Light at Night and Risk of Pancreatic Cancer in the NIH-AARP Diet and Health Study

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ABSTRACT

Circadian disruption may play a role in carcinogenesis. Recent research suggests that light at night (LAN), a circadian disruptor, may be a risk factor for cancer. Moreover, LAN has been linked to obesity and diabetes, two risk factors for pancreatic ductal adenocarcinoma (PDAC). Here we examine the relationship between LAN and PDAC in an epidemiologic study of 464,371 participants from the NIH-AARP Diet and Health Study. LAN was estimated from satellite imagery at baseline (1996), and incident primary PDAC cases were ascertained from state cancer registries. Cox proportional hazards models were used to estimate HRs and two-sided 95% confidence intervals (CI) for the association between quintiles of LAN and PDAC in the overall population stratified by sex. Over up to 16.2 years of follow-up, a total of 2,502 incident PDAC were identified in the cohort. Higher estimated LAN exposure was associated with an elevated PDAC risk. Compared with those living in areas in the lowest LAN quintile, those in areas in the highest quintile had a 27% increase PDAC risk [HR (95% CI), 1.24 (1.03–1.49)], with similar risk for men [1.21 (0.96–1.53)] and women [1.28 (0.94–1.75)]. In addition, stronger associations were observed in normal and overweight groups compared with the obese group ($P_{interaction} = 0.03$). Our results support the hypothesis that LAN and circadian disruption may be risk factors for PDAC.

Significance: Our study suggests that higher LAN is a risk factor for pancreatic cancer, contributing to the growing literature that demonstrates the potentially adverse health effects of light pollution.

Introduction

Pancreatic cancer is the most lethal type of cancer and the fourth leading cause of cancer mortality in the United States in both men and women (1, 2). Pancreatic ductal adenocarcinoma (PDAC) is the most common subtype, representing more than 85% of all pancreatic cancers (3). Few risk factors have been consistently identified beyond family history, heavy alcohol use, current smoking, diabetes, and overweight and obesity (4–11). Genetic susceptibility also plays a role (12). The causes of PDAC are still insufficiently known, and a better understanding of its etiology and identifying additional risk factors are essential for the primary prevention of this disease.

A growing body of research has suggested that circadian disruption may play a role in cancer etiology in general, and PDAC risk more specifically (13). For example, night shift work has been classified as a probably carcinogen to humans by the International Agency for Research on Cancer (14), and has been linked to a more than 2-fold increase in risk of pancreatic cancer in men (15). Although night shift work may cause multiple changes in health behaviors and environmental exposures that may lead to elevated cancer risk, it has been postulated that the disruption of circadian rhythms among shift worker may be a main driver of the carcinogenic effect (16). In addition, an earlier study reported that residing in the western regions of time zones, a risk factor for circadian disruption, was also associated with higher pancreatic cancer risk (17). Moreover, shift work and sleep deficiency, an indicator and potential cause of circadian disruption, have been consistently linked with type 2 diabetes and obesity (18–21), two important risk factors for PDAC. Together, these findings raised the possibility that circadian disruption may be a risk factor for PDAC.

Light at night (LAN) is a well-established disruptor of the circadian rhythm (22). In modern societies, the growing exposure to artificial LAN and its potential disruptive effect on human circadian rhythms have become a public health concern (23). Studies have linked LAN to multiple health conditions including obesity (24–26) and incident diabetes (27). Moreover, using satellite data, several studies have shown that higher outdoor LAN may be a risk factor for breast and prostate cancer (28–30). However, no epidemiologic study has examined LAN in relation to PDAC risk. To fill this gap, we studied the association between satellite-estimated LAN and the risk of PDAC in a large U.S. cohort of middle-to-older aged men and women. We hypothesize that higher levels of LAN are associated with elevated risks for PDAC.

Materials and Methods

Study population

The NIH-AARP Diet and Health study was established in 1995–1996 and recruited AARP (formerly known as the American Association of Retired Persons) members (age 50–71) from six U.S. states (CA, FL, LA, NJ, NC, and PA) and two metropolitan areas (Atlanta, GA and Detroit, MI). Details of the study were reported previously (31). The study was approved by the NCI Special Studies Institutional Review Board.

