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Reviewer A

Comment 1: Previous studies found contradict evidence on solar UVR and lung cancer (PMID:22539073, PMID:23863757 and PMID: 11920550). They may be helpful for the Introduction on reviewing the literature. However, the current manuscript did not include and discuss the literature comprehensively.

Reply 1: Sincerely thank you for your comprehensive evaluation and professional insights on our manuscript. Your comprehensive comments, as well as rigorous revision suggestions have played an important role in guiding us to revise the manuscript. According to your Comment 1, we include the literature mentioned above in order to make the Introduction more comprehensively: "Similarly, Lin SW et al (1) also found RAD was significantly associated with decreased risks of squamous cell lung cancer but no significant association with lung adenocarcinoma, and Grant WB et al (2) found there is a strong inverse correlation between lung carcinoma mortality and RAD, while Shih-Wen Lin et al (3) found a weak positive association with deaths from lung cancer, but no consensus have been reached, deep, global learning of which is scarce" **(see Page 6-7, line 113-119)**.

Changes in the text: We added some discussion about contradict conclusions of literature (1-3)mentioned in Comment 1 **(see Page 6-7, line 113-119)**.

References:

1. Lin SW, Wheeler DC, Park Y, et al. Prospective study of ultraviolet radiation exposure and risk of cancer in the United States. Int J Cancer 2012;131:E1015-23.

2. Grant WB. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. Cancer 2002;94:1867-75.

3. Lin SW, Wheeler DC, Park Y, et al. Prospective study of ultraviolet radiation exposure and mortality risk in the United States. Am J Epidemiol 2013;178:521-33.

Comment 2: Solar radiation (RAD) measured by Google Earth Engine has not been validated. I am not sure whether this measurement is related to solar UVR exposure, such as The NASA Total Ozone Mapping Spectrometer (TOMS) database or the the AVerage daily total GLObal solar radiation (AVGLO) ground-based estimates.

Reply 2: Solar radiation measured by Google Earth Engine is amount of solar radiation (also known as shortwave radiation) reaching the surface of the Earth (both direct and diffuse) minus the amount reflected by the Earth's surface (which is governed by the albedo). Radiation from the Sun (solar, or shortwave, radiation) is partly reflected back to space by clouds and particles in the atmosphere (aerosols) and some of it is absorbed. The rest is incident on the Earth's surface, where some of it is reflected. The difference between downward and reflected solar radiation is the surface net solar radiation. This variable is accumulated from the beginning of the forecast time to the end of the forecast step. The units are joules per square meter (J m-2). The ECMWF convention for vertical fluxes is positive downwards. Approximately, 50% RAD is in the visible spectral region (400- 760 nm), 7% is in ultraviolet spectral region (<400 nm), 43% is in infrared spectral region (>760 nm). In addition, the ultraviolet spectral region part is exactly solar UVR exposure mentioned in Comment 2, which could be divided into 3 more parts, long-wave UVA (320-400 nm), medium-wave UVB (280-320 nm) and short-wave UVC (200- 280 nm)(4,5). Therefore, RAD includes UVR but isn't equal to UVR. Considering that the impact of various wavelengths of light in RAD on cancer remains unclear, and that people's daily exposure to sunlight is RAD rather than just UVR, we chose RAD instead of UVR as the object in this manuscript.

Changes in the text: The description of RAD is in Methods: "We downloaded raw raster data with a resolution of 11132 meters from Google Earth Engine (https://developers.google.com/earth-engine/datasets/catalog/ECMWF_ERA5_LAND_MONTHLY)(6). The data we used were a subset of the full ERA5-Land dataset post-processed by ECMWF. ERA5-Land is a reanalysis dataset which combines model data with observations from all over the world into a globally complete and consistent dataset following the physical laws. We

chose surface net solar radiation band in this dataset as our original radiation data, which is calculated as the amount of solar radiation (also called shortwave radiation) reaching the Earth's surface (both direct and diffuse) minus the amount reflected by the surface of the Earth (which is governed by the albedo) and the units are joules per square metre (J m-2). It is noteworthy that this reanalysis data were reprocessed from the raw remote sensing data which is accurate to hours into a data with an accuracy of months and we calculated the average annual value of it. Then, we added this raw raster data as a layer on a country boundaries layer formed by a vector data. Finally, we used the country boundaries to control the raster data and calculated mean radiation value within each country boundaries as our solar radiation data distributed by countries and years (7,8)" (Page 10-11, line 192-209) and Discussion: "Thirdly, as we all know, approximately, 50% RAD is in the visible spectral region (400- 760 nm), 7% is in ultraviolet spectral region (<400 nm), 43% is in infrared spectral region (>760 nm). In addition, the ultraviolet spectral region part could be divided into 3 more parts, long-wave UVA (320-400 nm), medium-wave UVB (280-320 nm) and short-wave UVC (200- 280 nm)(4,5). In order to have deeper knowledge into which light with certain range of wavelength have the exact impact on lung cancer, separate studies for each kind of light are required" (Page 20, line 407-414).

