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Associations between artificial light at night and risk for thyroid cancer: a large U.S. cohort study

Dong Zhang[1], **Rena R. Jones**[2], **Peter James**[3,4], **Cari M. Kitahara**[5], **Qian Xiao**[6]

[1]Department of Family and Preventive Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA.

[2]Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD, USA

[3]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA

[4]Department of Environmental Health, Harvard TH Chan School of Public Health, Boston, MA, USA

[5]Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA.

[6]Department of Epidemiology, Human Genetics and Environmental Health, School of Public Health, the University of Texas Health Science Center at Houston, Houston, TX, USA.

Abstract

Background—Light at night (LAN) inhibits nighttime secretion of melatonin and may cause circadian disruption, which may be a risk factor for cancer. Recent studies have linked high LAN with elevated breast cancer risk. Given that breast cancer may share a common hormone-dependent etiology with thyroid cancer, and circadian rhythms play a role in regulating thyroid function, we hypothesize that exposure to LAN is positively associated with thyroid cancer incidence.

Methods—We examined the association between LAN and thyroid cancer incidence in the NIH-AARP Diet and Health Study. LAN exposure was estimated from satellite data and were linked to residential addresses at baseline. Incident thyroid cancer cases were ascertained via linkage to state cancer registries. We used Cox regression to determine the relationship between LAN and thyroid cancer risk, adjusting for sociodemographic, lifestyle and other environmental factors.

Correspondence: Qian Xiao, Department of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, University of Texas Health Science Center at Houston, Houston, TX 77225 (qian.xiao@uth.tmc.edu; phone: 713-500-9233), Dong Zhang, Department of Family and Preventive Medicine, University of Arkansas for Medical Sciences, Little Rock, AR 72205, (dzhang@uams.edu).

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Results—Among 464,371 participants, we found a positive association between LAN and thyroid cancer risk. Specifically, when compared to the lowest quintile of LAN, the highest quintile was associated with a 55% increase in risk (HR (95% CI), 1.55 (1.18, 2.02)). The association was primarily driven by papillary thyroid cancer and stronger in women (1.81 (1.26, 2.60)) than in men (1.29 (0.86, 1.94)). In women, the association was stronger for localized cancer, while in men the association was stronger for more advanced stage. Results were consistent across different tumor sizes.

Conclusions—LAN was positively associated with thyroid cancer risk. Future studies are needed to confirm this association and identify underlying biological mechanisms.

Introduction

The incidence of thyroid cancer has been rising rapidly in the U.S. over several decades, from 4.56 per 100,000 person-years in mid 1970s to 14.42 per 100,000 person-years in early 2010s.[1] Since the mid-2010s, it has started to gradually decline but remained high when comparing to historical figures.[2] In 2020, it is projected that there will be 52,890 new cases of thyroid cancer, including 40,170 cases in women.[3] The increase in thyroid cancer since the 1970s has been largely attributed to increased detection.[4,5] However, recent studies reported that the rising incidence was observed across all tumor sizes and stages and for more aggressive subtypes.[6,7] Moreover, a small increase in thyroid mortality was also observed in the last two decades.[1,8] Therefore, the evidence suggests that there may be a modest but true increase in the disease. Decades of epidemiological research has identified several risk factors for thyroid cancer, including advanced age,[9] female sex,[9,10] non-Hispanic white race/ethnicity,[11] alterations in thyroid stimulation hormone (TSH) level,[12,13] ionizing radiation,[14,15] iodine deficiency,[9,16] and obesity.[17,18] However, these factors cannot fully explain variation in thyroid cancer risk.[19]

The mammalian circadian rhythm is orchestrated by a master clock in the suprachiasmatic nucleus (SCN) and numerous peripheral clocks located in various organs.[20] Master and peripheral clocks maintain autonomous circadian cycles driven by transcription-translation feedback loops of circadian genes, and are also influenced by external stimuli, such as light at night (LAN).[20] As part of the hypothalamic–pituitary–thyroid (HPT) axis, the thyroid gland, thyroid hormones and other hormones that influence thyroid function, are tightly regulated by the SCN.[21] Growing evidence has suggested that circadian disruption is a potential risk factor for thyroid cancer.[21] For example, an investigation in the Women's Health Initiative study reported that more severe insomnia symptoms were associated with a higher thyroid cancer risk in postmenopausal women,[22] supporting a role of sleep deficiencies and circadian dysregulation in thyroid cancer development. Moreover, a study found that circadian clock gene expression patterns were altered in thyroid carcinoma tissue samples, when compared with tissue from normal thyroid and benign nodules.[23] Finally, night shift work, an established circadian disruptor, has been linked to altered plasma levels of TSH[24] and obesity,[25] both of which are risk factors for thyroid cancer.

