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Original Article

Light at night and lung cancer risk: A worldwide interdisciplinary and time-series study

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ABSTRACT

Background: Light at night (LAN) has become a concern in interdisciplinary research in recent years. This global interdisciplinary study aimed to explore the exposure–lag–response association between LAN exposure and lung cancer incidence.

Methods: LAN data were obtained from the Defense Meteorological Satellite Program's Operational Linescan System. Data of lung cancer incidence, socio-demographic index, and smoking prevalence of populations in 201 countries/territories from 1992 to 2018 were collected from the Global Burden of Disease Study. Spearman correlation tests and population-weighted linear regression analysis were used to evaluate the correlation between LAN exposure and lung cancer incidence. A distributed lag nonlinear model (DLNM) was used to assess the exposure–lag effects of LAN exposure on lung cancer incidence.

Results: The Spearman correlation coefficients were 0.286–0.355 and the population-weighted linear regression correlation coefficients were 0.361–0.527. After adjustment for socio-demographic index and smoking prevalence, the Spearman correlation coefficients were 0.264–0.357 and the population-weighted linear regression correlation coefficients were 0.346–0.497. In the DLNM, the maximum relative risk was 1.04 (1.02–1.06) at LAN exposure of 8.6 with a 2.6-year lag time. After adjustment for socio-demographic index and smoking prevalence, the maximum relative risk was 1.05 (1.02–1.07) at LAN exposure of 8.6 with a 2.4-year lag time.

Conclusion: High LAN exposure was associated with increased lung cancer incidence, and this effect had a specific lag period. Compared with traditional individual-level studies, this group-level study provides a novel paradigm of effective, efficient, and scalable screening for risk factors.

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Introduction

Lung cancer is one of the most common cancers and is still the leading cause of cancer mortality worldwide.[1] World Health Organization data show there were 2.2 million new cases of lung cancer and 1.8 million deaths in 2020.[2] Therefore, implementing primary and secondary prevention measures is crucial to decrease lung cancer mortality.

The most studied risk factors for lung cancer are tobacco consumption, air pollution, and occupational exposures.[3,4] Some lung cancer risk factors are still unidentified, and therefore additional studies are needed to further understand the risks for lung cancer.

Circadian rhythm is orchestrated by a master clock in the hypothalamic suprachiasmatic nucleus. Studies have shown that exposure to electric light, especially light at night (LAN), can lead directly to the disruption of endogenous circadian clocks and rhythms. Besides, as the enabler of activities or behaviors such as night shift work, LAN can also lead indirectly to circadian disruption.[5]

LAN has been associated with health problems such as obesity,[6] diabetes,[7] depression,[8,9] and cancer,[10-12] and increasing evidence has suggested that circadian disruption may impact the development and growth of tumors.[13-17] Many epidemiological studies have reported an association between high LAN levels measured from satellite imagery and increased risk for cancer, particularly breast cancer.[18] However, direct evidence linking LAN to lung cancer risk is scarce. To our knowledge, no study has examined the relationship between LAN exposure and lung cancer incidence in human populations.

The distributed lag nonlinear model (DLNM) simultaneously considers both the lagged effect of exposure factors and the nonlinear relationship between exposure and response.[19] In 2006, Armstrong[20] used the DLNM in a study of temperature–health effects for the first time. In 2010, Gasparrini et al[21] introduced a cross-basis process into the DLNM based on traditional models, such as generalized linear models and additive models. Subsequently, further optimizations of the DLNM have been performed,[22-24] and the DLNM has increasingly been used in environmental epidemiology studies.[25-28] Furthermore, the DLNM has been used extensively to investigate the relationships between risk factors and health outcomes.

The accumulated data and computational advances in the geographic information sciences have made it possible to obtain continuous high-precision remote sensing data of LAN exposure.[29-31] In addition, the cross-fertilization of geographic information sciences and the life and health sciences has made it possible to explore the correlation and lagged effect of LAN exposure on lung cancer incidence using data provided by the Global Burden of Disease (GBD) Study. These kinds of achievements were unthinkable a few years ago.