References:

4. Hölzle E, Hönigsmann H. [UV-radiation--sources, wavelength, environment]. J Dtsch Dermatol Ges 2005;3 Suppl 2:S3-10.

5. Muhammad I. Chapter 2 - THERMAL RADIATION. In: Muhammad I, editor. An Introduction to Solar Radiation. Academic Press; 1983. p. 29-42.

6. J MS. ERA5-Land monthly averaged data from 1981 to present. Copernicus Climate Change Service (C3S) Climate Data Store (CDS). 2019. https://cds.climate.copernicus.eu/cdsapp#!/dataset/10.24381/cds.68d2bb30?tab=overview. Accessed November 15th 2021.

7. Runchen W, Qixia W, Jianfu L, et al. Light at night and lung cancer risk: A worldwide interdisciplinary and time-series study. Chinese Medical Journal Pulmonary and Critical Care Medicine 2024;2:56-62.

8. Xu Q, Zhou Q, Chen J, et al. The incidence of asthma attributable to temperature variability: An ecological study based on 1990-2019 GBD data. Sci Total Environ 2023;904:166726.

Comment 3: As smoking is the most risk factor for lung cancer, adjusting for population-level smoking prevalence rather than individual-level smoking status is open to bias when studying the association between country-level UVR exposure and lung cancer incidence. In addition, country-level UVR exposure is unlikely to be an accurate measurement.

Reply 3: Thank you for your valuable feedback. We acknowledge that adjusting for population-level smoking prevalence rather than individual-level smoking status may introduce bias when studying the association between country-level RAD exposure and lung cancer incidence. However, firstly, our choice to use age-standardized smoking prevalence data and country-level solar radiation data is based on the availability and consistency of these datasets globally. Individual-level smoking data is often incomplete and not uniformly available at the national level. By using age-standardized estimates, we mitigate the impact of age-related differences, enhancing data comparability. Secondly, our study aims to explore the environmental exposure at a country level, making national-level data suitable and relevant for our objectives. This methodological approach has been validated in numerous environmental epidemiological studies that also employ country-level data.

As for the question to country-level RAD exposure measurement accuracy, RAD is calculated as the amount of solar radiation reaching the Earth' s surface (both direct and diffuse) minus the amount reflected by the surface of the Earth and this reanalysis data was reprocessed from the raw remote sensing data which is accurate to hours into a data with an accuracy of months and we calculated the average annual value of it. Then, we added this raw raster data as a layer on a country boundaries layer formed by a vector data. Finally, we used the country boundaries to control the raster data and calculated mean radiation value within each country boundaries as our solar radiation data distributed by countries and years.

Changes in the text: The description of smoking prevalence is in Methods: "We used the age- standardized estimates of smoking tobacco use prevalence to describe smoking prevalence with an age group of 15+ years and we used age-standardized tracheal, bronchus, and lung cancer (GBD case ID: 426) incidence estimates to represent for lung cancer incidence with an age group start at 10- 14 years and end at 95+ years" (Page 9, line 169-173) and the procession of RAD data is in Methods "We chose surface net solar radiation band in this dataset as our original radiation data, which is calculated as the amount of solar radiation (also called shortwave radiation) reaching the Earth's surface (both direct and diffuse) minus the amount reflected by the surface of the Earth (which is governed by the albedo) and the units are joules per square metre (J m-2). It is noteworthy that this reanalysis data were reprocessed from the raw remote sensing data which is accurate to hours into a data with an accuracy of months and we calculated the average annual value of it. Then, we added this raw raster data as a layer on a country boundaries layer formed by a vector data. Finally, we used the country boundaries to control the raster data and calculated mean radiation value within each country boundaries as our solar radiation data distributed by countries and years (7,8)" (Page 10-11, line 198-209). We added references to prove the scientificalness of our calculation and the use of country-level data (7,8).

References:

7. Runchen W, Qixia W, Jianfu L, et al. Light at night and lung cancer risk: A worldwide interdisciplinary and time-series study. Chinese Medical Journal Pulmonary and Critical Care Medicine 2024;2:56-62.

