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Outdoor Exposure to Artificial Light at Night and Breast Cancer Risk: A Case–Control Study Nested in the E3N-Generations Cohort

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Background: Exposure to light at night (LAN), particularly blue light, is suspected to disrupt circadian rhythm, inhibit melatonin production, and eventually increase the risk of breast cancer.

Objectives: We assessed the association between exposure to outdoor LAN and breast cancer risk in the E3N-Generations cohort, a large population-based cohort study of French women followed-up from 1990 to 2011.

Methods: We conducted a nested case–control study in the cohort, including 5,222 incident breast cancer cases and 5,222 matched controls. Outdoor LAN exposure at residential addresses was assessed using radiance-calibrated satellite images from the Defense Meteorological Satellite Program (DMSP). Logistic regression models were used to obtain odds ratios (OR) and 95% confidence intervals (CIs), adjusting for socio-demographic, reproductive, hormonal, and lifestyle-related factors, as well as exposure to air pollutants (NO_2, $PM_{2.5}$) evaluated from land use regression and chemistry-transport models, and proximity to greenspaces estimated from the Normalized Difference Vegetation Index (NDVI) in a buffer of 300 m.

Results: Before adjustment for environmental covariates, the ORs associated for LAN exposure increased monotonically from the first to the fourth quartile. This increasing trend was less pronounced after adjustment for air pollutants (NO_2 and $PM_{2.5}$) and NDVI, but the fully adjusted OR per interquartile range (IQR) of LAN exposure (261 $nW/cm^2/sr$) remained slightly elevated [$OR_{IQR} = 1.11$; 95% confidence interval (CI): 1.02, 1.20]. The adjusted ORs were slightly more elevated in postmenopausal ($OR_{IQR} = 1.10$; 95% CI: 1.02, 1.18) than in premenopausal women and in women living in urban areas with low greenness.

Conclusion: The weak positive associations observed in this study that persist after adjustment for environmental covariates, support the hypothesis that outdoor LAN may increase breast cancer risk. Our results, suggesting that urban greenness could mitigate the role of LAN exposure in breast cancer risk, should be investigated further. Future studies on cancer risk in relation to outdoor LAN should assess exposure to indoor sources, including electronic devices, and characterize the light spectrum, particularly the blue light. https://doi.org/10.1289/EHP15105

Introduction

Artificial light has become omnipresent in the modern world, and the extensive use of electric light has resulted in artificial light emerging as one of the fastest-growing environmental pollutants.[1] According to the recent atlas of the night sky, light emission is growing globally at the rate of 2% annually,[2] with more than 80% of the world's population living under light-polluted night sky.[3,4] Exposure to high levels of artificial light at night (LAN) has been associated with several adverse health effects such as cardiovascular diseases, cancers, metabolic disorders, impaired sleep, and depression.[5]

Exposure to LAN may disrupt normal circadian functioning and affect the nocturnal secretion of melatonin, metabolic functions, sleep–wake patterns, or cell-cycle regulation. Melatonin, a hormone produced by the pineal gland in the dark phase of the 24-h cycle,[6] suppresses estrogen levels and promotes antioxidant, apoptotic, and antiproliferative effects on cancerous cells.[7] It has been hypothesized that circadian disruptions and the subsequent impairment of physiological functions like melatonin suppression, are implicated in carcinogenesis, particularly hormone-dependent cancers such as breast cancer.[6,8]

In 2007, the International Agency for Research on Cancer (IARC) classified "shift work involving circadian disruption" as probably carcinogenic (Group 2A) and reaffirmed this classification in 2019, highlighting a consistent association with breast cancer.[9,10] The hypothesized link between breast cancer and exposure to indoor LAN during night shifts attributed to disruptions in circadian rhythms[5] and the suppression of melatonin secretion and its oncostatic effects[11] add plausibility to the association of outdoor exposure to LAN and breast cancer risk. Although the IARC classification was primarily focused on occupational exposure to LAN at night-shift work, understanding the environmental exposure to LAN and its potential carcinogenic effects remains limited because the current literature provides conflicting results.

Breast cancer, the most frequently diagnosed cancer and the leading cause of cancer-related deaths among women,[12] is observed to have higher incidences in geographic regions with elevated levels of light pollution[13–16] as ascertained through nighttime satellite photometry data. Previously conducted studies using satellite-based images to assess the visible range of light (350–600 nm) observed a link between outdoor LAN exposure and increased breast cancer risk,[17–21] whereas some reported no association.[22–25] The MCC-Spain case–control study[18] demonstrated that breast cancer had a notably positive association with the Melatonin Suppression Index (MSI), an indicator of blue light exposure ($\sim$480 nm).[26]

The relationship between breast cancer risk and outdoor exposure to LAN is inherently complex, given the concurrent presence

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of various urban environmental exposures such as air pollution, noise pollution, and proximity to green spaces.[27] Previous epidemiological studies have provided conflicting results. The studies reporting a positive association between outdoor LAN exposure and breast cancer risk[18–21] are limited by their inability to account for these environmental covariates, whereas two cohort studies[22,25] that adjusted for these environmental covariates reported null association. This divergence in results from previous studies underscores the need to carefully account for the effect of these environmental covariates to study the association of outdoor LAN with breast cancer risk. There is substantial evidence that exposure to road traffic–related air pollution[28] or noise pollution[29] may increase the risk of breast cancer. Moreover, proximity to greenspaces is hypothesized to be protective against breast cancer risk, although the underlying mechanism remains poorly understood.[30] In addition, measures of the association between LAN and breast cancer may also be influenced by socioeconomic disparities.[16] Given the conflicting evidence for the link between outdoor LAN and breast cancer, new large-scale studies with detailed exposure data are needed to disentangle the intricate effects of LAN from those of environmental and other factors. In this study, we examined the role of LAN on breast cancer by carefully controlling for potential confounders, including air pollution and residential greenness, using data from a large case–control study nested within the E3N-Generations cohort.