This global and interdisciplinary study aimed to explore the exposure–lag–response association between LAN exposure measured by satellite imagery and lung cancer incidence by constructing a DLNM. The results will not only help to clarify the relationship between LAN exposure and lung cancer incidence, but also provide a paradigm to investigate the risk factors of diseases such as lung cancer.

Methods

LAN

Traditionally, LAN data from the Defense Meteorological Satellite Program's (DMSP)/Operational Linescan System (OLS) have been widely used for many types of research. The DMSP, which was initiated in the 1970s by the United States Air Force, uses a sun-synchronous satellite that orbits around the Earth's poles at an altitude of 830 km. The satellite orbits the Earth once every 101 minutes, equivalent to 14 times a day, typically passing over areas for nighttime observation between 20:30 and 21:20 local time, thus providing daily global LAN data. Over time, six independent satellites in the DMSP sequence gradually shifted towards earlier transit times, transitioning from day/night orbits to dawn/dusk orbits. Therefore, DMSP/OLS has been replaced by the Visible Infrared Imaging Radiometer Suite (VIIRS), which now collects LAN data.

Consequently, to obtain temporally continuous global LAN data, it is necessary to integrate the DMSP/OLS and VIIRS data. In this study, we used the integrated data from *Li* et al,[32] which highly align with relevant socio-economic reference measures (correlation $P = 0.95$) and population distribution (correlation $P = 0.97$), and the quadratic polynomial model fit has an R^2 coefficient of determination of 0.98. Therefore, the integrated data can better support long-term time series studies based on LAN imagery and have been widely used in various fields, including the life sciences.[32-37]

In this study, we used continuous LAN data from 1992 to 2018 integrated by Li et al.[32] We downloaded raw raster data with a spatial resolution of 30 arcsec from the figshare database (https://doi.org/10.6084/m9.figshare.9828827.v2). Gray scale images ranging from 0 to 256 were used to represent the LAN exposure. All the data were double entered and checked using ArcGIS v10.7 (Esri, Redlands, CA, USA). Finally, we obtained the mean value for each country for further analysis. Additional details about the LAN data are available in Li et al.[32]

Lung cancer incidence

The data on lung cancer incidence, socio-demographic index (SDI), and smoking prevalence from 1992 to 2018 were collected from the GBD website, which provides a comprehensive annual estimation of global, regional, and national incidence and mortality for causes of death, and prevalence of exposure to several risk factors.

We used age-standardized tracheal, bronchus, and lung cancer incidence estimates to represent lung cancer incidence. Age-standardized smoking prevalence estimates and SDI were used for model adjustment in the statistical analysis. Additional details about the data are available at http://ghdx.healthdata.org/gbd-2019.

Countries and territories that lacked data on LAN, lung cancer incidence, SDI, or smoking prevalence for at least one year were excluded from this study. Kashmir and Western Sahara were excluded from this study.

Statistical analysis

No patients or other members of the public were involved in the design, conduct, reporting, or dissemination plans of this study.

Correlation between LAN and lung cancer incidence was established by calculating Spearman correlation and population-weighted linear regression coefficients. Long-term association between LAN and lung cancer was estimated by quasi-Poisson regression analysis with a DLNM. The basis matrix for the two dimensions of LAN, exposure intensity and lag time, was generated by the cross-basis function, a natural spline function with degree of freedom 3 and 15-year lag time based on the Akaike information criterion.[21]

Finally, the unadjusted DLNM was expressed as:

$$Y_t \sim \text{quasiPoission}\left(\mu_t\right)$$

$$\mu_t = \beta_0 + \beta_1 * \text{crossbasis (LAN)}$$

The adjusted DLNM was expressed as:

$$Z = \bar{Y} + \delta$$

$$Z_t \sim \text{quasiPoission}\left(\mu_t\right)$$

$$\mu_t = \beta_0 + \beta_1 * \text{crossbasis (LAN)}$$

where Y is the actual incidence of lung cancer without adjustment of SDI and smoking prevalence, Z is the actual incidence of lung cancer

with adjustment of SDI and smoking, μ is the expected number of lung cancer incidences, t is the number of observation years, δ is the residuals after regression of lung cancer incidence and adjusted factors (SDI and smoking prevalence), β_0 is the overall intercept, and β_1 is the regression coefficient for LAN.

