhaled toxicants, environmental exposures, and socioeconomic influences) may persist. This remains an inherent limitation of the available nationwide dataset.⁴⁸”