Methods

The E3N-Generations Cohort Study

We conducted a case–control study nested in the E3N-Generations cohort, a national prospective cohort in France established to investigate risk factors for cancer and other chronic diseases in women. Details of the cohort can be found elsewhere.[31] Participants were women 40–65 y of age who were recruited between June 1990 and November 1991 from members of the *Mutuelle Générale de l'Éducation Nationale* (MGEN), a national health insurance plan that mainly covers teachers. The women lived in one of France's 94 metropolitan departments, excluding Corsica. A department is an administrative area with an average population of half a million people, consisting of a capital city, suburbs, secondary cities, and rural areas, providing a large diversity of residential situations.[32] Of the 500,000 women contacted, 98,995 agreed to participate by completing a self-administered questionnaire on lifestyle and reproductive factors, anthropometry, medical history, and family history of cancer. Follow-up questionnaires were sent by postal mail every 2–3 y, and blood samples were taken from $\sim 25\%$ of the cohort members between 1994 and 1999. Each follow-up questionnaire collected information on the occurrence of breast or other cancers and the reasons for any hospitalization or medical care at home, specifying the month and year of each event. A copy of the pathology report or any medical examination confirming the diagnosis of breast cancer was requested from the patient or the physician. Tumor characteristics, including histological type and hormone receptor status, were extracted from these reports.[33]

Identification of Breast Cancer Cases

A total of 6,540 breast cancer diagnoses were self-reported or identified by linkage with the National Service on Causes of Death in $\sim 1\%$ of the cases. After reviewing the medical reports, 242 women were excluded from the case group because the self-reported disease was not a breast cancer or was not an incident primary breast cancer. Nineteen cases with phyllodes tumor or Paget's disease were also excluded. Of the remaining 6,279 self-reported cases, the diagnosis of incident primary breast cancer was confirmed in 6,010 (95.7%), but a medical report confirming the diagnosis could not be obtained in 269 (4.3%). Because the diagnosis of primary breast cancer was most likely in these 269 women, they were not excluded from the case group.

The Nested Case–Control Study

The case–control study nested in the E3N-Generations cohort involved the 6,279 incident cases of primary invasive breast cancer diagnosed between date of enrollment in the cohort and December 2011.[34] Each case was individually matched to one control randomly selected from women with no previous cancer at the case's date of diagnosis. Matching was based on age (± 1 y), French department of residence (94 departments in mainland France, excluding Corsica), date, and menopausal status at the time of blood collection (± 3 months) for the 25% subset of women with a blood sample or at the time of enrollment in the cohort for other women. Women with missing data on matching variables and their pair (three pairs) and those with missing information on residential address or having resided outside mainland France during follow-up (1,054 pairs) were excluded, leaving 5,222 breast cancer cases and 5,222 controls in the analysis.

The study was approved by the French National Commission for Data Protection and Privacy (CNIL). A written informed consent was obtained from all study participants.

Geocoding of the Residential History

The residential history of the women collected in the follow-up questionnaires was geocoded using the ArcGIS Software [ArcGIS Locator; version 10.0; Environmental System Research Institute (ESRI)] and the address database, BD Adresse, from the National Geographic Institute. Detailed methods of address management and the geocoding process have been described elsewhere.[33,35]

Outdoor LAN Exposure Assessment

Outdoor exposure to LAN was assessed at each address occupied by women from their inclusion in the cohort to the date of diagnosis by using satellite images of the Operational Linescan System (OLS) available in the Defense Meteorological Satellite Program (DMSP) of the US National Oceanic and Atmospheric Administration (NOAA).[36] We used the Radiance Calibrated Nighttime Lights products, which are high-dynamic-range images that provide annual composites of the nighttime illuminance after removing luminance from the sun and moon, cloud coverage, atmospheric lighting, and ephemeral events such as fires. The processed images have a spatial resolution of a 30-arc second grid ($\sim 650 \times 650$ m).[37] The illuminance was measured in nanowatts per square centimeter per steradian ($\mathrm{nW/cm^2/sr}$). The radiance-calibrated images were available for the years 1996 (16 March 1996–12 February 1997), 1999 (19 January–11 December 1999), 2000 (3 January–29 December 2000), 2003 (30 December 2002–27 November 2003), 2004 (18 January–16 December 2004), 2006 (28 November 2005–24 December 2006), 2010 (11 January–9 December 2010), and 2011 (11 January–31 July 2011). For the years when the DMSP images were unavailable, the values from the closest year were applied. The 1996 image was used for 1990 to 1997 (with an assumption that the street lighting remained unchanged during this period); the 1999 image was applied to 1998; the 2003 image was used for 2002; the 2006 image was applied to 2005, 2007, and 2008; and the 2010 image was applied to 2009. These images were cross-referenced with geocoded locations of each residential address in a geographic information system (GIS) software ArcGis Pro 3.0, which provided the luminosity value at each geocoded residential address.

Exposure to outdoor LAN was assessed annually from inclusion in the cohort until the date of diagnosis of the matched case–control pair. Several exposure metrics were considered in the analysis, including exposure to LAN at inclusion, exposure to LAN at diagnosis, and average exposure to LAN from inclusion to diagnosis. Because DMSP data were unavailable before 1990, the average exposure to LAN from inclusion to diagnosis was calculated over 1–21 y, depending on the length of follow-up before diagnosis. To avoid heterogeneous exposure assessment duration across study subjects, we also calculated the average LAN exposure in the last 5 y before diagnosis restricted to participants with at least 5 y of follow-up ($n = 9{,}182$) and the average LAN exposure in the last 10 y before diagnosis restricted to participants with at least 10 y of follow-up ($n = 6{,}781$). We found that LAN exposure at diagnosis was strongly correlated with the average LAN exposure from inclusion to diagnosis ($r = 0.91$) and with the average LAN exposure in the last 5 y ($r = 0.97$) and the last 10 y ($r = 0.99$) before diagnosis, whereas the correlation was weaker with LAN exposure at inclusion ($r = 0.68$) (see Table S1). Therefore, LAN exposure at diagnosis was considered as an appropriate proxy for past exposure and was selected as the primary exposure metric in the analysis. This selection ensured homogeneity in exposure assessment across study participants and avoided loss of sample size. Sensitivity analyses using alternative exposure metrics were conducted separately.

Covariate Assessment

Information on potential breast cancer risk factors was obtained from the self-administered questionnaires at inclusion and every 2–3 y during follow-up. Age at first full-term pregnancy, breastfeeding, family history of breast cancer, and education level were collected at inclusion and were used in the analyses because no change was expected to occur during follow-up. Information on other covariates such as body mass index (BMI), alcohol consumption, smoking, oral contraceptive use, menopausal status, and menopausal hormonal therapy use was collected regularly during follow-up. For the analyses, we used information on these covariates that was available in the last follow-up questionnaire dating back at least 1 y prior to diagnosis.

Exposure to air pollution was assessed as average annual exposure to nitrogen dioxide (NO_2), particulate matter (PM) with an aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$), and PM with an aerodynamic diameter ≤ 10 μm (PM_{10}) at the participants' residential addresses from 1990 through 2011, the detailed methods being described elsewhere.[38] In brief, exposure to the air pollutants was estimated using a land use regression (LUR) model and a chemistry-transport model (CHIMERE) with a resolution of 50 m. Baseline LUR models demonstrated robust performance, with CV-R^2 values of 0.69 for NO_2, 0.56 for $PM_{2.5}$, and 0.66 for PM_{10}. Our analyses used mean annual NO_2, $PM_{2.5}$, and PM_{10} concentration estimates ($\mu g/m^3$) at the residential address for the year of diagnosis.