Subgroup analysis was performed in the DLNM based on two grouping criteria: (1) developing or developed country; and (2) continent to which the countries belong.

Zone statistical analysis was performed in the Python (Python Software Foundation, Python v2.7, www.python.org) coding environment with tools provided by ArcGIS. Other statistical analyses were performed in R v4.0.5 (The R Core Team, R Foundation for Statistical Computing, Vienna, Austria) running on R Studio 1.4.1106 (R Studio Team, R Studio Inc., Boston, MA, USA) with packages dlnm, ggplot2, tidyverse, dplyr, corrplot, reshape2, readxl, and Hmisc. Statistical significance was set at two-sided $P < 0.05$.

Results

Descriptive data analysis

A total of 201 countries/regions were included in the study, after excluding 54 countries and territories because of missing data or disputes over territorial sovereignty.

The data, which include lung cancer incidence, SDI, smoking prevalence, and LAN exposure, were quantified by country/region and matched by year. In 2005, LAN exposure was highest in Singapore (57.00), Monaco (54.75), and San Marine (46.48); lung cancer incidence unadjusted for SDI and smoking was highest in Greenland (93.89 per 100,000 population), Monaco (78.17 per 100,000 population), and Hungary (61.99 per 100,000 population); and lung cancer incidence adjusted for SDI and smoking was also highest in Greenland (89.70 per 100,000 population), Monaco (76.62 per 100,000 population), and Hungary (57.81 per 100,000 population). Detailed data can be found in Supplementary Table 1.

The lung cancer incidences unadjusted and adjusted for SDI and smoking data were matched with the LAN data. The trend of LAN exposure and lung cancer incidence is shown in Fig. 1A, B, and the distribution of lung cancer incidence grouped according to LAN exposure is shown in Fig. 2A, B.

Effects of LAN on lung cancer incidence

The Spearman correlation analysis results by year are shown in Supplementary Table 2. The 1992–2018 results, including lung cancer incidence unadjusted and adjusted for SDI and smoking, were statistically significant ($P < 0.001$). For lung cancer incidence unadjusted for SDI and smoking, the highest Spearman correlation coefficient (r) was 0.355 occurring in 2010, and the lowest was 0.286 occurring in 2017. For lung cancer incidence adjusted for SDI and smoking, the highest r was 0.357 occurring in 2010, and the lowest was 0.264 occurring in 2017.

The population-weighted bubble plot of 2015 and the distribution of LAN exposure and corresponding lung cancer incidence in developed and developing countries are shown in Fig. 2C, D. LAN exposure and lung cancer incidence were lower in developing countries, unadjusted and adjusted for SDI and smoking.

The population-weighted linear regression analysis results by year are shown in Supplementary Table 3. The population-weighted linear regression analysis results for all years, including lung cancer unadjusted and adjusted for SDI and smoking, were statistically significant. For the population-weighted linear regression analysis unadjusted for SDI and smoking, the highest r was 0.527 occurring in 1992, and the lowest was 0.361 occurring in 2017. For the population-weighted linear regression analysis adjusted for SDI and smoking, the highest r was 0.497 occurring in 1998, and the lowest was 0.346 occurring in 2017.