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Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

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At baseline, 617,119 questionnaires were returned and after removing duplicates and respondents who had missing key demographic variables, were not the intended respondent, skipped substantial portions of the questionnaire, had >10 recording errors, or requested to be removed from the study, a total of 566,389 questionnaires were deemed satisfactorily completed. At baseline, participants provided their residential addresses, which were linked with satellite data to obtain LAN exposure status (details below), as well as information on demographic factors, lifestyle behaviors, and medical history including cancer. In 2004–2006, an updated list of residential addresses was constructed for administering a follow-up survey. We used these addresses in the sensitivity analysis (detailed in *Statistical analysis*) to examine the association between long-term exposure to LAN and PDAC among people who were living in the same area at baseline and follow-up, defined as <1 km in distance between the two addresses. Of the 566,389 participants with satisfactory baseline questionnaire, we excluded participants who reported a personal history of cancer at baseline ($N = 50,591$), were identified through National Death Index with cancer as the underlying cause of death but had no information on timing of diagnosis date or cancer histology ($N = 6,702$), requested to be withdrawn or had moved out of the study areas before baseline ($N = 57$), and whose residential location could not be geocoded to an exact street address or point address ($N = 44,641$). The final analytical cohort included 464,371 men and women. For the sensitivity analysis, we included 251,298 participants (55%) who were living in the same area at baseline and follow-up.

Assessment of outdoor LAN

Residential addresses at baseline were geocoded into latitude/longitude coordinates, and linked with satellite imagery data using ArcGIS (v. 10.7, ESRI). Annual composite measures of LAN were obtained from the archive of the U.S. Defense Meteorological Satellite Program's Operational Linescan System, maintained by the National Oceanic and Atmospheric Administration's Earth Observation Group (32). The images were processed to remove light signals from sun and moon luminance, glare, clouds, atmospheric lightning, and ephemeral events such as fires, and therefore mainly consist of artificial light. Images were georectified to a 30 arc-second grid (equivalent to $\sim$1 km^2; ref. 33). To avoid saturation at higher levels of light intensity, particularly in urban areas, we used the Global Radiance Calibrated Nighttime Lights high-dynamic range data, which were derived by combing data from three fixed-gain settings, with the lowest gain setting set to avoid saturation in areas with the brightest lighting. LAN measures were transformed into units of radiance [nanowatts/cm^2/steradian (sr); ref. 33]. We used the LAN data in 1996 to estimate the baseline LAN exposures for participants.

Cohort follow-up and ascertainment of incident PDAC

Cancer cases were identified by linking the study cohort to the eight original and three additional (AZ, NV, and TX) state cancer registry databases from 1995 until December 31, 2011. A previous validation study found that approximately 90% of cancers in the cohort were identified through registry linkage (34). The vital status of participants was also ascertained by linkage to the Social Security Administration Death Master File, supplemented by the National Death Index and responses to study mailings. Incident first primary cases of PDAC were identified using the International Classification of Diseases for Oncology Third Edition (codes C250–C259) and histologic types (8140, 8255, 8490, 8500, 8507, 8510, 8514, 8521, 8523, 8560, 8570, 8440, 8470, 8504, 8144, 8450, 8453, 8471, 8503, 8480, 8481, 8000, 8010, 8440, 8470, 8504). Our case definition included 2,502 PDAC cases, while excluding 128 (4.9%) pancreatic tumors other than PDAC, including pancreatic endocrine tumors, acinar cell, and other rare pancreatic tumors and some poorly specified pancreatic cancers (all of the other histologic types). We excluded non-PDAC cases because these rarer subtypes differ from the PDAC not only in clinical presentations and prognosis, but also in cell of origin and possibly disease etiology and risk factors (35, 36).

Covariates

At baseline, participants provided information on a broad range of covariates, including demographic characteristics such as age, race/ethnicity, education, and marital status; lifestyle factors, such as smoking, alcohol use, diet, body mass index (BMI kg/m^2), and physical activity; and medical history of cardiovascular diseases and diabetes. Baseline addresses were linked to the 2000 U.S. Census, which allowed us to derive a number of neighborhood measures at the census tract level, such as population density, median home value, and percent of population below poverty line. We used population density as an indicator of urbanicity, and the percent of population below poverty line and median home value as indicators of neighborhood socioeconomic status.