Over the past century, global nightscapes have been drastically changed by the rapid growth of electric lighting. It has been estimated that LAN has been growing by 5–20% annually in

many cities since the mid-20th century.[26] Although electric lighting has tremendous benefits, including promoting commerce activities, enhancing social interactions and improving public safety, a growing body of literature suggests that pervasive exposure to LAN may have serious public health implications. Exposure to artificial LAN suppresses melatonin, a critical regulator of circadian rhythms, and subsequently may cause circadian disruption.[27] Multiple epidemiological studies have reported an association between higher levels of LAN measured from satellite imagery and elevated cancer risks, particularly breast cancer.[28–30] It has been hypothesized that the association with breast cancer may be partially driven by melatonin's effect on estrogen pathways.[31] Estrogen has also been implicated in thyroid cancer etiology,[32] raising the possibility that LAN may also be associated with thyroid cancer incidence. However, to the best of our knowledge, no study has examined the relationship between LAN and thyroid cancer in human populations. To test the hypothesis that greater exposure to LAN is associated with increased risk of thyroid cancer, we studied artificial outdoor LAN measured by satellite imagery in relation to thyroid cancer risk in a large U.S. cohort of middle-to-older aged men and women.

Methods

Study Population

The NIH-AARP Diet and Health Study is a large cohort of American adults aged 50–71 years at baseline in 1995–1996. The study was approved by the National Cancer Institute Special Studies Institutional Review Board, and study details were reported previously[33]. Briefly, the study was established by recruiting AARP members from six US states (California, Florida, Louisiana, New Jersey, North Carolina and Pennsylvania) and two metropolitan areas (Atlanta, Georgia and Detroit, Michigan). A total of 566,398 participants satisfactorily completed the baseline questionnaire, in which they reported residential addresses and provided information on and a wide range of sociodemographic variables, lifestyle factors and disease histories. Moreover, in 2004–2006, the study obtained the most up-to-date addresses for all baseline study participants, and we used the distance between the 2004–2006 address and the baseline address to define moving status (nonmovers, distance<1 km, 54% of the overall sample; movers distance≥1 km). For this analysis, we excluded those with poorly geocoded addresses (unable to match to a point or exact street address, including those who reported P.O. boxes, N=49,627), reported a history of cancer diagnosis at baseline (N=46,494), had a missing diagnosis date for the incident primary cancer (N=5,850), or requested to be withdrawn or had moved out of the study area before baseline (N=50). Our final analytic cohort included 464,371 participants (183,103 women and 281,268 men).

Assessment of LAN

We used data obtained from the U.S. Defense Meteorological Satellite Program (DMSP) to measure outdoor artificial LAN. The DMSP's LAN data have been described in detail previously.[34,35] Briefly, nighttime satellite imagery was captured by the DMSP's Operational Linescan System (OLS); LAN data are extracted and maintained by the National Oceanic and Atmospheric Administration's Earth Observation Group. The database contains annual composite measures of LAN after excluding the outer quarters of the

satellite swath, sun and moon luminance, glare, clouds, atmospheric lightning, and ephemeral events such as fires.[34] The resolution of the processed imagery data is at ~30 arc-second grid, or approximately 1 km^2. For the current study, we used the high-dynamic range data from the DMSP-OLS Global Radiance Calibrated Nighttime Lights product to avoid saturation in urban areas with high LAN levels.[36] The raw LAN values were transformed into units of radiance (nanowatts/cm^2/sterradian(sr)). Finally, address geocodes of study participants were linked with LAN data from 1996 using ArcGIS (ESRI, Redlands, CA) as a measure of baseline exposure to outdoor LAN.

Incident thyroid cancer ascertainment

The current study focused on first primary thyroid cancer cases. Incident cancer cases were identified through December 31, 2011 by probabilistic linkage with eight original and three additional (Arizona, Nevada and Texas) state cancer registry databases, which included multiple cancer variables such as diagnosis date, cancer site, cancer stage, and tumor size. A previous validation study found that approximately 90% of cancers were identified through registry linkage.[37] Thyroid cancer cases were determined using *International Classification of Disease for Oncology*, 3rd Edition (ICD-O-3) codes C73,[38] and histologic types of thyroid cancer were classified using ICD-O-3 morphological codes (8050, 8260, 8340, 8341, 8342, 8343, 8344, and 8350 for papillary type; 8290, 8330, 8331, and 8335 for follicular type; 8345 and 8510 for medullary type; 8020, 8021 and 8032 for anaplastic type). Of the histologic types originating from the follicular epithelium, papillary and follicular thyroid cancers are well differentiated and anaplastic are poorly differentiated. Medullary types, however, arise from the calcitonin-producing C-cells.[39] We further classified cancer cases by stage at diagnosis using the Surveillance, Epidemiology and End Results Program summary stage (localized, regional or distant). Tumor size (≥1.0, 1.1–2.0, 2.1–4.0, and >4 cm) was classified according the American Joint Committee on Cancer thyroid cancer staging system.[40]

Statistical methods

To examine the relationship between LAN and thyroid cancer risk, we used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Person-years of follow-up time were calculated from 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. We checked and confirmed the proportional hazards assumption for our models by including interaction terms with time and using the Wald χ^2 procedure to test whether coefficients equaled zero. The LAN variable was divided into quintiles for the main analysis, with the lowest quintile serving as the reference group. We used tertiles in the analysis for follicular, medullary and anaplastic types to preserve power. We also calculated the HR and 95% CI associated with 1 quintile increase in LAN by modeling quintiles as an ordinal variable.