Residential greenness was assessed using the Normalized Difference Vegetation Index (NDVI), a unitless indicator that assesses vegetation functioning by comparing the values of absorptions and reflection of red to near-infrared parts of electromagnetic radiations.[39] The values of NDVI range from -1 to $+1$, where values closer to -1 indicate water bodies, and values closer to 0 indicate total urban spaces comprising roads, ground, stones, pavements, and buildings, whereas values closer to $+1$ indicate a healthy and higher density of plants and vegetation. NDVI was calculated using the images from the Landsat 5 satellite with a spatial resolution of ~ 30 m.[40] To limit problems of cloud cover over the territory, we used the images from 1 May to 31 July, which is the period with the highest vegetation activity and lowest cloud coverage interference.[41,42] We retrieved images for 4 reference years—1990, 2000, 2005, and 2010—from the Landsat satellites.[43] For the year 1990, we used data from 1990 and 1991; for 1995, we used the data from 1995 and 1996; for 2000, we used data from 3 y (1999, 2000 and 2001) because of the cloud coverage issues; for 2005 we used the data from 2005 and 2006. Then, the image of 1990 was assigned to the geocoded locations for the years 1990–1993, the image of 1995 was assigned to the years 1994–1998, the image of the year 2000 was assigned to the years 1999–2003, the image of 2005 was assigned to the years 2004–2008, and the image of 2010 was assigned to the years 2009–2011. For our analyses, we used the mean values of NDVI within the 300-m buffer around the residential addresses of women at the year of diagnosis.

We developed a variable called "urban greenness," based on the NDVI value among urban residents. Study subjects were classified as residing in urban or rural areas using the urban–rural classification of residential addresses at diagnosis given by the *Institut national de la statistique et des études économiques* (INSEE) for all geographical units in France.[44] Urban greenness was used to characterize the presence of greenness around the residence in the form of parks, gardens, or other vegetations in urban areas and was therefore defined for nonrural residents only. In the analyses, urban greenness was used as a dichotomous variable classifying urban residents into high or low greenness using median NDVI among urban resident controls as a cutoff.

Socioeconomic status (SES) was assessed at the individual level using educational attainment at inclusion in the cohort and at neighborhood level using the deprivation index, Fdep. Fdep is a composite index created using population census data from 1999 and household income data from 2001, detailed methods being described elsewhere.[45] In brief, this index is built using information on median household income, percentage of high school graduates, percentage of blue-collar workers, and unemployment rate in each commune, which is the smallest administrative unit in France.[45] Positive values of Fdep indicate lower SES, and negative values indicate higher SES. In our study, the Fdep values were based on the residential addresses at inclusion in the cohort.

Statistical Analyses

The descriptive characteristics between the cases and controls were compared using chi-square tests for categorical variables and Wilcoxon signed-rank tests for continuous variables. Pearson correlation coefficient was used to assess the correlation between different exposure metrics and environmental covariates. Conditional logistic regression models were used to calculate the odds ratios (ORs) of association between exposure to outdoor LAN and breast cancer accounting for the 1:1 matched pair of cases and controls. The models were conditioned on the matching factors: age; date; department of residence; menopausal status at blood collection or inclusion, as explained above; and availability of blood samples. ORs with 95% confidence intervals (CIs) were calculated for higher quartiles (Q) of LAN exposure (Q2, Q3, and Q4) with reference to Q1. We also conducted continuous analyses for one interquartile range increase in LAN exposure [interquartile range (IQR) $= 216.26\ nW/cm^2/sr$ based on the distribution among controls], because the test for nonlinearity using cubic splines did not demonstrate a significant departure from linearity (results not reported). To test for potential dose–response relationships between outdoor LAN and breast cancer risk across the quartiles of outdoor LAN, we performed test for trends by using the median value of each quartile as the continuous term in the models.[46] The minimal adjustment sets for the multivariable models were identified from a directed acyclic graph (DAG)[47] (see Figure S1). In the main analyses, along with the covariates identified through the DAG including the well-established hormonal and reproductive

risk factors for breast cancer,[12] other covariates such as education, deprivation index, and residential greenness were also used to acknowledge their effect on the outdoor LAN and breast cancer risk association.

Model 1 was adjusted for age at diagnosis (continuous). Model 2 was adjusted for parity and age at first full-term pregnancy (no children, 0–2 children, and <30 y of age; 0–2 children, and ≥30 y of age; and >30 y of age), breastfeeding (ever, never, missing), history of breast cancer among first-degree relatives at (yes, no), oral contraceptive pills use (ever, never, missing), menopausal status and use menopausal hormonal therapy (MHT) (premenopausal, postmenopausal with never use of MHT, postmenopausal with ever use of MHT), BMI (<18.5 kg/m^2, 18.5–24.9 kg/m^2, 25–29.9 kg/m^2, ≥30 kg/m^2), alcohol consumption (nondrinkers, <10 g/d, ≥10 g/d, missing), tobacco smoking (nonsmokers, current smokers, former smokers), education (≤secondary, 1- to 2-y university degree, ≥3-y university degree) and deprivation index (continuous). To examine the effect of the co-occurring environmental exposures, we further added to Model 2 air pollution (NO_2 or $PM_{2.5}$ in continuous form) or residential greenness (NDVI in a 300-m buffer in continuous form), separately first and then simultaneously. Missing values of <5% were replaced with median values for continuous variables and with modal values for categorical variables, and more than 5% of missing values for any categorical variables were included as a separate category.

We studied the risk of breast cancer associated with outdoor LAN exposure according to menopausal status by introducing an interaction term between outdoor LAN (in continuous form) and menopausal status (in categories) into the model. Considering the naturally elevated NDVI in rural areas, we investigated urban greenness as a potential modifier of breast cancer risk in urban residents only. We also tested interaction between LAN (in continuous form) and each air pollutant (in categories based on the median values) restricted to urban residents. All interaction analyses were conducted using unconditional logistic regression models adjusting for all the matching factors (age, menopausal status at inclusion, and department of residence at inclusion) and covariates described in Model 1.

Subgroup analyses were conducted for different hormone receptor statuses of the breast tumors: estrogen receptor (ER) positive, ER negative, progesterone receptor (PR) positive, PR negative, hormone receptor negative (ER− and PR−), and hormone receptor positive (ER+ or PR+).

Sensitivity analyses were conducted using the LAN exposure at inclusion and average LAN exposure from inclusion to diagnosis for all women, as well as average LAN exposure during the 5 and 10 y before diagnosis, restricted to women with at least 5 and 10 y of exposure information, respectively. Conditional logistic regression models were employed, using the same set of covariates as those in the main analyses. We also conducted sensitivity analyses to explore the potential link between residential greenness and breast cancer risk using conditional logistic regression and adjusting for reproductive, hormonal, and lifestyle-related covariates used in the main analyses.

For all the statistical tests, the significance level was set at $p < 0.05$. All statistical analyses were performed using SAS software (version 9; SAS Institute Inc.).