8. Xu Q, Zhou Q, Chen J, et al. The incidence of asthma attributable to temperature variability: An ecological study based on 1990-2019 GBD data. Sci Total Environ 2023;904:166726.

Comment 4: The main results showed contradict findings (negative correlation but positive association). While positive associations (RR>1) were observed in some lag-year models, negative associations (RR<1) were observed with longer lag years. This is a complicative observation, but the author did not consider and discuss the contradict

findings.

Reply 4: Thank you for pointing out the seemingly contradictory findings in our results. The observed variations, where positive associations (RR>1) were noted in some lag-year models while negative associations (RR<1) were noted with longer lag years, indicate a complex relationship between solar radiation and lung cancer incidence over different time periods. In Figure 5, exp= 12700000 serves as a critical threshold, beyond which the association changes significantly. This may suggest a possible hysteresis effect, where the protective effects of sunlight on lung cancer may manifest differently over varying time lags. However, due to the lack of relevant research on this specific delayed protective effect of sunlight on lung cancer, further studies are necessary to understand these dynamics comprehensively. The variations observed might be due to differences in cumulative exposure, biological adaptation, or other intervening environmental or genetic factors that modulate the long-term risk. Future research should focus on these aspects to elucidate the underlying mechanisms driving these complex associations.

Changes in the text: We have added some comments about this contradictory finding and modified our text in Discussion from "However, there is no relevant research on the hysteresis of protective effects of sunlight on lung cancer, so it needs further researches." to "This may suggest a possible hysteresis effect, where the protective effects of sunlight on lung cancer may manifest differently over varying time lags. However, due to the lack of relevant research on this specific delayed protective effect of sunlight on lung cancer, further studies are necessary to understand these dynamics comprehensively. The variations observed might be due to differences in cumulative exposure, biological adaptation, or other intervening environmental or genetic factors that modulate the long-term risk. Future research should focus on these aspects to elucidate the underlying mechanisms driving these complex associations" **(see Page 18, line 356-364)**.

Comment 5: I agree solar radiation include a list of wavelength, though only UVB has been associated with vitamin D production. Little is known about the association

between vitamin D and lung cancer. Therefore, discussion on vitamin D is a bit beyond your scope.

Reply 4: Thank you for your insightful feedback. We understand that the discussion on vitamin D might seem beyond the primary scope of our study. However, the role of solar radiation, particularly UVB, in vitamin D synthesis is well-documented (9), and vitamin D has been shown to modulate the proliferation and differentiation of cancer cells (10-12), including lung cancer cells (13,14). Our inclusion of this information aims to provide a comprehensive understanding of the potential mechanisms through which solar radiation could influence lung cancer incidence. While direct evidence linking vitamin D specifically to lung cancer is limited, the biological plausibility of vitamin D's anti-carcinogenic effects supports our findings of a negative association between overall solar radiation and lung cancer incidence. We acknowledge the need for further research to elucidate these mechanisms more clearly and to confirm the potential protective effects of vitamin D in lung cancer.

Changes in the text: Related illustration is in Discussion: "Vitamin D can be synthesized in the body if there is adequate sun exposure. The work of Webb AR et al explained the mechanism of sunlight on Vitamin D absorption clearly. It said the first stage of vitamin D synthesis is the convert of the 7-dehydrocholesterol (7-DHC) to the precursor of vitamin D3 within the skin, which requires radiation of wavelengths in the UVB (280-320 nm) portion of the electromagnetic spectrum (9). Furthermore, Vitamin D and several analogs of Vitamin D have been proved to modulate proliferation and differentiation of cancer cells (10-12), which is consistent with our research results that lung cancer incidence is overall negatively associated with RAD. Vitamin D3 transform to 25-(OH)-D3 in liver and then convert to 1,25-(OH)2-D3 in kidney. And 1,25-(OH)2-D3 was proved to be significant in the inhibition of cell proliferation in the NCI-H82 and NCI-H209 small cell lung carcinoma and the EBC-1 and H520 non-small cell carcinoma cell lines (13,14)" (Page 18-19, line 370-382).