We considered a series of models: Model 1 was the base model and included age (<55, 55–59, 60–64, ≥65 years) and sex (female, male) alone. Model 2 included confounders that were determined *a priori*. These included self-reported sociodemographic variables (i.e. age (<55, 55–59, 60–64, ≥65 years), sex (female, male), race (white, black, other), education

(less than high school, high school graduate, some college, college and higher), and marital status (married, widowed, divorced or separate, never married)), state of residence (California, Florida, Louisiana, New Jersey, North Carolina, Pennsylvania, Georgia and Michigan), as well as neighborhood variables derived from census data (i.e. median home value, percent below the 2000 Federal poverty line, population density at the census tract level (all continuous)). Model 3 included all variables in Model 2 and was additionally adjusted for several lifestyle and health factors that could be part of the underlying causal pathway because these factors could be associated with or even impacted by LAN and the associated neighborhood environment and may also influence thyroid cancer risk. These variables include smoking (never, former, current), vigorous physical activity (never, rarely, 1–3 times/month, 1–2, 3–4 or 5+ times/week), alcohol consumption (non-drinker, less than 2 drinks/week, 2 drinks/week-1 drink/day, 1+ drinks/day), sleep duration (<5, 5–6, 7–8 and 9+ hours), body-mass index (<25, 25–29.9, 30–34.9, ≥35 km/m^2), and diabetes (yes, no). We consider Model 2 as our main model.

To assess whether moving status had an impact on our results, we assessed the relationship between LAN and overall thyroid cancer incidence among movers and nonmovers separately. Moreover, because of the well-established sex differences in thyroid cancer risk,[10] we performed analyses in the overall population and in men and women separately to report sex-specific associations. In addition, we also performed subgroup analysis stratifying by several sociodemographic variables (i.e. age, race, education and poverty level at census tract) that are closely related to screening utilization to evaluate the potential impact of cancer screening on the observed associations. We also performed subgroup analysis by BMI in the overall sample, and by ever/never use of hormone replacement therapy (HRT) in women to assess whether the results differ by factors that are related to estrogen levels.

Results

Baseline study characteristics according to quintiles of LAN are presented in Table 1. Participants in the higher quintiles of LAN were more likely to be female, report current smoking, higher alcohol consumption and a larger intake of fruits and vegetables, and had a history of diabetes at baseline (Q5 only); but they were less likely to be non-Hispanic white or married, report high levels of vigorous physical activity (5+ times/week) or 7–8 hours of sleep, or report a history of heart disease at baseline. Moreover, we found that LAN levels were strongly and positively correlated with population density, but had a J-shaped relationship with the percent below poverty and a reverse J-shaped relationship with home value at the census tract level.

Over an average of 12.8 years (standard deviation, 4.6 years) of follow up, we identified 856 cases of thyroid cancer (384 in men and 472 in women). The majority of these cases were papillary thyroid cancer (N=635), followed by follicular (N=134), medullary (N=29) and anaplastic types (N=29). Overall, we found a positive association between higher LAN and elevated risk for overall thyroid cancer (Table 2). When compared to Q1, the highest quintile of LAN was associated with a 55% increase in the risk of developing incident thyroid cancer (HR $_{Q5\ vs\ Q1}$ [95% CI], 1.55 [1.18, 2.02], *p-trend, 0.0002*, Model 2). In sex-stratified analysis, we found that this association was stronger in women (1.81 [1.26, 2.60], *0.001*)

than in men (1.29 [0.86, 1.94], *0.04*), although the p-value for interaction between sex and LAN was not statistically significant (*p-interaction, 0.44*). We calculated that each 10-unit ($nW/cm^2/sr$) increase in LAN was associated with ~5% increase in thyroid cancer in the overall study sample (1.05 [1.01, 1.08]), and in men (1.05 [1.01, 1.10]) and women (1.04 [0.99, 1.09]) separately. These associations remained nearly identical after adjusting for potential lifestyle and health factors of the association (Model 3), and did not appear to differ substantially among movers and nonmovers (Supplementary Table 1).

We found that the results were similar for the main subtype, papillary thyroid cancer (Table 2), which showed a strong positive association with LAN in the overall study population (1.61 [1.18, 2.21], *0.001*) and in women (2.35 [1.55, 3.57], *0.0002*), but not in men (0.90 [0.54, 1.52, *0.50*].Results for other subtypes of thyroid cancer are presented in Supplementary Table 2. We found that tertiles of LAN were not associated with follicular ($HR_{T3\ vs\ T1}$ [95% CI], 1.05 [0.64, 1.72], *p-trend, 0.88*) or medullary types (0.81 [0.23, 2.85], *0.64*). In contrast, we observed a strong association between tertiles of LAN and incidence of anaplastic thyroid cancer (6.80 [1.72, 26.83], *0.01*).

We examined the relationship between LAN and overall incidence of thyroid cancer according to cancer stage and the results are presented in Table 3. Overall the associations were comparable for localized ($HR_{Q5\ vs\ Q1}$ [95% CI), 1.58 [1.12, 2.22], *p-trend, 0.01*) and regional/distant cancer (1.77 [1.02, 3.06), *0.01*). In sex-specific analysis, we found that the association was stronger for localized cancer than for regional/distant cancer in women (1.95 [1.27, 2.99] and 1.39 [0.61, 3.17] for localized and regional/distant stages, respectively), but the opposite pattern was observed in men (1.05 [0.58, 1.89] and 2.63 [1.24, 5.58]).