Results

Table 1 shows the comparisons of sociodemographic, reproductive, hormonal, and lifestyle-related characteristics between cases and controls. The median duration of follow-up before breast cancer diagnosis of the cases and of their matched controls was 11 y, with a minimum of 0.1 y and a maximum of 22.4 y. Age at diagnosis, mean age at menarche, breastfeeding, ever use of oral contraceptives, menopausal status, BMI, and tobacco smoking status were similar among cases and controls. Cases were more likely than controls to be nulliparous ($p < 0.0001$), to have first full-term pregnancy at 30 y of age or later ($p < 0.0001$), to have a history of benign breast disease ($p < 0.0001$), to have a history of breast cancer among first-degree relatives ($p < 0.0001$). In comparison with the controls, cases were more educated ($p < 0.001$), lived more often in urban areas ($p = 0.03$), and lived in less-deprived areas ($p = 0.02$). Overall, the mean NDVI was similar in the cases and in the controls. Among urban residents, however, the NDVI was negligibly lower among cases ($p = 0.10$). The mean exposure to air pollutants (NO_2, $PM_{2.5}$, and PM_{10}) were similar in the two groups.

Table 2 shows the mean and median LAN exposure at diagnosis, at inclusion, and average from inclusion to diagnosis and during the preceding 5 or 10 y before diagnosis. Overall, the LAN exposure at diagnosis was higher than LAN exposure at inclusion in the cohort, reflecting an increase in outdoor LAN exposure over time.

The ORs for the association between exposure to outdoor LAN and breast cancer risks from the conditional logistic models are detailed in Table 3. Model 1, conditioned for the matching factors and adjusted for age at diagnosis, shows a regular increase in the ORs in the second (29.6–110.3 $nW/cm^2/sr$), third (110.4–290.7 $nW/cm^2/sr$), and fourth (290.8–2,021.6 $nW/cm^2/sr$) quartiles with reference to the lowest quartile (0–29.5 $nW/cm^2/sr$) with an OR in the fourth quartile of 1.20 (95% CI: 1.06, 1.37), and an OR per IQR increase (261.26 $nW/cm^2/sr$) of 1.12 (95% CI: 1.06, 1.18). Adjustment for reproductive, hormonal, lifestyle-related factors, education, and deprivation index in Model 2 resulted in a reduction of the ORs in the fourth quartile. Further reduction of the ORs was observed in models that adjusted for air pollutants NO_2, $PM_{2.5}$, and NDVI, alternatively or in combination, although the ORs per IQR increase changed only slightly. The final model adjusting for NO_2, $PM_{2.5}$, and NDVI resulted in a weakly elevated OR of 1.07 (95% CI: 0.89, 1.29) in Q4 vs. Q1 and an OR of 1.11 (95% CI: 1.02, 1.20) per IQR increase.

In sensitivity analyses using alternative exposure metrics (LAN at the time of inclusion in the cohort, average from inclusion to diagnosis, average LAN exposures during the 5 or 10 y before diagnosis) (Table S2), the ORs per IQR increase in the models adjusting for both air pollutants and NDVI were similar, with the exception of LAN measured at inclusion in the cohort (OR = 1.04; 95% CI: 0.97, 1.12).

Table 4 shows the results of our examination of the association between LAN and breast cancer according to urban greenness in urban residents using unconditional logistic regression models adjusting for the matching factors. Overall, among urban residents, the OR per IQR increase in the fully adjusted model was 1.06 (95% CI: 0.99, 1.13). Stratification on low or high greenness resulted in a small increase in OR among women living in areas with less greenness (OR = 1.07; 95% CI: 0.99, 1.16), whereas no apparent association was seen in women living in areas with higher greenness (OR = 0.95; 95% CI: 0.81, 1.11) (interaction $p = 0.10$). Stratification on low or high exposure to NO_2 or $PM_{2.5}$ in urban areas produced similar ORs in the two exposure categories.

Table 5 shows the results of our examination of the association between LAN and breast cancer by menopausal status at diagnosis among all women. The OR per IQR increase in the fully adjusted model was slightly higher in postmenopausal than in premenopausal women, although the interaction was not statistically significant (interaction $p = 0.85$). We also conducted stratified analyses based on the period of diagnosis and observed that in comparison with the women diagnosed during the years 1990–

Table 1. Descriptive characteristics of the study participants in the case–control study nested within the E3N-Generations cohort, France 1990–2011.

Characteristics	Total $n = 10{,}444$	Cases $n = 5{,}222$	Controls $n = 5{,}222$	p-Values[a]
Age at diagnosis (y)				
Mean ± SD	60.6 ± 8.1	60.6 ± 8.1	60.6 ± 8.1	0.95
10 y age groups				
40–50 y	1,076	538 (10.3)	538 (10.3)	0.99
50–60 y	3,889	1,950 (37.3)	1,939 (37.1)	—
60–70 y	4,107	2,047 (39.2)	2,060 (39.5)	—
70–80 y	1,291	646 (13.4)	645 (12.3)	—
80–90 y	81	41 (0.8)	40 (0.8)	—
Follow-up (y)				
Median (Q1–Q3)	11.3 (6.6–15.6)	11.2 (6.6–15.6)	11.3 (6.6–15.6)	0.95
Min–max	0.1–22.4	0.1–22.4	0.1–22.4	—
≤10 y (diagnosis from 1990 to 2000)	4,784	2,392 (45.8)	2,392 (45.8)	—
>10 y (diagnosis from 2001 to 2011)	5,660	2,830 (54.2)	2,830 (54.2)	—
Education level [n (%)]				
≤Secondary education	1,676	802 (15.4)	874 (16.7)	<0.001
1–2 y university degree	5,118	2,497 (47.8)	2,621 (50.2)	—
≥3 y university degree	3,650	1,923 (36.8)	1,727 (33.1)	—
Deprivation index[b]				
Mean ± SD	−0.295 ± 1.034	−0.322 ± 1.045	−0.269 ± 1.022	0.02
Urbanization [n (%)]				—
Rural	1,768	846 (16.2)	922 (17.7)	0.03
Urban	8,676	4,376 (83.8)	4,300 (82.3)	—
History of breast cancer among 1st-degree relatives [n (%)]				
No	9,003	4,336 (83.0)	4,997 (89.4)	<0.0001
Yes	1,441	886 (17.0)	555 (10.6)	—
Personal history of benign breast disease [n (%)]				
Never	7,733	3,688 (70.6)	4,045 (77.5)	<0.0001
Ever	2,711	1,534 (29.4)	1,177 (22.5)	—
Age at menarche				
Mean ± SD	12.8 ± 1.4	12.8 ± 1.4	12.8 ± 1.4	0.08
In categories [n (%)]				—
<12 y	2,148	1,098 (21.0)	1,050 (20.1)	0.38
12–14 y	5,406	2,704 (51.8)	2,702 (51.7)	—
≥14 y	2,890	1,420 (27.2)	1,470 (28.2)	—
Parity [n (%)]				
Nulliparous	1,236	674 (12.9)	562 (10.8)	<0.0001
1 or 2	6,299	3,198 (61.2)	3,101 (59.4)	—
≥3	2,909	1,350 (25.9)	1,559 (29.8)	—
Age at first full-term pregnancy[c]				
<30 y	7,968	3,867 (85.0)	4,101 (88.0)	<0.0001
≥30 y	1,240	681 (15.0)	559 (12.0)	—
Breastfeeding at least 1 child [n (%)][b]				
Never	3,520	1,709 (37.6)	1,811 (38.9)	0.21
Ever	5,688	2,839 (62.4)	2,849 (61.1)	—
Oral contraceptive use [n (%)]				
Never	4,305	2,147 (41.1)	2,158 (41.3)	0.83
Ever	6,139	3,075 (58.9)	3,064 (58.7)	—
Menopausal status [n (%)]				
Premenopausal	1,680	874 (16.7)	806 (15.4)	0.07
Postmenopausal	8,764	4,348 (83.3)	4,416 (84.6)	—
Menopausal hormonal therapy [n (%)][d]				
Never	4,464	2,102 (53.2)	2,362 (59.8)	<0.0001
Ever	3,434	1,848 (46.8)	1,586 (40.2)	—
Missing	866	398	468	—
BMI [n (%)]				
<18.5 kg/m^2	299	142 (2.7)	157 (3.0)	0.09
18.5–24.9 kg/m^2	7,193	3,553 (68.0)	3,640 (69.7)	—
25–29.9 kg/m^2	2,316	1,210 (23.2)	1,106 (21.2)	—
≥30 kg/m^2	636	317 (6.1)	319 (6.1)	—
Alcohol consumption [n (%)]				
Never	2,434	1,116 (26.4)	1,197 (28.5)	0.02
>0–10 g per day	3,203	1,608 (38.1)	1,640 (39.1)	—
>10 g per day	2,868	1,502 (35.5)	1,359 (32.4)	—
Missing	1,939	996	1,026	—
Smoking [n (%)]				
Current smokers	885	441 (9.4)	444 (9.5)	0.57
Former smokers	3,443	1,755 (37.5)	1,688 (36.1)	—
Never-smokers	5,032	2,489 (53.1)	2,543 (54.4)	—
Missing	1,084	537	547	—