References:

9. Webb AR, Holick MF. The role of sunlight in the cutaneous production of vitamin D3. Annu Rev Nutr 1988;8:375-99.

10. Porojnicu AC, Robsahm TE, Dahlback A, et al. Seasonal and geographical variations in lung cancer prognosis in Norway. Does Vitamin D from the sun play a role? Lung Cancer 2007;55:263-70.
11. Norton R, O'Connell MA. Vitamin D: potential in the prevention and treatment of lung cancer. Anticancer Res 2012;32:211-21.
12. Muñoz A, Grant WB. Vitamin D and Cancer: An Historical Overview of the Epidemiology and Mechanisms. Nutrients 2022;14.
13. Higashimoto Y, Ohata M, Nishio K, et al. 1 alpha, 25-dihydroxyvitamin D3 and all-trans-retinoic acid inhibit the growth of a lung cancer cell line. Anticancer Res 1996;16:2653-9.
14. Güzey M, Sattler C, DeLuca HF. Combinational effects of vitamin D3 and retinoic acid (all trans and 9 cis) on proliferation, differentiation, and programmed cell death in two small cell lung carcinoma cell lines. Biochem Biophys Res Commun 1998;249:735-44.

Reviewer B

Comment 1: Sincerely thank you for your comprehensive evaluation and professional insights on our manuscript. First, the abstract need some revisions. The background needs to explain the potential clinical significance of this research focus and what the current knowledge gap is. The methods need to specify how the incidence data of lung cancer and RAD and the adjusted smoking data were obtained. The results need to describe the RAD and lung cancer incidence data. The conclusion needs more detailed comments for the public health implications of the findings.

Reply 1: Thanks for your advice. Firstly, we added the potential clinical significance of this research focus and what the current knowledge gap is in the Background of Abstract: "Recently, solar radiation (RAD) has attracted increasing attention on its effects on diseases globally. However, the association between RAD and lung cancer remains largely unknow and no consensus have been reached. The aim of this study was to

investigate the lag exposure- response of RAD on lung cancer and provide robust scientific evidence for updating prevention and treatment strategies of lung cancer" **(see Page 3, line 41-46)**.

Secondly, as for the incidence data of lung cancer and RAD and the adjusted smoking data, we directly downloaded from Google Earth Engine: https://developers.google.com/earth-engine/datasets/catalog/ECMWF_ERA5_LAND_MONTHLY (6) and Global Burden of Disease (GBD): http://ghdx.healthdata.org/gbd-2019(15), so we didn't make modifications to the original text in Methods of Abstract: "The data of RAD was obtained from Google Earth Engine, which was post- processed by European Centre for Medium- Range Weather Forecasts (ECMWF). Lung cancer incidence, smoking prevalence and socio- demographic index (SDI) were collected from Global Burden of Disease (GBD)" **(see Page 3, line 47-50).**

Thirdly, we have added description of the RAD and lung cancer incidence data in Results: "There were 204 countries and territories and selected subnational locations were estimated in GBD and radiation exposure were calculated in 272 countries and territories. After excluding missing and abnormal data, as well Kashmir and Western Sahara which were two disputed districts, 186 countries from 1992 to 2019 were included in this study" **(see Page 3, line 54-58)**. In the Conclusions of Abstract, we have added detailed comments for the public health implications of the findings: "This study shows properly exposure to sunlight is a potential approach to the prevention of lung cancer, which provides scientific support for the formulation of future health strategies" **(see Page 4, line 66-68)**.

Changes in the text: We have modified our text as advised, **see (Page 3, line 41-46), (Page 3, line 47-50), (Page 3, line 54-58) and (Page 4, line 66-68)**.

References:

6. J MS. ERA5-Land monthly averaged data from 1981 to present. Copernicus Climate Change Service (C3S) Climate Data Store (CDS). 2019. https://cds.climate.copernicus.eu/cdsapp#!/dataset/10.24381/cds.68d2bb30?tab=overview. Accessed November 15th 2021.

15. Global, regional, and national burden of respiratory tract cancers and associated risk factors from 1990 to 2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Respir Med 2021;9:1030-49.

Comment 2: Second, in the introduction of the main text, the authors need to more insights to theoretically link solar radiation and lung cancer, as well as the known environmental risk factors for lung cancer and the accumulating exposure of environmental factors. The authors also need to briefly review the analysis method of the lagged or accumulating effect of environmental factor. The last paragraph is overstated, which should be tone down.