Table 4 presents associations between LAN and overall incidence of thyroid cancer by tumor size. We found for all tumor size categories, there was a suggestive trend indicating a relationship between higher LAN and elevated incidence. The associations appeared to be the strongest for the biggest (>4.0 cm) tumor size group ($HR_{Q5\ vs\ Q1}$ [95% CI], 3.14 [1.44, 6.82]), while results for the three smaller groups were relatively similar to each other (1.57 [0.89, 2.75], 2.02 [1.04, 3.90] and 1.28 [0.63, 2.62], for the ≤1.0, 1.1–2.0, and 2.1–4.0 cm groups respectively).

Finally, we conducted subgroup analysis stratified by age, race, education, poverty level at the census tract level and BMI (Table 5 for results from Model 2 and Supplementary Table 3 for results from Model 3). In general, we found that the positive relationship between LAN exposure and elevated risk for thyroid cancer was fairly consistent across all subgroups, and none of the p-values for interaction reached statistical significance. We also examined the relationship according to HRT status in women, and the results were similar between women who reported never using HRT and those were currently on HRT at baseline or had used HRT before (Supplementary Table 4).

Discussion

To our knowledge, this is the first study to evaluate the hypothesis that greater exposure to LAN is associated with a higher risk of thyroid cancer. Using data from a large U.S.

cohort study of middle-to-older adults, we found that higher LAN exposure, as estimated by satellite data, was positively associated with risk of thyroid cancer, particularly papillary thyroid carcinoma, the most common histologic type. Our results also suggested potential sex differences in the relationship between LAN and risk of total and papillary thyroid cancer, with stronger associations observed in women than men. In women, the association was stronger for localized cancer, while in men the association was stronger for more advanced stage disease. The association appeared to be similar across tumor size groups and subpopulations with different sociodemographic characteristics and BMI. We also observed a strong association between LAN and risk of anaplastic thyroid carcinoma, a rare but highly aggressive thyroid cancer subtype, but this finding was based on a small number of cases.

Multiple studies have reported an association between LAN and higher risks for various chronic diseases, including cancer.[41] For example, artificial outdoor LAN assessed by satellite imagery has been linked to an increased risk of breast cancer in several large cohorts of middle-to-older aged women, including the AARP Diet and Health Study.[30,35,42] Specifically, these studies reported that when compared to women living in the lowest quintile of LAN, those in the highest quintile had an 11%−14% increase in breast cancer risk and the association appeared to be stronger for estrogen receptor positive (ER+) breast cancer.[30] It has been suggested that exposure to LAN reduces nighttime production of melatonin, which acts as a tumor suppressor partially through its antiestrogenic actions.[31] Specifically, melatonin can both inhibit enzyme activities involved in estradiol synthesis and counteract the stimulatory effect of estradiol by modulating key components of estrogen signaling pathways, both of which may protect against estrogen-dependent tumorigenesis.[31]

It has been proposed that thyroid cancer may share common biological mechanisms with breast cancer, and estrogen-mediated pathways may also play a role in thyroid cancer etiology.[32,43] Earlier studies have found ER expression in both normal and malignant thyroid tissues.[44] Moreover, overexpression of ERα, the ER type that promotes cell proliferation, has been observed in both thyroid cancer tissues and thyroid stem cells that may give rise to thyroid cancer.[45,46] In addition, functional studies showed that estrogen can stimulate growth in thyroid cell lines, activate cellular signaling pathways that are involved in thyroid cancer proliferation, and enhance metastatic potential of thyroid cancer cells.[47–50] In human populations, it is well established that the incidence of thyroid cancer is 3–4 times higher in women than in men and the sex-difference emerges in early adolescence, also suggesting a role for female reproductive hormones in thyroid carcinogenesis.[3,51] The breast-thyroid cancer link is further supported by a recent meta-analysis, which reported that women who are diagnosed with either breast or thyroid cancer had a significantly higher risk of developing the other cancer as a secondary malignancy.[52] Taken together, these findings suggested that the observed LAN-thyroid cancer relationship in our study may be driven by an estrogen-dependent mechanism. In our study, the results were similar for men and women, and according to hormone-related factors including BMI and HRT use in women. Although these results do not clearly support a role of estrogen in the association between LAN and thyroid cancer, it is also possible that the estrogen-mediated effects of LAN act independently from other estrogen-related factors to influence thyroid cancer risk. Future mechanistic studies may provide further insights on the potential role of melatonin and estrogen in thyroid cancer etiology.

Thyroid cancer is classified into several types according to histopathological features, with papillary thyroid cancer accounting for ~60–70% of the cases. Due to the rarity of the non-papillary types, there has been a limited understanding of their etiology. However, previous studies found that different thyroid types differed in their somatic mutational profiles, suggesting that different molecular pathways may be involved.[53,54] We found that the relationship between LAN and thyroid cancer seemed to differ across subtypes, and was only observed for papillary and anaplastic thyroid cancer. Previous studies reported that papillary and anaplastic types share a number of genetic mutations, and untreated papillary carcinoma may naturally evolve into anaplastic tumor, a rare and more lethal form of thyroid cancer[55]. These suggested that common biological causes of papillary and anaplastic tumors may contribute to the observed link between LAN exposure and increased risk of thyroid cancer, and future studies are needed to identify these underlying biological mechanisms.