Table 1. (*Continued.*)

Characteristics	Total $n = 10{,}444$	Cases $n = 5{,}222$	Controls $n = 5{,}222$	p-Values[a]
NDVI within 300-m buffer				
Mean ± SD	0.525 ± 0.151	0.521 ± 0.152	0.528 ± 0.150	0.38
Mean ± SD in rural areas	0.682 ± 0.094	0.680 ± 0.095	0.684 ± 0.093	0.37
Mean ± SD in urban areas	0.493 ± 0.140	0.491 ± 0.141	0.495 ± 0.138	0.10
Air pollution				
NO_2 ($\mu g/m^3$)				
Mean ± SD	13.4 ± 11.6	13.5 ± 11.7	13.3 ± 11.5	0.27
Mean ± SD in rural areas	8.3 ± 6.8	8.4 ± 6.5	8.2 ± 7.0	0.20
Mean ± SD in urban areas	14.4 ± 12.1	14.5 ± 12.2	14.3 ± 11.9	0.92
$PM_{2.5}$ ($\mu g/m^3$)				
Mean ± SD	10.6 ± 7.4	10.6 ± 7.4	10.5 ± 7.4	0.95
Mean ± SD in rural areas	9.1 ± 6.3	9.2 ± 6.3	9.0 ± 6.4	0.36
Mean ± SD in urban areas	10.9 ± 7.5	10.9 ± 7.6	10.9 ± 7.5	0.84
PM_{10} ($\mu g/m^3$)				
Mean ± SD	14.8 ± 10.2	14.9 ± 10.2	14.8 ± 10.2	0.80
Mean ± SD in rural areas	12.8 ± 8.7	12.9 ± 8.5	12.7 ± 8.9	0.34
Mean ± SD in urban areas	15.3 ± 10.4	15.3 ± 10.5	15.2 ± 10.4	0.86

Note: —, no data; BMI, body mass index; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤10 μm; SD, standard deviation.
[a]p-Values derived from Wilcoxon signed-rank test for continuous variables and chi-square test for categorical variables.
[b]Neighborhood-level socioeconomic status.
[c]Among parous women only.
[d]Among postmenopausal women only.

2000, those diagnosed during the period 2001–2011 displayed some increase in the OR (1.12; 95% CI: 1.00, 1.26). Table 5 also shows our findings regarding the association of LAN exposure with tumor subtypes defined by the hormone receptor status and found no clear difference between subtypes.

Discussion

In this large case–control study nested in the French nationwide E3N-Generations Cohort, exposure to outdoor LAN remained positively associated with breast cancer risk, albeit weakly, after adjusting for potential confounders, including environmental covariates such as air pollution, assessed by NO_2 and $PM_{2.5}$, and residential greenness, measured by the NDVI. Among urban residents, this association was apparent in women living in areas with lower greenness but not in women in areas with higher greenness. We found little evidence of effect modification by menopausal status, although the association of LAN with breast cancer was more pronounced among postmenopausal women. No clear difference between tumor subtypes defined by hormone receptor status was seen.

Overall, our results lend some credence to Stevens's circadian disruption hypothesis,[8] which suggests that nocturnal melatonin inhibition resulting from LAN-induced circadian disruption leads to a heightened risk of breast cancer. Exposure to LAN in the context of night-shift work has been classified by the IARC as a probable carcinogen for breast cancer.[10] Our results among non-night-shift–working women underscore that this risk may extend beyond the occupational exposure to LAN, encompassing a wider population residing in areas with environmental exposure to outdoor artificial LAN.

Comparison with the Literature

Three previous cohort studies[19–21] and two case–control studies[17,18] have reported a minor and augmented risk of breast cancer for the highest exposure to outdoor LAN in comparison with the lowest, whereas other studies provided no evidence of a positive association.[22–25] Among the studies reporting a positive association, our risk estimates are comparable to those from the California Teachers Study,[19] reporting a hazard ratio (HR) of 1.12 (95% CI: 1.00, 1.26) for women exposed to the highest levels of LAN (54–175 $nW/cm^2/sr$) in comparison with the lowest, using a very comparable sample size (cases ∼5,000) during a similar follow-up period. Despite reporting a positive association, the California Teachers Study[19] and other studies[17,20,21] do not adjust for other environmental exposures. In comparison, the studies that acknowledged the possible confounding by air pollution (NO_2), noise pollution, and greenness[22,24,25] are also the ones that reported null association. The US Sister Study cohort reported no apparent increase in the risk of breast cancer after adjustment for NO_2, $PM_{2.5}$, green space, and noise (HR = 0.89,

Table 2. Mean annual exposure to outdoor LAN exposure ($nW/cm^2/sr$) using different time periods before diagnosis in the case–control study nested within the E3N-Generations cohort, France, 1990–2011.