Reply 2: Thank you for your valuable feedback. Firstly, we have added more insights to theoretically link solar radiation and lung cancer in Introduction: "According to Webb AR et al (9), Higashimoto Y et al (13), Güzey M et al (14), RAD, particularly UVB radiation (280-320 nm), initiates the first stage of vitamin D synthesis by converting 7-dehydrocholesterol (7-DHC) in the skin to the precursor of vitamin D3. The active form of vitamin D, 1,25-(OH)2-D3, has been shown to significantly inhibit cell proliferation in various lung cancer cell lines, including NCI-H82 and NCI-H209 small cell lung carcinoma and EBC-1 and H520 non-small cell carcinoma cell lines. This suggests that adequate sun exposure, facilitating vitamin D production, may have a protective effect against lung cancer by inhibiting the proliferation of cancer cells" **(see Page 6, line 105-113).**

Secondly, the known environmental risk factors for lung cancer and the accumulating exposure of environmental factors had been also added in Introduction: "Recently, in addition to widely studied high-risk factors for lung cancer such as smoking (16,17), unhealthy diet, physical inactivity (18), genetic predisposition (19,20) and hormone effect (21), increasing published research focuses on various environmental risk factors, such as atmospheric particulate matter exposure (22,23), air temperature, relative humidity (24) and wildfire Exposure (25). But there are still numerous risk factors remained to be found, for instance, solar radiation (RAD)" **(see Page 5-6, line 91-96)** and "One of the reason why the above research reached different conclusions is risk

factors may have delayed influence on disease (26), while exposure-lag-response associations reveal the duration of radiation-induced diseases onset (27)" **(see Page 7, line 121-123).**

Thirdly, we acknowledge the need to briefly review the analysis method for assessing the lagged or accumulating effects of environmental factors, we have added this content in Introduction: "Common methods to capture the temporal dynamics and cumulative effects of environmental exposures on health outcomes, providing a deeper understanding of their long-term impacts include distributed lag model (DLM) and time-series models such as autoregressive integrated moving average model (ARIMA) (28,29). However, these methods are often limited by their assumptions of linear relationships or their focus on short-term effects, making them less suitable for capturing complex, non-linear, and delayed effects of environmental exposures, which is where distributed lag non- linear model (DLNM) excels. DLNM, first introduced by Armstrong (30), allows for the consideration of both delayed effects and non-linear relationships in time series data (31), making it particularly suitable for our analysis of the lagged effects of RAD on lung cancer incidence" **(see Page 7, line 123-134).**

Lastly, we have revised the last paragraph of the Introduction to tone down the claims and reflect a more balanced perspective. We have acknowledged the pioneering aspect of our study while emphasizing the need for further research to confirm our findings and extend the methodology to other areas: "It is noteworthy that this study is the first to explore the time lag exposure-response association between radiation exposure and lung cancer on a global scale using DLNM. This research provides valuable insights into the relationship between RAD exposure and lung cancer incidence and sets a methodological example for investigating the risk factors of various diseases, though further studies are needed to confirm these findings and extend the methodology to investigate other potential risk factors for various diseases" **(see Page 8, line 151-157).**

Changes in the text: We have modified our text as advised **see (Page 6, line 105-113), (Page 5-6, line 91-96), (Page 7, line 121-123), (Page 7, line 123-134) and (Page 8, line 151-157).**

References:

9. Webb AR, Holick MF. The role of sunlight in the cutaneous production of vitamin D3. Annu Rev Nutr 1988;8:375-99.

13. Higashimoto Y, Ohata M, Nishio K, et al. 1 alpha, 25-dihydroxyvitamin D3 and all-trans-retinoic acid inhibit the growth of a lung cancer cell line. Anticancer Res 1996;16:2653-9.

14. Güzey M, Sattler C, DeLuca HF. Combinational effects of vitamin D3 and retinoic acid (all trans and 9 cis) on proliferation, differentiation, and programmed cell death in two small cell lung carcinoma cell lines. Biochem Biophys Res Commun 1998;249:735-44.

16. Smith DR, Behzadnia A, Imawana RA, et al. Exposure-lag response of smoking prevalence on lung cancer incidence using a distributed lag non-linear model. Sci Rep 2021;11:14478.

17. Deros DE, Hagerman CJ, Kramer JA, et al. Change in amount smoked and readiness to quit among patients undergoing lung cancer screening. J Thorac Dis 2021;13:4947-55.

18. Khaltaev N, Axelrod S. Global lung cancer mortality trends and lifestyle modifications: preliminary analysis. Chin Med J (Engl) 2020;133:1526-32.

19. Liang C, Pan W, Zhou Z, et al. Identification of prognostic biomarkers of smoking-related lung cancer. J Thorac Dis 2024;16:1438-49.

20. Hanash S. Lung cancer susceptibility beyond smoking history: opportunities and challenges. Transl Lung Cancer Res 2022;11:1230-2.

21. Yang Z, Wang F, Tan F, et al. Menstrual factors, reproductive history, and risk of lung cancer: a multi-center population-based cohort study in Chinese females. Transl Lung Cancer Res 2021;10:3912-28.

