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Journal

Cancer Causes and Control, 34(2)

Authors

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Publication Date

2023-02-01

DOI

10.1007/s10552-022-01632-4

Peer reviewed

HHS Public Access

Author manuscript

Cancer Causes Control. Author manuscript; available in PMC 2023 June 02.

Published in final edited form as:

Cancer Causes Control. 2023 February ; 34(2): 181–187. doi:10.1007/s10552-022-01632-4.

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

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Abstract

Purpose.—Outdoor light at night (LAN) can result in circadian disruption and hormone dysregulation and is a suspected risk factor for some cancers. Our study is the first to evaluate the association between LAN and risk of endometrial cancer, a malignancy with known relationship to circulating estrogen levels.

Methods.—We linked enrollment addresses (1996) for 97,677 postmenopausal women in the prospective NIH-AARP cohort to satellite imagery of nighttime radiance to estimate LAN exposure. Multivariable Cox models estimated hazard ratios (HR) and 95% confidence intervals (95%CI) for LAN quintiles and incident endometrial cancer overall (1,669 cases) and endometrioid adenocarcinomas (991 cases) through follow-up (2011). We tested for interaction with established endometrial cancer risk factors.

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Author Contributions: All authors contributed to the study conception and design. Conceptualization, Rena R. Jones; Data curation, Danielle N. Medgyesi and Britton Trabert; Formal analysis, Danielle N. Medgyesi and Qian Xiao; Funding acquisition, Peter James; Methodology, Jared A. Fisher and Peter James; Resources, Alexandra J. White; Software, Alexandra J. White; Supervision, Jessica M. Madrigal and Rena R. Jones; Writing – original draft, Danielle N. Medgyesi, Britton Trabert and Qian Xiao; Writing – review & editing, Jared A. Fisher and Jessica M. Madrigal.

Competing Interests: The authors have no relevant financial or non-financial interests to disclose.

Ethics Approval: The study was approved by the National Cancer Institute Special Studies Institutional Review Board.

Results.—We observed no association for endometrial cancer overall (HR_{Q1vsQ5}=0.92; 95%CI=0.78–1.08; *p*trend=0.67) or endometrioid adenocarcinoma (HR_{Q1vsQ5}=1.01; 95%CI=0.82–1.24; *p*trend=0.36). Although body mass index and menopause hormone therapy were both associated with risk, there was no evidence of interaction with LAN (*p*interactions=0.52 and 0.50, respectively).

Conclusion.—Our study did not find an association between outdoor LAN and endometrial cancer risk, but was limited by inability to account for individual-level exposure determinants. Future studies should consider approaches to improve characterization of personal exposures to light.

Keywords

Lighting; Circadian Rhythm; Endometrial Neoplasms; Cancer; Environmental Epidemiology

INTRODUCTION

Most urban populations live under skies illuminated by artificial outdoor light at night (LAN) [1]. Exposure to LAN can lead to circadian disruption and hormone dysregulation [2]. Several studies show night shift work, which is correlated with late chronotype and linked to circadian disruption, is associated with elevated estrogen levels, metabolic syndrome, and cancers of the breast, prostate, colon and rectum [3, 4]. Risk factors for endometrial cancer include increased estrogen levels and obesity [5], which may be more strongly associated with endometrioid adenocarcinoma subtype [6].

Two studies found night shift work for ≥20 years (versus never night shift workers) and late chronotype (versus early chronotype) were associated with endometrial cancer risk [7, 8]. A Spanish case-control study found no significant association between night shift work, sleep duration or chronotype and risk of endometrial cancer [9]. However, no epidemiologic studies to date have evaluated LAN in relation to this cancer. The known relationship between circadian disruption and circulating estrogen levels, and between estrogen levels and endometrial cancer, provide a compelling rationale for investigating this hypothesis.

We investigated the role of LAN in the development of endometrial cancer, and specifically endometrioid adenocarcinoma, among postmenopausal women in a large, multi-state prospective U.S. cohort. We investigated whether risk was greater among women with exposure to higher levels of both LAN and obesity or estrogen therapy, both established risk factors for this cancer.

METHODS

Study population

NIH-AARP Diet and Health Study participants were recruited from AARP members aged 50–71 years living in six states (California, Florida, Louisiana, North Carolina, New Jersey, Pennsylvania) and two cities (Atlanta, Georgia; Detroit, Michigan) in 1995–1996 [10]. Over 500,000 participants completed a questionnaire on demographics and lifestyle factors. Approximately one year after study start (1996–1997), a second risk factor questionnaire

detailing estrogen/progestin use was completed by approximately 65% of the cohort. In 2004–2005, a follow-up questionnaire was sent to living participants. The cohort was linked with statewide cancer registries (through December 31st, 2011) for recruitment states plus three other states where participants frequently moved post-enrollment; this linkage captured an estimated 90% of incident cancers [11]. Incident primary endometrial cancers among N=225,467 female participants were identified via International Classification of Diseases (ICD) coding systems 9 and 10 (endometrioid adenocarcinomas were identified with ICD-O-3 codes) [12].