DLNM to measure the lag effect

In the DLNM of lung cancer incidence unadjusted for SDI and smoking, the highest relative risk (RR) was 1.04 (1.02–1.06) occurring at LAN exposure = 8.6 and lag = 2.6 years, and the lowest was 0.46 (0.17–1.21) occurring at LAN exposure = 8.6 and lag = 15.0 years (Fig. 3A). In the DLNM of lung cancer incidence adjusted for SDI and smoking, the highest RR was 1.05 (1.02–1.07) occurring at LAN exposure = 8.6 and lag = 2.4 years, and the lowest was 0.41 (0.14–1.21) occurring at LAN exposure = 8.6 and lag = 15.0 years (Fig. 3B).

The subgroup analysis detected different exposure–lag–response associations in developed and developing countries, as well as in different continents. The highest RRs were 1.01 (0.95–1.08) and 1.03 (0.99–1.07) and the lowest were 0.90 (0.84–0.95) and 0.83 (0.72–0.96) in developing and developed countries, respectively. The highest RRs for the continent subgroups were 1.18 (1.03–1.34) for Asia, 1.03 (0.92–1.29) for Africa, 1.18 (1.13–1.24) for Europe, 1.19 (1.09–1.30) for North America, 1.05 (1.02–1.08) for South America, and 1.51 (1.37–1.67) for Oceania. The lowest RRs for the continent subgroups were 0.82 (0.70–0.96) for Asia, 0.91 (0.80–1.04) for Africa, 0.79 (0.75–0.85) for Europe, 0.98 (0.93–1.03) for North America, 0.69 (0.59–0.79) for South America, and 0.53 (0.44–0.64) for Oceania (Supplementary Fig. 1).

The lag–response relationship between LAN and lung cancer incidence was an approximately inverted V-shaped curve (Fig. 4A, Supplementary Fig. 2), showing the cumulative effect of LAN on lung cancer incidence adjusted for SDI and smoking, with a 15-year lag time. The positive peak value of RR appeared earlier with greater LAN exposure. The exposure–response relationship between LAN and lung cancer incidence adjusted for SDI and smoking also had an approximately inverted V-shape (Fig. 4B, Supplementary Fig. 3), and the exposure–response curves varied according to the lag period. In general, RR increased when LAN exposure was < 6 and decreased when LAN exposure was >6. The exposure–response relationship between LAN and lung cancer incidence unadjusted for SDI and smoking showed similar trends for different LAN exposure and different lag periods (Supplementary Figs. 4–5).

Discussion

To our knowledge, this study aimed to examine the exposure–lag response association between LAN exposure measured by satellite imagery and lung cancer incidence globally in humans. The DLNM framework was used to explore exposure–lag–response associations between LAN and lung cancer incidence with the complex pattern of potentially nonlinear and delayed associations. Al-Naggar et al[38] concluded that artificial LAN was significantly correlated with lung cancer incidence; however, the measurement methods for LAN need to be updated, and further studies are needed to explore the exposure–lag–response associations between LAN and lung cancer.

The results from the Spearman correlation tests and population-weighted linear regression analysis showed a correlation between LAN exposure and lung cancer incidence, supporting the hypothesis that LAN exposure might be a potential risk factor for cancer incidence. The DLNM analysis showed complex nonlinear relationships between LAN and lung cancer incidence. Increases in LAN exposure might be expected to increase the RR above 1 to form a peak in the lag response curve, followed by a decline towards the end of the lag period. However, unexpectedly, the RR decreased with increases in LAN exposure in the later lag times. This pattern may be explained by the harvesting paradox[39] whereby the initial risk is partly discounted by the depletion of the pool of susceptible individuals after an extreme LAN event. Under the premise of harvesting, the observed population becomes “healthier” than the counterfactual population after a series of LAN days because of depletion of the susceptible pool. This premise emphasizes that harvesting should not be interpreted as a true protective association at longer lags but rather as an artifact due to a change in the underlying population following stress, which affects the counterfactual condition.