In recent decades, the increased use of diagnostic imaging in the detection of thyroid cancer has played a major role in driving thyroid cancer incidence in US and globally. Because LAN is closely correlated with urbanicity and economic activities, both of which may influence access to healthcare, it is important to assess to what degree the association may be explained by overdiagnosis. If the higher incidence of thyroid cancer in places with higher LAN is driven by better access to care and higher detection in these areas, we would expect to observe a stronger association for cancers of smaller tumor sizes and localized stage, as their incidence is more heavily influenced by cancer screening. Moreover, we would also expect the association to be weaker among participants with more disadvantaged backgrounds (e.g. racial minority groups, low socioeconomic status (SES)). In our analysis according to cancer stage and tumor size, we found that the relationship between LAN and thyroid cancer did not strengthen with smaller tumor size. In contrast, the largest group of tumor size (>4.0 cm) showed the strongest association with the largest effect size. In addition, cancer stage did not appear to modify the relationship between LAN and thyroid cancer, although we did observe a stronger association for localized cancer in women. Finally, the results were generally consistent across subgroups of different age, race/ethnicity, education and neighborhood poverty level, although the number of participants in racial and ethnic minority and low education groups were limited. Therefore, although we cannot fully exclude the possibility that overdiagnosis played a role in our results, at least in women, it is unlikely that our findings are due to overdiagnosis alone.

Our study is strengthened by the large study sample that allowed us not only to examine the relationship between LAN and thyroid cancer incidence in the overall population, but also within important population subgroups. We were also able to perform analysis according to histologic type, stage and tumor size, which helped us to better understand the potential underlying mechanisms and evaluate the role of cancer diagnosis in the observed associations.

Our study also has limitations. First, estimation of the LAN was based on satellite imagery, which measures the level of outdoor LAN. We did not have information on indoor LAN levels or important factors that may influence the LAN exposure, such as nighttime activities, sleep schedules, window treatments, and illumination at home. Therefore, our LAN measurement only serves as a proxy measure of actual exposure to LAN, and as

several previous studies have demonstrated, satellite-based measures tend to have low correlation with direct indoor LAN measurements.[56,57] Second, we used a one-time LAN measurement at baseline, which may not reflect long-term LAN exposure. Although the subgroup results among movers and nonmovers revealed similar patterns, suggesting moving status did not have a major impact on our findings, future studies should obtain repeated LAN exposure along with complete residential history to accurately capture cumulative LAN exposure over time. Third, we only had a limited number of non-papillary thyroid cancer cases, giving us low power to detect associations between LAN and follicular, medullary, and anaplastic thyroid cancer. Fourth, we did not have measures of melatonin or other markers of the internal circadian rhythm, and therefore were not able to assess the role of circadian disruption in the observed relationship between LAN and thyroid cancer. Fifth, as our participants were between 50 and 71 years old, close to 90% of women participants were postmenopausal at baseline, and it remains unclear if and how LAN is associated with thyroid cancer risk among premenopausal women. Finally, our study population was predominantly non-Hispanic White and of high SES. As a result, we had too few thyroid cancer cases to evaluate the association for LAN within certain racial/ethnic minority populations and low SES participants, and our findings cannot be generalized to these populations.

In conclusion, we found that higher LAN levels were associated with higher thyroid cancer incidence in middle-to-older aged adults in the United States. These findings do not appear to be explained completely by detection bias, as we found stronger associations for regional/distant thyroid cancer than localized thyroid cancer in men, and the association did not diminish with increasing tumor size. The association for high LAN and thyroid cancer is also biologically plausible as LAN suppresses melatonin, a modulator of estrogen activity that may have important anti-tumor effects. Future epidemiologic studies are needed to confirm these findings. Mechanistic studies may also shed light on the biological pathways underlying the relationship between LAN and thyroid cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Study characteristics by quintiles of baseline LAN in 464,371 participants in the NIH-AARP Diet and Health Study.