Exposure

We estimated LAN exposure at the participants' geocoded enrollment address by linking satellite imagery from the U.S. Defense Meteorological Satellite Program's Operational Linescan System [13], which includes annual composites of LAN at approximately 1km resolution. Visible band digital number was used to derive estimates of nighttime light expressed as units of radiance (nanowatts[nW]/cm^2/steradian[sr]). Participants were assigned the 1996 LAN value to coincide with the enrollment period.

Statistical analysis

Our analysis excluded women with a pre-enrollment cancer diagnosis except non-melanoma skin cancer (N=23,998), those whose death was attributed to cancer but were not found in registries (N=1,430) and who were premenopausal at enrollment (N=7,270) or their menopause status was unknown (N=2,106). We further excluded those who reported a hysterectomy at enrollment (N=82,819) and those whose address was not geocoded or geocoded with poor precision (e.g., ZIP code centroid; N=8,925). Our main analysis included 98,919 women.

We parameterized levels of LAN as quintiles and evaluated proportions of participants across covariates of interest collected at enrollment. A secondary risk factor questionnaire (1996–1997) completed by 64,719 (65%) women in our analytic group included type of menopause hormone therapy (MHT) use: never, estrogen only, sequential estrogen plus progestin (<15 days progestin/month), continuous estrogen plus progestin therapy, or unknown. MHT status was evaluated as a separate category for women who did not complete the survey. Geographic factors included state of residence, metropolitan area based on rural-urban continuum codes (RUCC; 1993), and 2000 U.S. Census tract estimates of persons below the federal poverty line (%). Levels of ambient fine particulate matter (<2.5 $\mu g/m^3$; $PM_{2.5}$) were estimated from a universal kriging model [14]. $PM_{2.5}$ levels from year 2000 were used due to sparsity of measurements before the late 1990s.

We estimated hazard ratios (HR) and 95% confidence intervals (95% CI) for the association between LAN and endometrial cancer overall and for endometrioid adenocarcinomas (59% of cases) using Cox proportional hazards models with age as the underlying time metric. We sequentially adjusted for potential confounders using three nested models: Model 1) enrollment age, race/ethnicity, persons below poverty line, and state of residence; Model 2) also included body mass index (BMI), years of contraceptive use, age at menopause, MHT use, and parity, and Model 3) added $PM_{2.5}$ (natural logarithm) and metropolitan area.

In sensitivity analyses, we restricted to women who did not change residence between enrollment and follow-up (N=65,947; 67%). We also investigated associations with LAN stratified by categories of BMI and MHT use, and tested for multiplicative interactions. Previous analyses in this cohort have described increased risk of endometrial cancer among overweight or obese women (compared to BMI<25) and women who used sequential estrogen plus progestin therapy (EPT) (compared to never MHT users) [15, 16]. Therefore, we repeated analyses by BMI and MHT with joint models using common reference groups. We investigated whether the effect of LAN exposure was differential by sleep duration (≤6 hours versus ≥7 hours) using stratified models. Sleep duration was self-reported in the secondary risk factor questionnaire, and therefore analyses were restricted to those who completed this survey.

RESULTS

A greater proportion of non-Hispanic Black women lived in areas with the highest LAN levels (Q5=12% versus Q1=2%). A greater proportion of women who ever gave birth lived in areas with lower LAN levels (Q1=85% versus Q5=77%). The average percentage of persons living below the poverty line at the census tract level was highest at the fifth LAN quintile (Q5=13% versus Q1=9%).

We found no association between increasing LAN quintiles and primary epithelial endometrial cancer overall (1,669 cases; Model 1 HR_{Q1vsQ5}=0.92, 95%CI=0.78–1.1; *p*trend=0.67) or restricted to endometrioid adenocarcinoma (991 cases; Model 1 HR_{Q1vsQ5}=1.0, 95%CI=0.82–1.2; *p*trend=0.36); Table 1. Results were similar in all three models. Our sensitivity analyses among non-movers also showed no evidence of an association with LAN quintiles (1,171 primary epithelial endometrial cancer cases; Model 1 HR_{Q1vsQ5}=0.96, 95%CI=0.79–1.2; *p*trend=0.90).