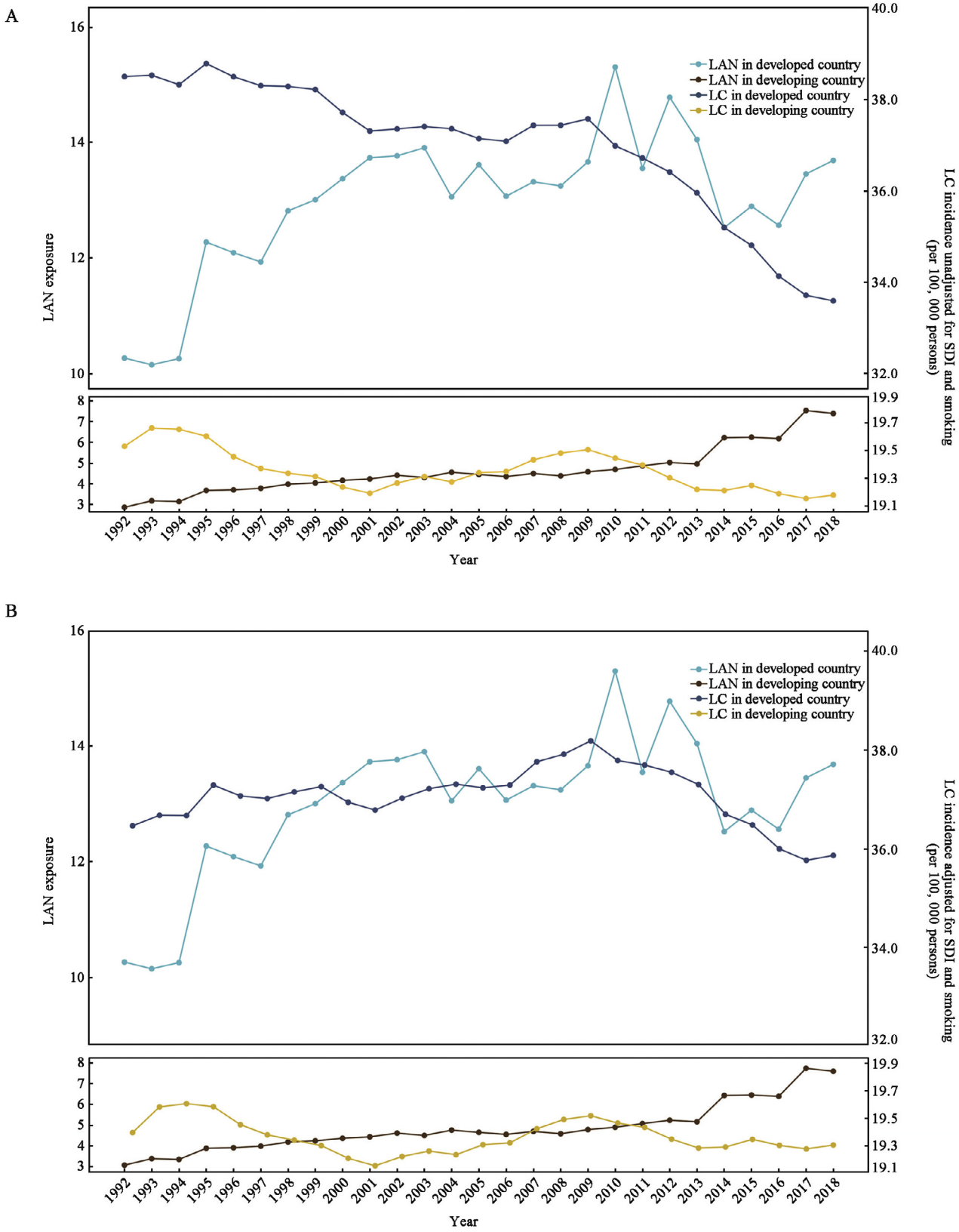

Fig. 1. (A) Lung cancer incidence unadjusted for SDI and smoking and LAN exposure by year in developing and developed countries. (B) Lung cancer incidence adjusted for SDI and smoking and LAN exposure by year in developing and developed countries. LAN: Light at night; LC: Lung cancer; SDI: Socio-demographic index.