	LAN in 1996				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
LAN, nW/cm^2/sr, median (IQR)	5.3 (3.2, 7.6)	14.2 (11.8, 17.0)	27.1 (23.5, 30.9)	44.6 (39.7, 49.9)	74.2 (64.8, 88.0)
Female, %	36.4	37.2	38.3	40.8	44.5
Age, year, mean (SD)	62.1 (5.3)	62.0 (5.4)	61.9 (5.4)	62.2 (5.3)	61.9 (5.4)
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
Married, %	77.3	73.3	70.7	67.1	58.4
Current smoker, %	11.7	11.5	11.5	11.6	13.1
Former smoker, %	34.6	34.9	35.2	35.3	34.9
Health Eating Index-2005, mean (SD)	66.2 (11.4)	66.6 (11.4)	66.9 (11.4)	62.1 (5.4)	66.7 (11.6)
Fruit and vegetable consumption, servings/1,000 kcal, mean (SD)	3.79 (1.76)	3.87 (1.79)	3.93 (1.82)	3.97 (1.86)	4.05 (1.97)
Vigorous physical activity, 5 or more times/week, %	20.7	19.9	19.2	18.8	17.3
Body-mass index, kg/m2, mean (SD)	27.1 (4.9)	27.1 (4.9)	27.0 (5.0)	27.0 (5.1)	27.1 (5.4)
Sleep, 7–8 hours/night, %	64.6	63.0	62.4	61.3	56.7
Alcohol consumption, 1–3 drinks/day, %	33.7	35.7	36.5	37.3	38.6
Census tract median home value, 1kUSD, mean (SD)	147 (115)	181 (151)	204 (153)	204 (143)	188 (139)
Census tract poverty rate, percentage, mean (SD)	8.8 (6.0)	7.2 (6.0)	6.9 (6.1)	7.5 (6.3)	10.9 (8.5)
Census tract population density, per km2, mean (SD)	298 (421)	894 (752)	1,425 (1,094)	2,019 (1,425)	3,743 (3,281)
Metropolitan counties[a], %	77.8	94.8	99.0	99.9	100.0
Chronic conditions					
Diabetes	8.9	8.8	8.7	8.8	10.1
Heart Disease	14.5	14.1	13.7	13.6	13.3
Stroke	2.3	2.2	2.0	2.1	2.2

[a]Metro status of counties was determined by the Office of Management and Budget using the 1993 Rural-Urban Continuum Codes.

Abbreviations: LAN, light at night; IQR, interquartile range; SD, standard deviation.

Table 2

Associations between baseline LAN and incidence of all thyroid cancer and papillary thyroid cancer in the NIH-AARP Diet and Health Study (1996–2011).

	LAN in 1996						
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	***p-trend***	**Per quintile increase**
OVERALL							
Thyroid cancer, overall							
No. of cases	139	159	171	196	191		
HR (95% CI)							
Model 1	Ref	1.14 (0.91, 1.43)	1.22 (0.97, 1.52)	1.38 (1.11, 1.72)	1.33 (1.07, 1.65)	*0.003*	1.08 (1.03, 1.13)
Model 2 (main)	Ref	1.16 (0.92, 1.47)	1.27 (1.01, 1.61)	1.51 (1.19, 1.91)	1.55 (1.18, 2.02)	*0.0002*	1.12 (1.06, 1.19)
Model 3	Ref	1.17 (0.93, 1.47)	1.28 (1.01, 1.62)	1.52 (1.20, 1.92)	1.55 (1.19, 2.03)	*0.0002*	1.12 (1.06, 1.19)
Thyroid cancer, Papillary							
No. of cases	98	123	128	144	142		
HR (95% CI)							
Model 1	Ref	1.24 (0.95, 1.62)	1.29 (0.99, 1.67)	1.43 (1.11, 1.85)	1.38 (1.06, 1.78)	*0.01*	1.08 (1.02, 1.14)
Model 2 (main)	Ref	1.26 (0.96, 1.65)	1.33 (1.01, 1.76)	1.56 (1.18, 2.05)	1.61 (1.18, 2.21)	*0.001*	1.12 (1.05, 1.21)
Model 3	Ref	1.27 (0.97, 1.66)	1.34 (1.02, 1.77)	1.57 (1.19, 2.06)	1.62 (1.18, 2.22)	*0.0001*	1.20 (1.09, 1.31)
WOMEN							
Thyroid cancer, overall							
No. of cases	68	87	89	106	122		
HR (95% CI)							
Model 1	Ref	1.25 (0.91, 1.72)	1.25 (0.91, 1.71)	1.40 (1.04, 1.90)	1.49 (1.11, 2.00)	*0.01*	1.09 (1.02, 1.16)
Model 2 (main)	Ref	1.32 (0.96, 1.83)	1.37 (0.99, 1.91)	1.61 (1.16, 2.23)	1.81 (1.26, 2.60)	*0.001*	1.15 (1.06, 1.24)
Model 3	Ref	1.34 (0.97, 1.85)	1.39 (1.00, 1.93)	1.63 (1.18, 2.26)	1.84 (1.28, 2.65)	*0.001*	1.15 (1.06, 1.25)
Thyroid cancer, Papillary							
No. of cases	46	70	71	79	106		
HR (95% CI)							
Model 1	Ref	1.49 (1.03, 2.16)	1.47 (1.02, 2.13)	1.55 (1.07, 2.22)	1.90 (1.35, 2.69)	*0.001*	1.14 (1.06, 1.22)
Model 2 (main)	Ref	1.57 (1.07, 2.28)	1.61 (1.10, 2.37)	1.78 (1.21, 2.62)	2.35 (1.55, 3.57)	*0.0002*	1.19 (1.09, 1.31)
Model 3	Ref	1.59 (1.09, 2.31)	1.64 (1.12, 2.41)	1.81 (1.23, 2.66)	2.39 (1.57, 3.62)	*0.0001*	1.20 (1.09, 1.31)