Statistical analysis

We used Cox proportional hazards models to calculate HRs and 95% confidence intervals (CI) for determining the association between LAN and PDAC risk. Person-years of follow-up time were calculated from the baseline until the date of primary cancer diagnosis, relocation from the registry areas, death, or the end of follow-up (December 31, 2011), whichever came sooner. All models used age as the underlying time metric. The quintiles for LAN were based on the distribution of the full cohort. The proportional hazards assumption was evaluated and confirmed by including interaction terms with follow-up time and using the Wald χ^2 procedure to test whether coefficients equaled zero. We took a stepwise approach to build our regression models. The minimal model (model 1) was adjusted for state of residence (CA, FL, LA, NJ, NC, PA, GA, MI) and sex (men, women). The second model (model 2) was additionally adjusted for race (white, black, other), education (less than high school, high school graduate, some college, college, and post graduate), smoking (former smoker and quit 10+ years, former smoker and quit 1–9 years, current smoker or quit <1 year, never smoked), alcohol use (nondrinker, <1 drink/day, 1–<3 drinks/day, ≥3 drinks/day), red meat intake (continuous), rural-urban continuum code (1, 2, 3, 4, 5+), and 2000 census tract percent below poverty (continuous), median home value (continuous), and population density (quintile). We consider model 2 as our main model. In a third model (model 3), we additionally adjusted for BMI (<25, 25–<30, 30+) and self-reported diabetes (yes, no), because they are well-established PDAC risk factors but can be influenced by LAN (37), making them unlikely to be confounders of the association. We also calculated the HR and 95% CI associated per quintile increase in LAN as well as *P value* for trend using LAN quintile as a continuous score by assigning a numeric value 1–5 to each quintile. Although we did not observe a statistically significant interaction between sex and LAN, we conducted analyses in the overall cohort, as well as in men and women separately to report sex-specific associations. In addition, we also performed stratified analyses by smoking, alcohol, BMI, diabetes, and study areas (six states and two metropolitan areas). Statistical significance for multiplicative interactions was tested using the Wald test. Finally, to assess how robust the results are when using a one-time estimate of LAN at baseline, we examined the relationship between LAN and PDAC among those who reported living in the same area at

baseline and follow-up. We used the 1996 LAN as the exposure variable for the sensitivity analysis because LAN levels remained largely stable across the study areas during this period, showing a correlation coefficient of 0.97 between LAN in 2004 and 1996. All analyses were performed using Stata 14 (StataCorp) and *P* values for statistical tests were two tailed.

Results

During up to 16.2 years of follow-up (median: 15.5 years), 1,571 men and 931 women were identified with incident PDAC in the baseline cohort. **Table 1** presents characteristics of study participants at baseline according to LAN quintiles. For both sexes, compared with those with the lowest LAN, participants with high LAN were less likely to be white, but were more likely to be college educated, report moderate alcohol use (<1 drink/day), and live in census tracts with higher population density and median home values; they also had lower levels of vigorous physical activity and red meat intake. We also observed a U-shaped relationship between LAN and census tract poverty levels.

Overall and sex-specific associations between LAN and PDAC risk are presented In **Table 2**. Higher levels of LAN were associated with higher risks for incident PDAC after adjusting for multiple confounders (model 2). Specifically, those in the highest quintile had a 24% greater risk of developing PDAC over follow-up [HR $_{Q5\ vs.\ Q1}$ (95% CI), 1.24 (1.03–1.49), P_{trend}, *0.005*), and this association was similar in both men [1.21 (0.96–1.53), *0.03*] and women [1.28 (0.94–1.75), *0.08*], although sex-specific results were only of borderline statistical significance. Additionally adjusting for BMI and diabetes had almost on impact on the results (all effect estimates remained the same). We further calculated that the risk for PDAC increased by 6%–7% for every quintile increase in LAN. In our sensitivity analysis, we found that restricting to those who lived in the same areas at baseline and in the follow-up produced largely similar results (Supplementary Table S1).

We observed that the association between LAN and PDAC differed by BMI status ($P_{interaction}$, *0.03*; **Table 3**; Supplementary Table S2), such that the association appeared stronger among participants who were normal weight [HR $_{Q5\ vs.\ Q1}$ (95% CI), 1.30 (0.94–1.80); P_{trend}, *0.08*) or overweight [1.31 (0.98–1.74); *0.02*] than among obese participants [1.04 (0.71–1.52); *0.65*], although none of these effect estimates reached statistical significance. The associations did not differ by smoking, alcohol use, and self-reported diabetes ($P_{interaction}$, *0.33, 0.80*, and *0.89* respectively; Supplementary Table S3). Finally, we presented results for each of the eight study areas in Supplementary Table S4. Although only the results in the two states with the largest study participants (CA and FL) reached statistical significance, they generally support an association between higher LAN and elevated risk of PDAC in each state, excepting NJ, for which no association was observed.