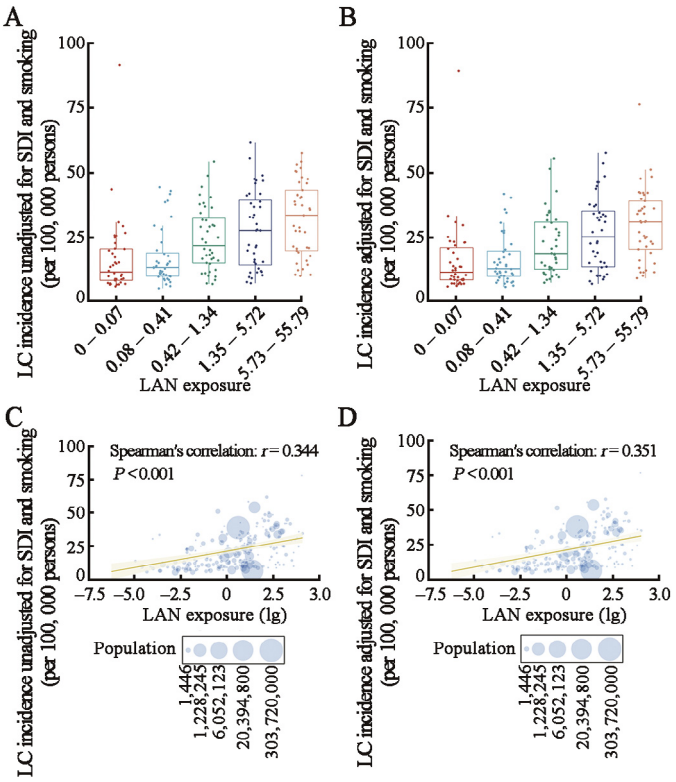

Fig. 2. (A) Trend graph of LAN exposure and lung cancer incidence unadjusted for SDI and smoking in 2005. (B) Trend graph of LAN exposure and lung cancer incidence adjusted for SDI and smoking in 2005. (C) Scatterplot showing the correlation between LAN exposure and lung cancer incidence unadjusted for SDI and smoking in 2005. (D) Scatterplot showing the correlation between LAN exposure and lung cancer incidence adjusted for SDI and smoking in 2005. *n*=201 LAN: Light at night; LC: Lung cancer; SDI: Socio-demographic index.

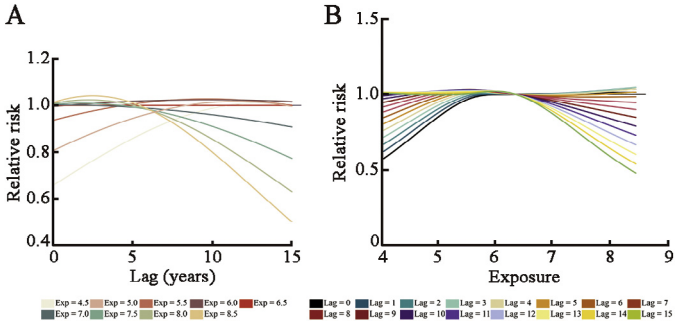

Fig. 4. (A) Cumulative lag–response curve of lung cancer incidence adjusted for SDI and smoking under different LAN exposures. (B) Cumulative exposure–response curve of lung cancer incidence adjusted for SDI and smoking in different lag years. LAN: Light at night; SDI: Socio-demographic index.