	LAN in 1996						
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	***p-trend***	**Per quintile increase**
				MEN			
Thyroid cancer, overall							
No. of cases	71	72	82	90	69		
HR (95% CI)							
Model 1	Ref	1.03 (0.74, 1.42)	1.19 (0.86, 1.63)	1.37 (1.00, 1.87)	1.13 (0.81, 1.58)	*0.12*	1.06 (0.99, 1.14)
Model 2 (main)	Ref	1.01 (0.73, 1.42)	1.18 (0.84, 1.65)	1.43 (1.02, 2.01)	1.29 (0.86, 1.94)	*0.04*	1.10 (1.00, 1.20)
Model 3	Ref	1.01 (0.72, 1.41)	1.18 (0.84, 1.64)	1.43 (1.02, 2.01)	1.29 (0.85, 1.93)	*0.05*	1.10 (1.00, 1.20)
Thyroid cancer, Papillary							
No. of cases							
HR (95% CI)	52	53	57	65	36		
Model 1	Ref	1.03 (0.70, 1.51)	1.12 (0.77, 1.64)	1.35 (0.94, 1.94)	0.81 (0.53, 1.23)	*0.97*	1.00 (0.92, 1.09)
Model 2 (main)	Ref	0.99 (0.67, 1.46)	1.08 (0.73, 1.61)	1.37 (0.91, 2.04)	0.90 (0.54, 1.52)	*0.50*	1.04 (0.93, 1.16)
Model 3	Ref	0.98 (0.66, 1.45)	1.08 (0.73, 1.61)	1.36 (0.91, 2.04)	0.90 (0.53, 1.51)	*0.51*	1.04 (0.93, 1.16)

Model 1: Adjusted for age and sex (for overall analysis only).

Model 2 (main): Adjusted for variables in Model 1 and race, education, marital status, state of residence and median home value, poverty rate and population density at census tract level.

Model 3: Adjusted for variables in Model 2 and smoking status, physical activity, alcohol consumption, diabetes, BMI, and sleep duration.

Abbreviations: BMI, body mass index; CI, confidence interval; LAN, light at night; HR, hazard ratio.

Table 3

Associations between baseline LAN and incidence of all thyroid cancer according to cancer stage in the NIH-AARP Diet and Health Study (1996–2011).

	LAN in 1996						
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	***p-trend***	**Per quintile increase**
OVERALL							
Localized							
No. of cases	91	101	113	105	123		
Model 2	Ref	1.17 (0.88, 1.56)	1.33 (1.00, 1.78)	1.29 (0.95, 1.74)	1.58 (1.12, 2.22)	*0.01*	1.10 (1.02, 1.19)
Model 3	Ref	1.18 (0.88, 1.57)	1.34 (1.00, 1.79)	1.30 (0.96, 1.77)	1.58 (1.13, 2.23)	*0.01*	1.11 (1.02, 1.19)
Regional/Distant							
No. of cases	29	33	39	54	49		
Model 2	Ref	1.14 (0.69, 1.90)	1.31 (0.79, 2.15)	1.82 (1.12, 2.96)	1.77 (1.02, 3.06)	*0.01*	1.18 (1.04, 1.33)
Model 3	Ref	1.15 (0.69, 1.90)	1.31 (0.79, 2.16)	1.83 (1.12, 2.98)	1.78 (1.03, 3.09)	*0.01*	1.18 (1.05, 1.34)
WOMEN							
Localized							
No. of cases	52	60	65	57	91		
Model 2	Ref	1.24 (0.85, 1.81)	1.37 (0.94, 2.01)	1.20 (0.80, 1.80)	1.95 (1.27, 2.99)	*0.01*	1.14 (1.03, 1.25)
Model 3	Ref	1.25 (0.86, 1.83)	1.39 (0.95, 2.04)	1.22 (0.81, 1.82)	1.98 (1.29, 3.04)	*0.01*	1.14 (1.03, 1.26)
Regional/Distant							
No. of cases	12	11	12	28	23		
Model 2	Ref	0.94 (0.41, 2.14)	0.96 (0.42, 2.20)	2.06 (0.99, 4.26)	1.39 (0.61, 3.17)	*0.10*	1.17 (0.97, 1.41)
Model 3	Ref	0.94 (0.41, 2.15)	0.96 (0.42, 2.19)	2.05 (0.99, 4.25)	1.39 (0.61, 3.19)	*0.09*	1.17 (0.97, 1.41)
MEN							
Localized							
No. of cases	39	41	48	48	32		
Model 2	Ref	1.07 (0.69, 1.68)	1.27 (0.81, 1.99)	1.40 (0.88, 2.24)	1.05 (0.58, 1.89)	*0.38*	1.06 (0.93, 1.20)
Model 3	Ref	1.07 (0.69, 1.68)	1.27 (0.81, 2.00)	1.40 (0.88, 2.24)	1.05 (0.58, 1.90)	*0.38*	1.06 (0.93, 1.20)
Regional/Distant							
No. of cases	17	22	27	26	26		
Model 2	Ref	1.37 (0.72, 2.62)	1.74 (0.91, 3.31)	1.88 (0.96, 3.69)	2.63 (1.24, 5.58)	*0.01*	1.25 (1.05, 1.47)
Model 3	Ref	1.36 (0.71, 2.61)	1.74 (0.91, 3.32)	1.88 (0.96, 3.70)	2.64 (1.24, 5.61)	*0.01*	1.25 (1.05, 1.48)

Model 2 (main): Adjusted for variables in Model 1 and race, education, marital status, state of residence and median home value, poverty rate and population density at census tract level.