Table 1. Baseline (1995–1996) study characteristics by quintiles of LAN among 464,371 participants in the NIH-AARP Diet and Health Study.

	LAN in 1996				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
LAN, nW/cm^2/sr, range	0.65–9.62	9.63–20.21	20.22–35.06	35.07–56.97	56.98–220.69
Age, year, mean (SD)	62.1 (5.3)	62.0 (5.4)	61.9 (5.4)	62.1 (5.4)	61.9 (5.4)
Women, %	36.4	37.2	38.3	40.8	44.5
White, non-Hispanic, %	96.6	95.1	93.8	92.7	83.4
College and post college, %	33.3	39.4	42.9	42.0	36.6
Smoking, %[a]					
Never	34.6	34.9	35.2	35.3	34.9
Former, quit 10+ years	37.5	37.0	36.9	36.6	34.4
Former, quit 1–9 years	10.8	11.2	10.9	11.0	11.3
Current or quit <1 year	13.4	13.3	13.3	13.4	15.0
Self-reported diabetes, %	8.9	8.8	8.7	8.8	10.1
Body mass index, kg/m^2, mean (SD)	27.1 (4.9)	27.1 (4.9)	27.0 (5.0)	27.0 (5.1)	27.3 (5.4)
Body mass index, kg/m^2, %[b]					
<25	33.2	34.2	35.4	35.6	34.6
25–29.9	43.2	42.6	41.8	41.1	39.5
30+	21.4	21.0	20.5	20.9	23.0
Vigorous physical activity > = 5 times/week, %	20.7	19.9	19.2	18.8	17.3
Alcohol use, %					
Nondrinker	27.7	23.3	21.7	22.2	24.4
<1 drink/day	49.8	53.2	54.8	55.2	55.4
1–3 drinks/day	14.9	15.7	15.9	15.4	13.4
>3 drinks/day	7.7	7.7	7.6	7.3	6.8
Red meat, g/1,000 kcal, mean (SD)	36.4 (21.2)	35.5 (21.4)	34.6 (21.6)	33.8 (21.6)	32.6 (22.2)
Healthy eating index-2005, mean (SD)	66.2 (11.4)	66.6 (11.4)	66.9 (11.4)	67.0 (11.4)	66.7 (11.6)
2003 rural-urban classification, nonmetro, %	21.4	5.0	0.8	0.02	0
Census tract median home value, 1,000 USD, mean (SD)	147.1 (115.2)	181.0 (150.8)	204.1 (153.5)	203.7 (142.7)	188.1 (139.0)
Census tract poverty rate, percentage, mean (SD)	8.8 (6.1)	7.2 (6.1)	6.9 (6.1)	7.5 (6.4)	10.9 (8.5)
Census tract population density, per square km^2, mean (SD)	298.8 (421.9)	894.5 (752.4)	1,425.3 (1094.6)	2,018.9 (1,425.0)	3,742.6 (3,280.5)

Abbreviation: LAN, light at night.
[a]Numbers do not add up to 100% due to missing data (3.9% of total population).
[b]Based on 289,252 participants who completed the Risk Factor Questionnaire, in which sleep duration was assessed.

Table 2. Overall and sex-specific associations [HR (95% CI)] between LAN and incidence of pancreatic cancer in the NIH-AARP Diet and Health Study.