Artificial LAN has greatly benefited societies by allowing people to drive, walk, bike, jog, work, and study at night.[40] However, the potential disruptive effect of LAN on human circadian rhythms has become a public health concern. Exposure to LAN can lead to various pathological changes, such as sleep deprivation, circadian rhythm disruption, and nocturnal melatonin suppression, potentially resulting in adverse health outcomes. A cohort study in Finland found that sleep deprivation (<7–7.5 h) significantly increased lung cancer risk after adjustments for age, examination years, cumulative smoking history, family cancer history, and Human Population Laboratory Depression Scale scores.[41] Additionally, similar to sleep deprivation, night shift work is classified as "probably carcinogenic to humans" by the International Agency for Research on Cancer (IARC).[42] A large cohort study among female nurses in the United States found that extended periods of night shift work increased the risk of lung cancer among smokers.[43]

Melatonin is a robust marker of circadian rhythmicity. In the absence of LAN, melatonin levels in the blood, cerebral spinal fluid, and saliva are normally high during the darkness of night.[5] The nighttime circadian melatonin signal is known to exert a suppressive role in various cancers.[44,45] Melatonin can scavenge oxygen free radicals and activate antioxidant enzymes,[46,47] and as an immunomodulator, melatonin can stimulate the immune response, which plays an important inhibitory role in tumor immune escape.[48,49] Therefore, a reduction in melatonin levels may weaken the body's anti-cancer ability and increase cancer incidence. Previous animal experiments have supported the relationship between melatonin and various types of tumors, including the inhibition of melatonin levels in lung cancer.[50] Similarly, in animal experiments, disruption of the circadian rhythm in rats was found to stimulate the growth of lung tumors.[51] A study showed that patients with non-small cell lung cancer had lower melatonin levels than healthy subjects.[52] A

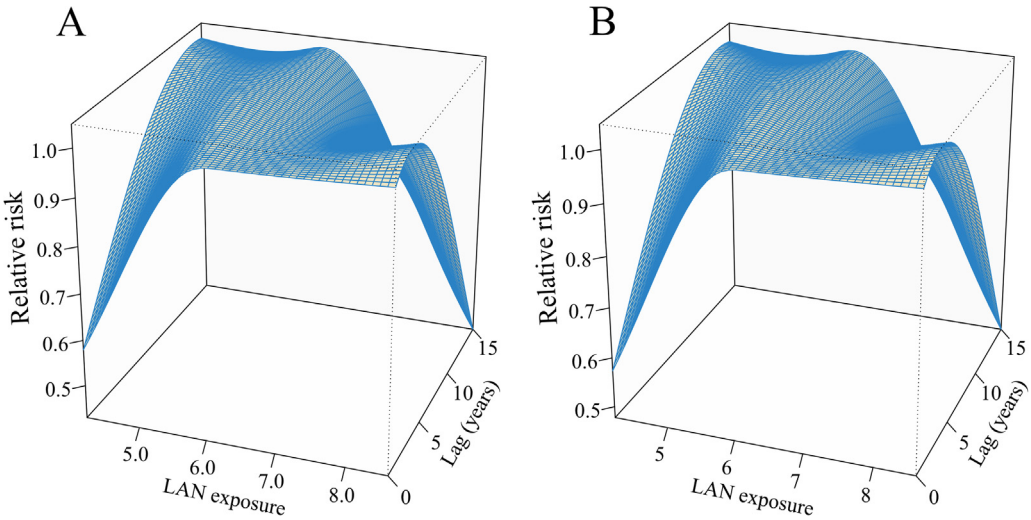

Fig. 3. (A) Three-dimensional plots of relative risks of LAN for lung cancer incidence unadjusted for SDI and smoking. (B) Three-dimensional plots of relative risks of LAN for lung cancer incidence adjusted for SDI and smoking. LAN: Light at night; SDI: Socio-demographic index.

dysfunctional biological clock was found to easily lead to uncontrolled growth and division of cells related to lung carcinogenesis.[53] Papagiannakopoulos et al[16] demonstrated that mutations in the circadian clock machinery minimized survival and encouraged lung cancer growth and development using a lung adenocarcinoma animal model. Genes related to the circadian clock were found to be lowly expressed in patients with cancer.[54] Shilts et al[55] found that the clock-robust signature was more perturbed in tumor samples than it was in normal samples. Existing evidence indicates that disruption of the circadian rhythm and melatonin suppression caused by LAN exposure may be a mechanism for the increased risk of lung cancer. Overall, the current knowledge of sleep deprivation, circadian rhythm disruption, and nocturnal melatonin suppression mechanisms strongly suggests they are associated with LAN and lung cancer.