No associations were observed in models stratified by BMI (*p*interaction=0.52) or MHT use (*p*interaction= 0.50); Table 2. Joint effects analysis between LAN quintiles and BMI categories (with a referent group of women with normal BMI and low (Q1) LAN exposure) showed that risk was elevated among obese women, but there was no increasing risk across LAN quintiles (Obese: HR_{Q1}=3.5, HR_{Q2}=3.1, HR_{Q3}=3.4, HR_{Q4}=3.3, HR_{Q5}=2.8). Likewise, joint effects between LAN quintiles and hormone use (with a referent of never users with Q1 LAN) showed elevated risk among sequential EPT users but non-monotonic associations with LAN categories (sequential EPT users: HR_{Q1}=1.2, HR_{Q2}=1.0, HR_{Q3}=1.2, HR_{Q4}=1.1, HR_{Q5}=1.4). We did not observe evidence of an interaction between LAN exposure and sleep duration (*p*interaction=0.34).

DISCUSSION

This first evaluation of the relationship between LAN and endometrial cancer was motivated by plausibility that circadian disruption can increase estrogen levels and lead to metabolic dysfunction, both of which are risk factors for this cancer [3–5]. We did not observe an association for overall endometrial cancer risk or for endometrioid adenocarcinomas, and found no differences in risk across categories of BMI or MHT use.

Although no prior studies have evaluated the relationship with LAN exposure, there are several studies that reported mixed findings for the relationship between night shift work or self-reported chronotype and endometrial cancer [7–9]. The Nurses' Health Study reported a greater risk of endometrial cancer in women who worked a rotating night shift for ≥20 years compared to never night shift workers [8]. Similarly, a case-control study in California found elevated risk for women with evening versus morning chronotypes [7]. In contrast, a recent Spanish case-control study reported no association between night shift work, sleep duration or chronotype and endometrial cancer risk [9]. While the relationship between circadian disruption and endometrial cancer risk remains unclear, the lack of association with LAN in our study may indicate a relatively weaker impact on circadian function compared to long-term rotating shift work or late chronotype. Our study population did not provide information about night shift work or chronotype, and therefore we could not account for these factors in our analyses. Additionally, LAN exposure estimated from satellite imagery may not reflect individual-level exposure influenced by time spent indoors and outdoors, shift work, and sources of light in the home (e.g., television, lamps) [17].

A recent analysis in this cohort observed a 10% increase in breast cancer risk at the highest versus lowest quintile of LAN [13]. That study, as well as others evaluating outdoor LAN [18] and light or television in the room while sleeping [19], suggested stronger effects among ER+ breast cancer, which suggests LAN could be associated with other estrogen-sensitive cancers. To further explore this hypothesis, we restricted analyses to endometrioid adenocarcinoma, a subtype more strongly associated with higher estrogen levels [6]. However, these analyses did not yield an association with LAN exposure.

We also hypothesized that endometrial cancer risk might be higher among women with exposure to both LAN and obesity or estrogen therapy, as these are established risk factors. Greater risk among obese women has been reported for night shift workers and women with evening chronotypes [7, 8]. However, our main findings did not change when we stratified models by BMI. Importantly, our joint analyses demonstrated the expected increase in risk among those with a BMI ≥25 (compared to BMI <25) and sequential EPT users (compared to never MHT users), consistent with previous cohort findings [15, 16].

We considered adjustment for other factors common to urban areas [20] with known or suspected roles in cancer risks. Correlations between LAN and $PM_{2.5}$, for which associations with lung, breast, and other cancers have been observed [21] was moderate (Spearman's rho=0.42), but $PM_{2.5}$ adjustment did not change our associations. Similarly, living in a metropolitan area or a census tract with higher percent of persons below the poverty line was also correlated with higher LAN levels, but adjustment for these factors also had no impact on associations. We did not evaluate the impact of other urban environmental factors, including noise, green space and built environment features, which are likely to be correlated with LAN and may be sources of unmeasured confounding in our analyses. However, few of these factors have been linked to endometrial cancer risk so we do not anticipate they would explain the lack of association with LAN in this study.