	LAN in 1996						
	Q1	Q2	Q3	Q4	Q5	P_{trend}	Per quintile increase
Overall							
No. of cases	463	462	527	515	535		
Person-years	1,188,800	1,192,477	1,192,566	1,187,807	1,181,370		
Model 1	ref	1.00 (0.87–1.13)	1.14 (1.00–1.29)	1.11 (0.98–1.27)	1.18 (1.03–1.34)	*0.004*	1.04 (1.01–1.08)
Model 2 (main)	ref	0.95 (0.82–1.11)	1.12 (0.95–1.31)	1.12 (0.95–1.33)	1.24 (1.03–1.49)	*0.005*	1.06 (1.02–1.11)
Model 3	ref	0.95 (0.82–1.10)	1.11 (0.95–1.31)	1.12 (0.95–1.33)	1.24 (1.03–1.49)	*0.004*	1.06 (1.02–1.11)
Men							
No. of cases	310	307	323	325	306		
Person-years	733,014	727,422	715,716	681.578	632,543		
Model 1	ref	1.00 (0.85–1.17)	1.06 (0.91–1.25)	1.11 (0.95–1.30)	1.12 (0.95–1.33)	*0.08*	1.03 (1.00–1.07)
Model 2 (main)	ref	0.95 (0.79–1.14)	1.04 (0.85–1.27)	1.13 (0.91–1.40)	1.21 (0.96–1.53)	*0.03*	1.06 (1.01–1.12)
Model 3	ref	0.95 (0.79–1.14)	1.04 (0.85–1.27)	1.13 (0.91–1.40)	1.21 (0.96–1.53)	*0.03*	1.06 (1.01–1.12)
Women							
No. of cases	153	155	204	190	229		
Person-years	455,436	464,477	474,681	506,397	549,183		
Model 1	ref	1.00 (0.79–1.24)	1.28 (1.03–1.58)	1.12 (0.90–1.39)	1.27 (1.03–1.58)	*0.02*	1.06 (1.01–1.11)
Model 2 (main)	ref	0.96 (0.75–1.24)	1.27 (0.97–1.66)	1.12 (0.84–1.50)	1.28 (0.94–1.75)	*0.08*	1.07 (0.99–1.14)
Model 3	ref	0.96 (0.74–1.24)	1.27 (0.97–1.66)	1.12 (0.84–1.50)	1.28 (0.94–1.75)	*0.08*	1.07 (0.99–1.14)

Note: Model 1: adjusted for state of residence (CA, FL, LA, NJ, NC, PA, GA, MI) and sex (men, women). Model 2: adjusted for variables in model 1 and race (white, black, other), education (less than high school, high school graduate, some college, college, and post graduate), smoking (former smoker and quit 10+ years, former smoker and quit 1–9 years, current smoker or quit <1 year, never smoked), alcohol (nondrinker, <1 drink/day, 1-<3 drinks/day, ≥3 drinks/day), red meat intake (continuous), rural-urban continuum code (1, 2, 3, 4, 5+), and 2000 census tract poverty rate (continuous), median home value (continuous), and population density (quintile). Model 2 is considered the main model. Model 3: adjusted for variables in Model 2 and BMI (<25, 25-<30, 30+) and self-reported diabetes (yes, no). $P_{interaction}$ for sex: 0.52.

Discussion

In this large cohort of middle-to-older aged American men and women, we found that higher outdoor LAN estimated by satellite imagery around the residential address was associated with an elevated risk of PDAC. We also found evidence suggesting that this association may differ by baseline BMI.

To the best of our knowledge, our epidemiologic study is the first to examine the association between LAN and PDAC in humans. Several earlier studies reported associations between higher levels of LAN estimated by satellite and other cancer types, particularly breast and prostate cancers. For example, the highest quintile of outdoor LAN was associated with a modest increase in breast cancer risk in the California Teachers Study [$HR_{Q5\ vs.\ Q1}$, 95% (CI), 1.12 (1.00–1.26); ref. 30] and the Nurses' Health Study II [1.14 (1.01–1.29); ref. 28]. Similar results were also observed in the NIH-AARP Diet and Health cohort, where higher levels of outdoor LAN was associated with higher postmenopausal breast cancer risk in older aged women (38). In addition, in a population-based case–control study in Spain, Garcia-Saenz and colleagues reported that higher exposure to outdoor LAN in the blue light spectrum, measured using recent images from the International Space Station, was associated with elevated risks of breast [$OR_{T3\ vs.\ T1}$, 95% (CI), 1.47 (1.00–2.17)] and prostate cancer [2.05 (1.38–3.03)]. The variety of cancer types that have been found to be associated with LAN in these studies and this study seem to suggest that there may be common mechanisms that may drive the association between higher LAN and higher risks of cancer.

Although speculative, circadian disruption is a biologically plausible mechanism that could potentially explain the association of LAN with PDAC risk. LAN suppresses nighttime secretion of melatonin, a

Table 3. Associations [HR (95% CI)][a] between LAN and incidence of pancreatic cancer by BMI in the NIH-AARP Diet and Health Study.