22. Hamra GB, Guha N, Cohen A, et al. Outdoor particulate matter exposure and lung cancer: a systematic review and meta-analysis. Environ Health Perspect 2014;122:906-11.

23. Chen Q, Wang Y, Yang L, et al. PM2.5 promotes NSCLC carcinogenesis through translationally and transcriptionally activating DLAT-mediated glycolysis reprograming. J Exp Clin Cancer Res 2022;41:229.

24. Guo H, Li X, Li W, et al. Climatic modification effects on the association between PM1 and lung cancer incidence in China. BMC Public Health 2021;21:880.
25. Zhang D, Xi Y, Boffa DJ, et al. Association of Wildfire Exposure While Recovering From Lung Cancer Surgery With Overall Survival. JAMA Oncol 2023;9:1214-20.
26. Wang Z, Peng J, Liu P, et al. Association between short-term exposure to air pollution and ischemic stroke onset: a time-stratified case-crossover analysis using a distributed lag nonlinear model in Shenzhen, China. Environ Health 2020;19:1.
27. Aßenmacher M, Kaiser JC, Zaballa I, et al. Exposure-lag-response associations between lung cancer mortality and radon exposure in German uranium miners. Radiat Environ Biophys 2019;58:321-36.
28. Ran J, Qiu H, Sun S, et al. Short-term effects of ambient benzene and TEX (toluene, ethylbenzene, and xylene combined) on cardiorespiratory mortality in Hong Kong. Environ Int 2018;117:91-8.
29. Zhang J, Nawata K. A comparative study on predicting influenza outbreaks. Biosci Trends 2017;11:533-41.
30. Armstrong B. Models for the relationship between ambient temperature and daily mortality. Epidemiology 2006;17:624-31.
31. Gasparrini A. Distributed Lag Linear and Non-Linear Models in R: The Package dlnm. J Stat Softw 2011;43:1-20.

Comment 3: Third, in the methodology, the authors need to describe how the incidence rate of lung cancer data from the GBD was obtained and how accurate of these data were. In fact, many country-specific data were not accurate and crudely estimated due to the lack of quality surveillance systems of diseases and mortality. The negative role of smoking on lung cancer is also lagged, but the authors' adjustment analysis did not consider this. The adjusting of smoking alone is not adequate since there are a variety of risk factors for lung cancer. In addition, please analyze the potential ecological fallacy of this study.

Reply 3: Thank you for your valuable feedback. Firstly, Incidence rate of lung cancer data was downloaded directly from the Global Burden of Disease (GBD) website:

http://ghdx.healthdata.org/gbd-2019. The GBD study, led by the Institute for Health Metrics and Evaluation (IHME), is the most comprehensive worldwide observational epidemiological study to date, offering a powerful resource to understand the changing health challenges facing people across the world in the 21st century. By tracking progress within and between countries, GBD provides an important tool to inform clinicians, researchers, and policymakers, promote accountability, and improve lives worldwide (32). In partnership with IHME, ***The Lancet*** has published global health estimates from the GBD study since 2010. In December 2018, the World Health Organization and IHME announced a formal partnership to collaborate and produce a single set of global health estimates, thereby strengthening the validity of the GBD and improving its policy relevance and use. Every year, these capstone papers are published in a special issue of ***The Lancet***, demonstrating the universally acknowledged accuracy of GBD data (32).

In GBD 2019, cancer incidence data were gathered from individual population-based cancer registries or aggregated databases of cancer registry data, including "Cancer Incidence in Five Continents (CI5)"(33-42), EUREG (43), and NORDCAN (44). Data were excluded if they were not representative of the coverage population (e.g., hospital-based registries), did not cover all malignant neoplasms as defined in ICD-9 (140–208) or ICD-10 (C00–C96), did not include data for both sexes and all age groups (except for pediatric cancer registries), were limited to years before 1980, or if the source did not provide details on the population covered. Preference was given to registries with national coverage over those with only local coverage, except for countries where GBD provides subnational estimates. Data input sources are available in the online GBD citation tool: http://ghdx.healthdata.org/gbd-2019. Details of the methodology of GBD 2019, processes for estimating the burden of cancers, and risk factor quantification have been presented in previous publications (15,45,46). Therefore, we have included a detailed description of how the incidence rate of lung cancer data from the GBD was obtained and discussed the accuracy of these data: "We downloaded the latest data of age-standardized smoking prevalence, lung cancer incidence and socio-demographic index (SDI) of 1992- 2019 directly from Global Burden of Disease (GBD) website:

http://ghdx.healthdata.org/gbd-2019. The GBD study, led by the Institute for Health Metrics and Evaluation (IHME), which was a comprehensive worldwide observational epidemiological study, tracked health progress within and between 204 countries and territories and selected subnational locations and offered a comprehensive annual estimation of the burden of diseases, injuries, and risk factors, providing valuable insights for clinicians, researchers, and policymakers (32)" **(see Page 9, line 161-169)** and "In GBD 2019, cancer incidence data were gathered from population-based cancer registries, including "Cancer Incidence in Five Continents (CI5)" (33-42), EUREG (43), and NORDCAN (44). Data were excluded if they were not representative, did not cover all malignant neoplasms, did not include data for both sexes and all age groups, or were limited to years before 1980. Preference was given to registries with national coverage. Methodological details of GBD 2019 have been presented in previous publications (15,45,46)" **(see Page 9, line 174-180).**

Secondly, we acknowledged that the negative role of smoking on lung cancer is also lagged. On the one hand, in our study, the distributed lag non-linear model (DLNM) we used inherently captures the lagged effects of smoking when adjusting for smoking prevalence by including it as a covariate in the model of RAD and lung cancer. This model allows us to simultaneously account for the temporal dependencies and exposure-response relationships. Therefore, the lagged effects of smoking has been already incorporated in our analysis. Our primary focus is on the lag effects of solar radiation on lung cancer incidence. On the other hand, the lagged effects of smoking on lung cancer have already been studied in the work of DR Smith et al (16), the findings of which indicating that the incidence rate ratio (IRR) for lung cancer peaks at a 6-year lag and shows a minimum at a 16-year lag. Thus, we did not separately discuss the lagged effects of smoking in our study, as this aspect is well-documented in existing literature.

Thirdly, age-standardized smoking prevalence estimates and SDI were used for models adjustment because they were considered the main risk factor for lung cancer incidence. What's more, we used age-standardized lung cancer incidence estimates to represent for lung cancer incidence with an age group start at 10- 14 years and end at

95+ years in order to control the impact of age on lung cancer. Hence we have considered the main risk factors such as smoking, SDI and age of lung cancer.

Finally, thank you for highlighting the potential ecological fallacy in our study. We acknowledge this limitation. While our study uses country-level data to explore the association between solar radiation and lung cancer incidence, this does not allow for inferences about individual-level relationships. Therefore, our findings should be interpreted with caution, and further research with individual-level data is necessary to confirm these associations. Thus, we have included a discussion of it in Discussion: "This may suggest a possible hysteresis effect, where the protective effects of sunlight on lung cancer may manifest differently over varying time lags. However, due to the lack of relevant research on this specific delayed protective effect of sunlight on lung cancer, further studies are necessary to understand these dynamics comprehensively. The variations observed might be due to differences in cumulative exposure, biological adaptation, or other intervening environmental or genetic factors that modulate the long-term risk. Future research should focus on these aspects to elucidate the underlying mechanisms driving these complex associations" **(see Page 18, line 356-364).**

Changes in the text: We have modified our text as advised **see (Page 9, line 161-169), (Page 9, line 174-180) and (Page 18, line 356-364).**

References:

15. GBD 2019 Respiratory Tract Cancers Collaborators. Global, regional, and national burden of respiratory tract cancers and associated risk factors from 1990 to 2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Respir Med 2021;9:1030-49.

16. Smith DR, Behzadnia A, Imawana RA, et al. Exposure-lag response of smoking prevalence on lung cancer incidence using a distributed lag non-linear model. Sci Rep 2021;11:14478.

32. The Lancet. https://www.thelancet.com/gbd/about. Accessed July 18th 2024.

33. Doll R, Payne P, Waterhouse J. Cancer Incidence in Five Continents I. Geneva: Union Internationale Contre le Cancer; 1966.

34. Doll R, Muir C, Waterhouse J. Cancer Incidence in Five Continents II. Geneva: Union Internationale Contre le Cancer; 1970.