Our study has many strengths. Using the detailed and objective measurements of LAN from satellites and the latest data from the 2019 GBD study, we investigated the relationship between LAN and lung cancer incidence globally. This study aimed to explore the risk factors of cancer by combining continuous high-precision remote sensing data and cancer data from GBD on a global scale. This approach provides a new paradigm for the exploration of other unknown or uncertain high-risk factors.

Compared with traditional cohort studies or questionnaire-based surveys, our study provides a new paradigm for quick and mass screening for potential risk factors, which has lower costs and is less time consuming. The current standard methods used to explore risk factors, cohort- or case-control studies, require a large workload and financial capacity for participant enrolment and data collection via questionnaires. In traditional individual-level studies, candidate risk factors are predesigned and fixed, thus lacking generalizability. In contrast, this group-level study effectively, efficiently, and scalably screened suspected risk factors by correlating risk factor exposure and disease incidence. Significant findings can provide a source for designing new individual-based studies. This study provides a new approach for analyzing and identifying potential risk factors recommended by experts in a short time with low costs, which will not only greatly ease the financial and budgetary pressures faced by countries and organizations, but will also help policy makers make quick decisions. Previous research has demonstrated that night shifts are a risk factor for various types of cancer, such as breast cancer, which has fewer exogenous risk factors than other cancers. These findings also underscore the role of LAN in causing adverse health outcomes.[56,57]

Our study also has limitations. First, the estimation of LAN was based on satellite imagery, which measures only the level of outdoor LAN. We did not have information on indoor LAN levels or on important factors influencing LAN exposure, such as nighttime activities, sleep schedules, window treatments, and illumination at home. Therefore, our LAN measurement serves only as a proxy measure of actual exposure to LAN. Second, we did not consider the properties of LAN, such as the light spectrum, and excessive blue light irradiation is known to be more likely to cause melatonin decline and be related to lung cancer risk.[46,47] Third, we did not have measures of biomarkers such as melatonin or other markers of the internal circadian rhythm. Therefore, the role of circadian disruption in the observed relationship between LAN and lung cancer incidence could not be assessed. Fourth, the limited data of lung cancer incidence prevented us from conducting the study at a smaller scale (city/region), which may lead to ecological fallacy. Fifth, although the DLNM has been used in studies of long-term effects,[58] it should still be used with caution. Last, despite our efforts to control for confounding factors such as smoking prevalence, SDI, and age standardization when collecting the lung cancer incidence data, as well as using the updated methods for collecting and processing LAN data and further filtering out outliers and potential confounders, there may still be residual confounding factors that could introduce bias. Therefore, in future research, more factors including gender, race, Townsend Deprivation Index, educational level, and dietary patterns should be taken into account.

More prospective studies are needed to validate our findings and further investigate the mechanisms underlying the associations between LAN exposure, sleep deprivation, circadian rhythm disruption, nocturnal melatonin suppression, and lung cancer.

In conclusion, this study shows that high exposure to LAN was a risk factor for lung cancer incidence globally, and the real effect was in certain lag years. A new paradigm was identified in the exploration of cancer risk factors, which provides a cost-effective way to screen additional potential risk factors. Further studies are warranted to confirm our results and fully clarify the mechanisms between LAN and lung cancer incidence.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Availability of data and material

Satellite data can be obtained from https://doi.org/10.6084/m9.figshare.9828827.v2.

Data of lung cancer incidence, smoking prevalence, and SDI can be obtained from http://ghdx.healthdata.org/gbd-2019.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pccm.2024.02.004.

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