		LAN in 1996						
BMI, kg/m^2	No. of cases/ Total *N*	Q1	Q2	Q3	Q4	Q5	P_{trend}	Per quintile increase
<25	825/160,589	Ref	0.99 (0.76–1.29)	1.13 (0.85–1.50)	1.12 (0.83–1.51)	1.30 (0.94–1.80)	*0.08*	1.07 (0.99–1.15)
25-<30	1,072/193,327	Ref	0.95 (0.76–1.19)	1.07 (0.84–1.37)	1.19 (0.92–1.54)	1.31 (0.98–1.74)	*0.02*	1.09 (1.02–1.16)
30+	605/110,455	Ref	0.91 (0.68–1.23)	1.17 (0.85–1.61)	1.04 (0.74–1.47)	1.04 (0.71–1.52)	*0.65*	1.02 (0.94–1.11)

Note: $P_{interaction} = 0.03$.

[a]Adjusted for state of residence (CA, FL, LA, NJ, NC, PA, GA, MI), sex (men, women), race (white, black, other), education (less than high school, high school graduate, some college, college, and post graduate), smoking (former smoker and quit 10+ years, former smoker and quit 1–9 years, current smoker or quit <1 year, never smoked), alcohol (nondrinker, <1 drink/day, 1-<3 drinks/day, ≥3 drinks/day), red meat intake (continuous), rural-urban continuum code (1, 2, 3, 4, 5+), and 2000 census tract poverty rate (continuous), median home value (continuous), and population density (quintile).

hormone that plays a key role in circadian regulation, and may lead to circadian disruption (39). Growing evidence supports a role for circadian disruption in the etiology of pancreatic cancer. For example, multiple variants in genes that regulate the molecular clock have been linked to a wide range of cancers, including pancreatic cancer (40). Moreover, a population-based case–control study in Canada found that night shift work was associated with a higher risk of pancreatic cancer in men [OR (95% CI), 2.31 (1.48–3.61); ref. 15]. In addition, another study examined the longitudinal position in a time zone in relation to cancer incidence using data from the Surveillance, Epidemiology and End Results program (17). Although people within the same time zone tend to follow similar work, school, and social schedules based on the same clock time, those living in more western locations are more likely to have a later circadian timing due to delayed sun light exposure, which usually lead to a larger circadian misalignment (41). Thus, the authors hypothesized that cancer incidence rates would increase from eastern to western locations within a time zone. Indeed, the study found that each five degrees of longitude toward the west was associated with increases in the incidence of multiple cancers, including an approximately 4% increase in pancreatic cancer incidence rate among both men and women. Taken together, these findings support a role of circadian disruption and LAN in PDAC risk.

The circadian clock plays a central role in orchestrating many physiologic functions in the human body, and the adverse effects of circadian disruption on metabolism may be particularly relevant to pancreatic cancer. Metabolic disorders, such as obesity and type 2 diabetes, are well-established risk factors for pancreatic cancer (42, 43). Night shift workers who commonly suffer circadian disruption experience larger weight gain (44) and are more likely to develop metabolic syndrome (45) and diabetes (46). Moreover, multiple studies have directly linked LAN with obesity and diabetes. For example, in a cross-sectional analysis in the Korea Genome and Epidemiology Study, results revealed a positive association between outdoor LAN and obesity when comparing high versus low LAN groups (1.20, 95% CI:1.06–1.36; ref. 25). In more than 700 elderly Japanese with photometer-measured LAN, Obayashi and colleagues reported that exposure to higher LAN was associated with higher gain in BMI and waist-to-height ratio over 21 months (47), and a more-than-2-fold increase in diabetes incidence after 42 months (27). Although including BMI and diabetes in our model did not have a meaningful impact on our results, these variables were measured at the same time when LAN was estimated, and we were not able to examine their role as potential mediators using formal mediation analysis. In our stratified analyses, we did observe differences in the association between LAN and pancreatic cancer among different BMI groups, with stronger associations observed among people with normal or overweight BMI. It is unclear why the results were stronger among nonobese participants. BMI is a well-established risk factor for PDAC (48). It is possible that the presence of obesity may mask the effects of LAN. Alternatively, compared with the other groups, the obese group has less cases and may not have as much power to observe associations. In our analysis stratified by type 2 diabetes status (Supplementary Table S3), the per-quintile increase in PDAC risk appeared greater among people with no history of diabetes at baseline, although the relatively small sample size for people with diabetes limited the statistical power and the ability to make a reliable comparison. More studies are needed to clarify the role of obesity and type 2 diabetes in the association between LAN and pancreatic cancer. Moreover, there are numerous other biological pathways that are critically involved in tumorigenesis and may be adversely affected by circadian disruption, including immune function, hormone release, cell proliferation, and cellular response to DNA damage (49, 50). Future research is needed to understand the underlying mechanisms that may explain the association between LAN, circadian disruption, and pancreatic cancer.