35. Waterhouse J, Muir C, Correa P, et al. Cancer Incidence in Five Continents III. Lyon: IARC; 1976.

36. Waterhouse J, Muir C, Shanmugaratnam K, et al. Cancer Incidence in Five Continents IV. Lyon: IARC; 1982.

37. Muir C, Mack T, Powell J, et al. Cancer Incidence in Five Continents V. Lyon: IARC; 1987.

38. Parkin D, Muir C, Whelan S, et al. Cancer Incidence in Five Continents VI. Lyon: IARC; 1992.

39. Parkin D, Whelan S, Ferlay J, et al. Cancer Incidence in Five Continents VII. Lyon: IARC; 1997.

40. Parkin D, Whelan S, Ferlay J, et al. Cancer Incidence in Five Continents VIII. Lyon: IARC; 2002.

41. Curado M, Edwards B, Shin H, et al. Cancer Incidence in Five Continents IX. Lyon: IARC; 2007.

42. Forman D, Bray F, Brewster D, et al. Cancer Incidence in Five Continents X. Lyon: IARC; 2014.

43. Eva S-F, Mark OC, Jacques F, et al. The European Cancer Observatory: A new data resource. European Journal of Cancer 2015;51:1131-43.

44. Engholm G, Ferlay J, Christensen N, et al. NORDCAN--a Nordic tool for cancer information, planning, quality control and research. Acta Oncol 2010;49:725-36.

45. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020;396:1223-49.

46. Fitzmaurice C, Akinyemiju TF, Al Lami FH, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2016: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol 2018;4:1553-68.

Comment 4: Finally, please cite several related papers:

1. Liang C, Pan W, Zhou Z, Liu X. Identification of prognostic biomarkers of smoking-related lung cancer. J Thorac Dis 2024;16(2):1438-1449. doi: 10.21037/jtd-23-1890.

2. Hanash S. Lung cancer susceptibility beyond smoking history: opportunities and challenges. Transl Lung Cancer Res 2022;11(7):1230-1232. doi: 10.21037/tlcr-22-477.

3. Deros DE, Hagerman CJ, Kramer JA, Anderson ED, Regis S, McKee AB, McKee BJ, Stanton CA, Niaura R, Abrams DB, Ramsaier M, Fallon S, Harper H, Taylor KL. Change in amount smoked and readiness to quit among patients undergoing lung cancer screening. J Thorac Dis 2021;13(8):4947-4955. doi: 10.21037/jtd-20-3267.

4. Yang Z, Wang F, Tan F, Cao W, Xu Y, Qin C, Yu Y, Zhao L, Wen Y, Wu Z, Zheng Y, Liu Y, Yu L, Wei D, Dong D, Cao J, Zhang S, Yan S, Wang N, Liao X, Du L, Li J, Li N, Chen W, He J. Menstrual factors, reproductive history, and risk of lung cancer: a multi-center population-based cohort study in Chinese females. Transl Lung Cancer Res 2021;10(10):3912-3928. doi: 10.21037/tlcr-21-552.

Reply 4: Thank you for your valuable suggestions regarding our study. We have incorporated the references you mentioned into the manuscript to enhance the discussion on high-risk factors for lung cancer. The specific modification is as follows: "Recently, in addition to widely studied high-risk factors for lung cancer such as smoking (16,17), unhealthy diet, physical inactivity (18), genetic predisposition (19,20), and hormone effect (21), increasing published research focus on various environmental risk factors, such as..." **(see Page 5-6, line 91-94)**. These references are crucial additions to our study, enriching our understanding of high-risk factors for lung cancer. The discussions on genetic loci and genetic susceptibility in smoking-related lung cancer patients, as well as the impact of hormonal effects on lung cancer incidence, provide valuable insights. Including these references not only strengthens the background of our study but also leads to future research directions. We appreciate your recommendations and guidance. We hope these revisions make the manuscript more comprehensive and robust.

Changes in the text: We have added references mentioned above in Introduction **(see Page 5-6, line 91-94).**

References:

16. Smith DR, Behzadnia A, Imawana RA, et al. Exposure-lag response of smoking prevalence on lung cancer incidence using a distributed lag non-linear model. Sci Rep 2021;11:14478.

17. Deros DE, Hagerman CJ, Kramer JA, et al. Change in amount smoked and readiness to quit among patients undergoing lung cancer screening. J Thorac Dis 2021;13:4947-55.

18. Khaltaev N, Axelrod S. Global lung cancer mortality trends and lifestyle modifications: preliminary analysis. Chin Med J (Engl) 2020;133:1526-32.

19. Liang C, Pan W, Zhou Z, et al. Identification of prognostic biomarkers of smoking-related lung cancer. J Thorac Dis 2024;16:1438-49.

20. Hanash S. Lung cancer susceptibility beyond smoking history: opportunities and challenges. Transl Lung Cancer Res 2022;11:1230-2.

21. Yang Z, Wang F, Tan F, et al. Menstrual factors, reproductive history, and risk of lung cancer: a multi-center population-based cohort study in Chinese females. Transl Lung Cancer Res 2021;10:3912-28.