Outdoor LAN exposure ($nW/cm^2/sr$)	Cases			Controls		
	Mean ± SD	Median (Q1–Q3)	Min-Max	Mean ± SD	Median (Q1–Q3)	Min–max
At diagnosis	215.1 ± 255.9	121.2 (32.8–302.5)	0.0–2,158.1	199.2 ± 237.2	110.3 (29.5–290.7)	0.0–2,021.6
Diagnosis 1990–2000	211.1 ± 258.6	112.8 (34.0–289.9)	0.0–2,158.1	189.5 ± 241.5	95.1 (28.4–258.4)	0.0–2,021.6
Diagnosis 2001–2011	218.5 ± 253.6	129.4 (31.5–309.8)	0.0–1,794.7	207.4 ± 233.2	126.9 (30.4–308.2)	0.0–1,794.7
At inclusion in the cohort	177.0 ± 206.7	94.4 (29.8–245.9)	0.0–1,144.6	165.9 ± 191.5	89.3 (29.4–238.1)	0.0–1,144.6
Average from inclusion to diagnosis (1990–diagnosis)	202.0 ± 229.3	114.5 (36.7–280.5)	0.0–1,390.5	187.8 ± 214.3	104.9 (34.0–269.3)	0.0–1,378.7
Over the last 5 y before diagnosis[a]	222.6 ± 262.5	126.2 (34.2–315.2)	0.0–1,746.8	205.7 ± 242.1	114.1 (29.7–301.4)	0.0–1,787.7
Over the last 10 y before diagnosis[b]	227.9 ± 260.4	132.2 (34.6–325.5)	0.0–1,536.0	211.7 ± 243.9	123.1 (31.2–310.3)	0.0–1,537.1

Note: LAN, light at night; max, maximum; min, minimum; nW, nanowatt; Q, quarter; SD, standard deviation, sr, steradian.
[a]Restricted to women with at least 5 y of exposure information available ($n = 4{,}591$).
[b]Restricted to women with at least 10 y of exposure information available ($n = 3{,}438$).

Table 3. ORs and 95% CIs for the association between outdoor LAN (at diagnosis) and risk of breast cancer, adjusting for different covariates in the case–control study nested within the E3N-Generations cohort, France 1990–2011.

	Outdoor LAN ($nW/cm^2/sr$)					
	Q1 (0–29.5)	Q2 (29.6–110.3)	Q3 (110.4–290.7)	Q4 (290.8–2,021.6)	p-Trend[a]	Per IQR increase
N (cases/controls)	1,038/1,306	1,298/1,305	1,341/1,306	1,375/1,305	—	5,222/5,222
Models						
Model 1	1.00 (Ref)	1.09 (0.97, 1.22)	1.14 (1.02, 1.28)	1.20 (1.06, 1.37)	0.01	1.12 (1.06, 1.18)
Model 2	1.00 (Ref)	1.06 (0.95, 1.19)	1.10 (0.97, 1.24)	1.16 (0.97, 1.28)	0.13	1.08 (1.03, 1.14)
Model 2 + NO_2	1.00 (Ref)	1.06 (0.95, 1.20)	1.10 (0.97, 1.24)	1.12 (0.96, 1.30)	0.23	1.10 (1.03, 1.18)
Model 2 + $PM_{2.5}$	1.00 (Ref)	1.06 (0.95, 1.19)	1.10 (0.97, 1.24)	1.11 (0.96, 1.29)	0.23	1.10 (1.03, 1.16)
Model 2 + NO_2 + $PM_{2.5}$	1.00 (Ref)	1.06 (0.95, 1.20)	1.10 (0.97, 1.24)	1.12 (0.96, 1.30)	0.23	1.10 (1.03, 1.18)
Model 2 + NDVI	1.00 (Ref)	1.04 (0.92, 1.18)	1.06 (0.93, 1.22)	1.07 (0.89, 1.27)	0.53	1.09 (1.01, 1.17)
Model 2 + NO_2 + NDVI	1.00 (Ref)	1.05 (0.93, 1.18)	1.07 (0.93, 1.23)	1.07 (0.89, 1.28)	0.55	1.11 (1.02, 1.20)
Model 2 + NO_2 + $PM_{2.5}$ + NDVI	1.00 (Ref)	1.05 (0.92, 1.18)	1.07 (0.93, 1.23)	1.07 (0.89, 1.29)	0.55	1.11 (1.02, 1.20)

Note: All estimates are from conditional logistic regression models adjusted in following order: Model 1: adjusted for age at diagnosis (continuous); Model 2: further adjustment on reproductive and hormonal factors (parity, age at first full-term pregnancy, breastfeeding, oral contraceptive use, history of breast cancer among first-degree relatives, menopausal status at diagnosis, and menopausal hormonal therapy use), lifestyle-related factors at diagnosis (BMI, smoking and alcohol consumption), education, and deprivation index. —, no data; BMI, body mass index; CI, confidence interval; IQR, interquartile range ($261.26\,nW/cm^2/sr$ based on distribution of LAN among controls only); LAN, light at night; NDVI, Normalized Difference Vegetation Index; NO_2, nitrogen dioxide; nW, nanowatt; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; Q, quarter; Ref, reference; sr, steradian.
[a]p-Values based on median of each quartile.

95% CI: 0.74, 1.06, for 279–2,778 $nW/cm^2/sr$)[25]; the CECILE study in France reported a reduction in the estimates after adjusting for air pollution (NO_2, $PM_{2.5}$, or PM_{10}),[24] whereas the Nurses Cohort Study in Denmark reported a further reduction in the estimates on adjusting for traffic noise (HR = 0.97, 95% CI: 0.77, 1.23 for 66–446 $nW/cm^2/sr$).[22] This divergence observed in the results between the studies based on whether environmental covariates were adjusted for, underscores the need to closely examine potential confounding effects by such factors on the association between outdoor LAN and breast cancer risk. Thus, to the best of our knowledge, this study is the only one to show a positive, albeit weak, association between breast cancer risk and outdoor LAN assessed from DMSP satellite images, after carefully adjusting for relevant covariates, including air pollution and residential greenness.

Confounding and Effect Modification

Assessing environmental exposures like outdoor LAN in isolation can often be challenging because they amalgamate with other environmental exposures, particularly air pollution. These environmental factors may confound the association between exposure to LAN and breast cancer because they correlate with outdoor LAN exposure and are suspected to be related to breast cancer risk. We found a strong correlation between these exposures in our study (see Tables S3, S4), with a gradual increase of air pollution exposure but a decrease in residential greenness across the quartiles of outdoor LAN (see Table S5). In our study we adjusted for $PM_{2.5}$ and NO_2. Exposure to NO_2, a proxy for traffic-related air pollution, has previously been reported to be associated with the risk of breast cancer in our study population[38] and others.[48,49] Conversely, residential greenness has been hypothesized to protect against breast cancer through promoting physical activity, enhancing mental health and social cohesion, and providing a physical barrier against outdoor exposures to LAN, air pollution, and noise.[30,50] A few studies have reported a negative association between proximity to greenspaces and breast cancer risk.[42,51] In our study, we found that exposure to residential greenness, as assessed by NDVI, was negatively associated with breast cancer risk (see Table S6). Acknowledging possible confounding by these environmental exposures is thus crucial to evaluating the role of outdoor LAN exposure in breast cancer risk. In addition to these environmental factors, we also adjusted for a number of hormonal and lifestyle-related breast cancer risk factors, as well as education and social deprivation index. Despite reduction of the risk estimates after adjustments, outdoor LAN exposure remained positively associated with breast cancer risk in our data.