Alternatively, our observed association may be from mere confounding by other environmental or individual factors. For example, LAN is closely correlated with urbanicity and economic activities, which are associated with differences in health behaviors, access to and utilization of health services and certain environmental exposures that are concentrated in metropolitan areas such as air pollution and traffic noise, all of which may have an impact on pancreatic cancer risk. Although we controlled for several environmental factors, including urbanicity defined by the rural-urban continuum code, census-tract level population density, and socioeconomic indicators; these variables do not fully capture the complex and multidimensional neighborhood attributes that may confound the association between LAN and PDAC. Moreover, because LAN and urbanicity are highly correlated, it is challenging to fully control for effects of urbanicity in our analytic models. To better understand to what degree our results are due to residual confounding or reflect true causal associations of LAN, future studies should examine how changes in LAN affect PDAC risk and other related health outcomes, such as diabetes and obesity. Indeed, small-scale experiments on human subjects and laboratory animals have suggested that light exposure at night not only disrupted circadian rhythms, but also led to metabolic dysfunction (51). However, it is challenging to conduct experimental studies in large human populations, and natural experiments may provide a useful alternative. For example, many cities and states have introduced, or are planning to introduce regulations on outdoor lighting, which could have an impact on LAN exposures across neighborhoods. It would be informative to investigate how such regulations, and other factors that may impact LAN levels, affect health outcomes, including cancer risks.

Our study has several strengths. First, we had a large number of PDAC cases provided by the large sample size, advanced age distribution and long follow-up of the NIH-AARP Diet and Health Study. Moreover, we were able to conduct sex-specific analyses and examine multiple risk factors for PDAC as potential confounders and effect modifiers of the association. Given the prospective design and long follow-up, our analyses are not likely influenced by reverse causation. However, our study does have some limitations. First, we used outdoor LAN as a proxy measure, while some previous studies found that satellite-estimated LAN only had low correlation with indoor LAN exposures (52, 53). Multiple factors can influence how well outdoor LAN reflects the actual LAN exposure at the individual level, such as indoor lighting, nighttime activities in both indoor and outdoor settings such as shift work, and the use of light-blocking materials such as window treatments and sleep masks. Unfortunately, our study did not collect information on these factors and therefore we were not able to assess how they may have affected our results. Although the use of satellite-based estimate of LAN present a crude measure of exposure, as an exploratory study, our investigation suggests a possible association between high LAN exposure and PDAC risk. Future studies should use personal devices to obtain measures that more accurately reflect the actual LAN exposure experienced by participants to expand and confirm our findings. Second, it has been shown that the blue light has a particularly strong effects on circadian disruption (54), and a recent study found that LAN in the blue spectrum had a stronger relationship with breast cancer than overall LAN levels (29). Unfortunately, the satellite images in 1996 did not measure the spectrum

of light, and we were not able to examine blue light exposure in relation to PDAC risk. Third, one-time estimate of LAN exposure at baseline may not reflect long-term accumulative exposures or changes in LAN. In our sensitivity analysis, we found that using baseline LAN measurement produced results similar to those using long-term LAN exposures among people who lived in the same areas at baseline and after 10 years of follow-up. However, exposure misclassification is still possible if LAN levels changed substantially in the same areas where people resided after baseline. The field would benefit from future studies with long-term residential histories and longitudinal LAN data to assess trajectories of LAN exposure among both movers and nonmovers to obtain a better understanding of the effects of timing and length of LAN exposure on PDAC risk. Finally, we did not have measures of circadian rhythms, and could not examine whether the observed association was mediated by circadian disruption.

In summary, our study supports the hypothesis that higher exposure to LAN is a risk factor for PDAC. Our findings contribute to the growing literature that demonstrates the potentially adverse effects of LAN on a wide range of chronic diseases, including cancer.

Authors' Disclosures

No disclosures were reported.

Authors' Contributions

Q. Xiao: Conceptualization, formal analysis, investigation, methodology, writing–original draft. **R.R. Jones:** Investigation, writing–review and editing. **P. James:** Investigation, writing–review and editing. **R.Z. Stolzenberg-Solomon:** Conceptualization, investigation, writing–review and editing.

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