Model 3: Adjusted for variables in Model 2 and smoking status, physical activity, alcohol consumption, diabetes, BMI, and sleep duration.

Table 4

Associations between baseline LAN and incidence of all thyroid cancer according to tumor size in the NIH-AARP Diet and Health Study (1996–2011).

	LAN in 1996						
Tumor size	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***p-trend***	**Per quintile increase**
≤1.0 cm							
No. of cases	31	39	38	42	45		
Model 2	Ref	1.27 (0.79, 2.06)	1.27 (0.77, 2.07)	1.41 (0.85, 2.32)	1.57 (0.89, 2.75)	*0.13*	1.10 (0.97, 1.25)
Model 3	Ref	1.28 (0.79, 2.06)	1.27 (0.78, 2.08)	1.41 (0.85, 2.33)	1.57 (0.89, 2.75)	*0.13*	1.10 (0.97, 1.25)
1.1–2.0 cm							
No. of cases	22	25	20	24	35		
Model 2	Ref	1.14 (0.63, 2.04)	0.94 (0.50, 1.76)	1.24 (0.66, 2.30)	2.03 (1.05, 3.92)	*0.06*	1.16 (0.99, 1.36)
Model 3	Ref	1.14 (0.64, 2.05)	0.94 (0.50, 1.76)	1.23 (0.66, 2.30)	2.02 (1.04, 3.90)	*0.06*	1.16 (0.99, 1.36)
2.1–4.0 cm							
No. of cases	22	19	31	27	25		
Model 2	Ref	0.87 (0.47, 1.63)	1.47 (0.82, 2.61)	1.33 (0.72, 2.45)	1.28 (0.63, 2.62)	*0.24*	1.10 (0.94, 1.29)
Model 3	Ref	0.89 (0.48, 1.66)	1.50 (0.84, 2.68)	1.37 (0.74, 2.53)	1.33 (0.65, 2.72)	*0.20*	1.11 (0.95, 1.30)
>4.0 cm							
No. of cases	13	17	22	34	29		
Model 2	Ref	1.51 (0.73, 3.14)	1.98 (0.97, 4.04)	3.34 (1.68, 6.64)	3.14 (1.44, 6.82)	*0.0003*	1.36 (1.15, 1.61)
Model 3	Ref	1.51 (0.72, 3.13)	1.98 (0.97, 4.05)	3.36 (1.68, 6.69)	3.17 (1.46, 6.90)	*0.0003*	1.36 (1.15, 1.61)

Model 2 (main): Adjusted for variables in Model 1 and race, education, marital status, state of residence and median home value, poverty rate and population density at census tract level.

Model 3: Adjusted for variables in Model 2 and smoking status, physical activity, alcohol consumption, diabetes, BMI, and sleep duration.

Table 5

Subgroup associations (HR (95% CI))[a] between baseline LAN and incidence of all thyroid cancer.

		LAN in 1996						
	No. of thyroid cancer cases	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***p-trend***	***p-interaction***
Age								*0.56*
<62	438	Ref	1.22 (0.88, 1.69)	1.36 (0.97, 1.89)	1.73 (1.24, 2.40)	1.73 (1.17, 2.53)	*0.001*	
≥62	418	Ref	1.12 (0.81, 1.55)	1.21 (0.87, 1.68)	1.33 (0.96, 1.86)	1.41 (0.97, 2.05)	*0.04*	
Race								*0.81*
White	790	Ref	1.11 (0.88, 1.41)	1.25 (0.99, 1.59)	1.49 (1.17, 1.90)	1.55 (1.17, 2.05)	*0.0002*	
Non-white[b]	66	Ref	3.89 (0.85, 17.86)	2.49 (0.52, 11.97)	2.99 (0.65, 13.71)	2.45 (0.53, 11.33)	*0.80*	
Blacks	41	Ref	3.92 (0.45, 33.96)	3.50 (0.40, 30.67)	3.29 (0.39, 27.88)	2.37 (0.28, 20.24)	*1.00*	
Education								*0.28*
HS graduate or lower	215	Ref	1.36 (0.89, 2.06)	1.22 (0.77, 1.93)	1.16 (0.72, 1.87)	1.52 (0.90, 2.57)	*0.28*	
Some college or higher	602	Ref	1.11 (0.83, 1.48)	1.24 (0.94, 1.65)	1.60 (1.21, 2.12)	1.63 (1.18, 2.25)	*0.0002*	
Poverty rate at census tract								*0.61*
< 6.3%	457	Ref	1.09 (0.78, 1.52)	1.35 (0.97, 1.88)	1.58 (1.12, 2.24)	1.88 (1.25, 2.82)	*0.0003*	
≥ 6.3%	399	Ref	1.26 (0.91, 1.74)	1.17 (0.82, 1.66)	1.48 (1.06, 2.08)	1.33 (0.92, 1.93)	*0.08*	

[a] Adjusted for variables in Model 2 (age, sex, race, education, marital status, state of residence and median home value, poverty rate and population density at census tract level).

[b] Included blacks, Hispanics and Asian, Pacific Islander, Native American combined.

Abbreviations: CI, confidence interval; LAN, light at night; HR, hazard ratio.