In further analyses, we investigated whether urban greenness could modify the outdoor LAN–breast cancer association. Because investigation of urban greenness aims at assessing presence of greenspaces like parks and gardens in urban settings, this analysis

Table 4. ORs and 95% CIs for the effect modification of the association between outdoor LAN (at diagnosis) and breast cancer risk restricted to urban residents only in the case–control study nested within the E3N-Generations cohort, France, 1990–2011.

Per IQR increase	N cases/controls	OR (95% CI)[a]	p-For interaction[b]
Women in urban areas	4,376/4,300	1.06 (0.99, 1.13)	—
Low greenness (NDVI <0.49)[c]	2,235/2,151	1.07 (0.99, 1.16)	0.10
High greenness (NDVI ≥0.49)	2,141/2,149	0.95 (0.81, 1.11)	—
Low NO_2 (<11.4 $\mu g/m^3$)[d]	2,194/2,150	1.04 (0.94, 1.16)	0.91
High NO_2 (≥11.4 $\mu g/m^3$)	2,182/2,150	1.07 (0.97, 1.17)	—
Low $PM_{2.5}$ (<10.0 $\mu g/m^3$)[e]	2,213/2,151	1.04 (0.94, 1.16)	0.45
High $PM_{2.5}$ (≥10.0 $\mu g/m^3$)	2,163/2,149	1.07 (0.96, 1.18)	—

Note: —, no data; CI, confidence interval; IQR, interquartile range ($261.26\,nW/cm^2/sr$ based on the distribution of LAN among all controls); LAN, light at night; NO_2, nitrogen dioxide; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm.
[a]ORs are from unconditional logistic regression models adjusted for age at diagnosis (continuous), menopausal status at inclusion, department of residence, parity, age at first full-term pregnancy, breastfeeding, oral contraceptive use, history of breast cancer among first-degree relatives, menopausal status at diagnosis and menopausal hormonal therapy use, BMI, smoking, alcohol consumption, education, deprivation index, and air pollution or residential greenness.
[b]p-Values for interaction are from the interaction terms between LAN (in continuous form) and the categories as indicated in the strata.
[c]Median NDVI among controls living in urban areas used as cutoff value.
[d]Median NO_2 among controls living in urban areas used as cutoff value.
[e]Median $PM_{2.5}$ among controls living in urban areas used as cutoff value.

Table 5. ORs and 95% CIs for the association between outdoor LAN (at diagnosis) and breast cancer risk by menopausal status and by tumor subtypes in the case–control study nested within the E3N-Generations cohort, France, 1990–2011.

Per IQR increase	*N* cases/controls	Model 2 + NO_2 + $PM_{2.5}$ + NDVI OR (95% CI)	*p*-For interaction[d]
Menopausal status at diagnosis[a]			
Premenopausal	874/806	0.97 (0.79, 1.19)	0.85
Postmenopausal	2,091/2,078	1.10 (1.02, 1.18)	—
By the period of diagnosis[b]			
1990–2000[c]	2,392/2,392	1.09 (0.99, 1.21)	0.26
2001–2011[c]	2,830/2,830	1.12 (1.00, 1.26)	—
ER and PR status[b]			
ER−	757/757	1.04 (0.85, 1.27)	—
ER+	3,399/3,399	1.08 (0.98, 1.19)	—
PR−	1,437/1,437	1.11 (0.96, 1.28)	—
PR+	2,595/2,595	1.05 (0.94, 1.17)	—
ER− and PR−	609/609	1.07 (0.86, 1.33)	—
ER+ or PR+	3,542/3,542	1.07 (0.97, 1.18)	—

Note: —, no data; BMI, body mass index; CI, confidence interval; ER, estrogen receptor; IQR, interquartile range (261.26 $nW/cm^2/sr$); LAN, light at night; NDVI, Normalized Difference Vegetation Index at 300-m buffer; NO_2, nitrogen dioxide; nW, nanowatt; PR, progesterone receptor; sr, steradian.
[a]ORs are from unconditional logistic regression models adjusted for matching factors (age at inclusion, menopausal status at inclusion, department of residence) and age at diagnosis (continuous), parity, age at first full-term pregnancy, breastfeeding, oral contraceptive use, history of breast cancer among first-degree relatives, menopausal hormonal therapy use (among postmenopausal women only), BMI, smoking, alcohol consumption, education, deprivation index, air pollution (NO_2 and $PM_{2.5}$) and residential greenness (NDVI).
[b]ORs are from conditional logistic regression models adjusted for age at diagnosis (continuous) menopausal status at inclusion, department of residence, parity, age at first full-term pregnancy, breastfeeding, oral contraceptive use, history of breast cancer among first-degree relatives, BMI, smoking, alcohol consumption, education, deprivation index, air pollution (NO_2 and $PM_{2.5}$), and residential greenness (NDVI).
[c]For each stratum, period-specific IQR are used, for 1990–2000, IQR = 230.0 $nW/cm^2/sr$, and for 2001–2011, IQR = 277.8 $nW/cm^2/sr$.
[d]*p*-Values for interaction are from the interaction terms between LAN (in continuous form) and the categories as indicated in the strata.

was restricted to urban residents. In a notable observation, we found that breast cancer risk slightly increased with outdoor LAN exposure in less green urban areas, whereas no apparent increase in risk was observed in greener urban areas. Despite the statistical insignificance, the observed difference in the ORs could suggest that presence of greenspaces might help in mitigating the LAN-related breast cancer risk. Further studies are warranted to confirm this finding and explain possible mechanisms. No effect modification of breast cancer risk by air pollution levels was observed.

Our results also provided some evidence of higher LAN-related risk in postmenopausal than in premenopausal women. This finding is in line with some studies[19,20,52] but in contradiction with others that suggested a higher risk in premenopausal women[23] or no evidence of effect modification by menopausal status.[18,22,24,25] We found no conclusive results regarding the association of outdoor LAN exposure with breast tumors subtypes classified by hormone receptor status of breast tumors. This finding is in line with the literature on breast cancer subtypes that remains inconclusive.[19,21,22,52]

In our study, we observed high levels of exposure ranging from 0 to 2,021.6 $nW/cm^2/sr$, which is comparable to the exposure levels in the Sister Study (0–2,776.52 $nW/cm^2/sr$).[25] This occurrence of high levels of exposure in our study could be explained by the large proportion of women living in urban areas (>70%), the transitioning of the traditional streetlights to energy-efficient light-emitting diode (LED) during the early 2000s,[53,54] and installation of more street lights in the past few decades.[55] In addition to the energy efficiency, LED lights also emit more light with a shorter wavelength (blue light ~480 nm), which is argued to be the most disruptive to the circadian rhythm.[6,18,56] The comparisons have shown that other types of streetlights used, including halogen lamps, fluorescent lights, and mercury vapor lights, also emit a considerable proportion of blue light, causing melatonin suppression.[26,57] These similarities in the blue light emissions from various sources and the development of streetlights over past decades could explain the overall higher exposure to LAN.

Strengths and Limitations

The use of a case–control study design nested within a prospective cohort, along with a large sample size, is one of the main strengths of our study. Although our control group was representative of the whole cohort at baseline,[31] the 1:1 matching also ensured the comparability of cases and controls. Our study is also one of the largest studies to examine breast cancer risk associated with environmental exposure to LAN, providing a maximum chance of detecting weak associations. The availability of comprehensive information allowed us to adjust for multiple potential confounders in the analyses. Because the E3N-Generations cohort consisted primarily of female teachers with standard working hours, confounding from exposure to night-shift work was highly unlikely. Matching cases and controls on the department of residence (94 departments in mainland France) raised the concerns about potential overmatching. However, given the wide spectrum of residential environments in each department, comprising both urban and rural areas, we believe that overmatching is not a concern in our study.

One of the main limitations is the assessment of outdoor LAN using DMSP images, which has been criticized for its low resolution, potential exposure saturation in urban areas, and nondifferentiation between the spectral wavelengths,[58] leading to possible exposure misclassification.[59] DMSP images have a resolution of ~650 m[37] and only capture the total visible light, whereas the images from the International Space Station (ISS) provide a higher resolution (30 m) along with differentiation of spectral components of visible light (blue, red, and green), allowing a detailed assessment of outdoor exposure to LAN.[60] The MCC-Spain study is the only study to date to have employed the ISS images to assess exposure to different wavelengths of visible light.[18] Using the MSI, a proxy indicator of blue light exposure, that study found an elevated risk of breast cancer but reported no association for the total visible light. For our study period (1990–2011), the ISS images were unavailable; thus, DMSP was the only source of satellite images. Nevertheless, we used radiance-calibrated high-dynamic images, which provided adequate variability in the exposure in urban areas[37] and addressed the limitation to a certain extent. A case–control study on colorectal cancer comparing visual light from various satellite sources, including DMSP, found that DMSP data underestimated LAN exposure in comparison with ISS visual light measurements, with pronounced differences at low and high exposure levels.[59] The results of that study suggest that DMSP is likely to result in exposure misclassification, differential or nondifferential, and underlines the importance

of using new satellite-based methodologies to assess LAN exposure in future epidemiological studies.

Another limitation is the LAN exposure assessment at the time of diagnosis, which may not capture the most etiologically important exposure time periods for breast carcinogenesis and does not account for the total duration of exposure from inclusion in the cohort up to the diagnosis. However, its high correlation with other exposure metrics covering up to 10 y of exposure made it the most appropriate metric for the primary analysis as a proxy for the total exposure. This choice benefited our analysis by maintaining homogeneity in the exposure assessment duration and preventing loss of sample size. Even though the information on LAN exposure over an extended period of time before diagnosis was not available for all women in our study, we conducted sensitivity analyses in the subsets of women based on exposure information during the 5 y or 10 y before diagnosis and observed similar results.

In our study, confounding was carefully addressed by adjusting for multiple possible confounders along with air pollution and residential greenness. However, confounding due to other unmeasured environmental and individual-level LAN exposure could not be ruled out. In particular, the actual amount of LAN exposure that penetrates the indoor sleep environment from the exterior was not known. We addressed this issue to a certain extent by adjusting for residential greenness, which may provide a physical barrier and masks outdoor exposure. However, the exposure arising from using electronic devices, indoor lighting, curtains/blinds, and sleep settings remained unmeasured. The studies using self-reported indoor exposure measures have reported conflicting results for its association with breast cancer risk.[61–65] Only a few studies have assessed both indoor and outdoor exposures to LAN.[18,19,25,61] Garcia-Saenz et al. reported a noteworthy association between breast cancer risk and blue light while adjusting for indoor exposure and other confounding factors.[18] Conversely, Sweeney et al. found a null association between outdoor LAN exposure and breast cancer, even among those reporting indoor LAN exposure from outdoor sources.[25] A Dutch study indicated that satellite-based measurement of outdoor LAN was uncorrelated with the actual indoor bedroom light, suggesting that outdoor LAN may not accurately reflect evening or nighttime personal exposure.[27] This finding highlights the importance of considering both indoor and outdoor exposure to fully assess the risks associated with each type of LAN exposure. Future investigations could benefit from objective measurements using sensors to assess indoor and outdoor LAN exposure, considering sleep habits involving curtains, blinds, sleep masks, or electronic device usage at night. Such precise measurements would allow the estimation intensity of outdoor LAN penetrating sleeping areas and improve exposure assessment.

In addition to the environmental and individual exposure to LAN, other elements such as sleep and meal schedules can also affect the circadian rhythm, potentially inhibiting nocturnal melatonin production. Ill-timed meals and irregular sleep cycles, whether occurring independently or in conjunction with LAN, can result in as well as contribute to circadian disruption.[5,66] Further studies assessing individual exposure to LAN along with these circadian disruptors could provide a detailed insight into the underlying mechanism. Furthermore, traffic-related noise pollution is another possible environmental risk factor for breast cancer[29,48,67] and has a speculated correlation with LAN, but this exposure was unavailable in our study.

Given the occupational homogeneity of the study sample, caution is advised when generalizing the results of our study to a broader population. We attempted to address some gaps in the existing literature, but this study is not exempt from the limitations mentioned. This factor underscores the need for further investigations with advanced LAN assessment using ISS images and objectively measured individual-level exposures while also considering possible confounding due to different environmental exposures.

Overall, in this nested case–control study in a prospective cohort, we observed a modest association between breast cancer risk and outdoor LAN exposure assessed using satellite images and adjusting for potential confounders like air pollution and residential greenness. Our findings lend credence to the hypothesis that LAN-induced circadian disruption and the subsequent melatonin inhibition leads to augmented risk for hormone-dependent cancer like breast cancer and also indicate that this risk may extend beyond the occupational night-shift workers to a broader population with heightened environmental LAN exposure. Further population-based studies with a more precise assessment of indoor and outdoor LAN are warranted, and inclusion of other factors of circadian disruptions like sleep and meal schedules and other urban exposures is warranted to assess in detail the interplay of environmental and individual exposures in breast cancer risk.

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