Strengths of this study include the cohort's widespread geographic coverage and varying levels of LAN exposure, long period of follow-up, large numbers of endometrial cancers and

detailed information on potential confounders and effect modifiers. We assigned participants the LAN radiance value in 1996, the earliest year of data available. This limited our ability to fully account for the latent period of endometrial cancer, but findings were unchanged among cases diagnosed beginning approximately 10 years after the start of follow-up (2006–2011). LAN levels between 1996 and 2010 were correlated and our findings were similarly consistent among non-movers during follow-up. While we were not able to account for historical residential mobility, residence history estimation on a subset of cohort participants found that participants had resided at their enrollment address for a median of 13 years prior to study start, indicating some residential stability [22]. Our exposure assessment could not distinguish components of the light spectrum (e.g., blue light) that may differentially effect hormone regulation [3, 23]. Light spectrum has been recently characterized using data from the International Space Station (2012–2013), but is not available in earlier years for which to estimate exposure for our study population [23]. Using satellite data to estimate LAN exposure could have resulted in misclassification and may in part explain our null findings. We were not able to capture the variability of outdoor LAN within spaces smaller than the resolution of our data (1km); this lack of spatial variability may be important in urban settings. We did not have information on individual determinants of light exposure, such as indoor nighttime activities, home characteristics (e.g., windows), and sleep timing. We also had no occupational information with which to assess shift work exposure, of which most epidemiologic evidence for circadian disruption and cancer outcomes is based. While this could lead to exposure misclassification and attenuation of risk estimates toward the null, several other analyses conducted in this cohort using the same methods to estimate LAN exposure have reported positive associations for other cancer types including risk of breast, pancreas, and thyroid cancers, as well as sleep deficiency and obesity [1–5]. This suggests that despite potential exposure misclassification, it has been possible to detect associations for other cancers and health outcomes suspected to be influenced by LAN using the same methodologic approach and study population. Nonetheless, studies of outdoor LAN may have unmeasured confounding by other urban environmental exposures (e.g., air pollution), therefore future studies should consider the collection of personal and indoor measurements of light, as well as the development of validated questions on light exposure, to improve the validity of studies evaluating LAN exposure and health outcomes. We were interested in evaluating the risk of endometrial cancer since there is compelling evidence that LAN may act as a hormone disruptor and given limited epidemiologic investigation of this research question, and our ability to conduct a well-powered study with large numbers of cases. Moreover, we demonstrated existing well-known risk factor relationships for endometrial cancer with our data, such as obesity and menopausal hormone therapy, which underscores that the study population showed expected patterns of risk for this malignancy [15, 16]. While we did not observe a relationship with LAN, we acknowledge a need for future analyses that can better estimate LAN exposure either through validated questionnaire data or personal collection of light exposure.

CONCLUSION

We found no association between outdoor LAN and endometrial cancer risk among postmenopausal women. Replication in other study populations and improved characterization of personal exposures will be important future work.

Funding:

This work was supported by the Intramural Research Program of the National Cancer Institute.

Data Availability:

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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Table 1.

Quintiles of LAN (nW/cm^2/sr) and risk of primary epithelial endometrial cancer and endometrioid adenocarcinoma (N= 97,677)[a]

	N	Cases	Model 1[b] HR (95%CI)	Model 2[c] HR (95%CI)	Model 3[d] HR (95%CI)
Primary endometrial cancer		**1669**			
0.65 – < 11.0	19532	356	REF	REF	REF
11.05 – < 23.1	19547	320	0.89 (0.76, 1.0)	0.89 (0.76, 1.0)	0.89 (0.76, 1.0)
23.08 – < 39.2	19560	318	0.88 (0.75, 1.0)	0.88 (0.76, 1.0)	0.90 (0.76, 1.1)
39.16 – < 62.0	19548	341	0.94 (0.80, 1.1)	0.92 (0.79, 1.1)	0.94 (0.79, 1.1)
61.98 – 220.7	19490	334	0.92 (0.78, 1.1)	0.91 (0.77, 1.1)	0.93 (0.77, 1.1)
*p*trend[e]			0.67	0.53	0.87
Endometrioid adenocarcinoma		**991**			
0.65 – < 11.0	19532	200	REF	REF	REF
11.05 – < 23.1	19547	180	0.89 (0.72, 1.1)	0.88 (0.72, 1.1)	0.89 (0.72, 1.1)
23.08 – < 39.2	19560	189	0.92 (0.75, 1.1)	0.93 (0.76, 1.1)	0.94 (0.76, 1.2)
39.16 – < 62.0	19548	221	1.1 (0.88, 1.3)	1.1 (0.87, 1.3)	1.1 (0.86, 1.3)
61.98 – 220.7	19490	201	1.0 (0.82, 1.2)	0.99 (0.81, 1.2)	1.0 (0.78, 1.3)
*p*trend[e]			0.36	0.45	0.44

[a] Excludes 1,242 women with missing covariates <1%

[b] Model 1 adjusted for: age, race/ethnicity, % persons below poverty line, and state of residence

[c] Model 2 additionally adjusted for: BMI, years of oral contraceptive use, age at menopause, hormone therapy use, parity

[d] Model 3 additionally adjusted for: Log transformed concentrations of $PM_{2.5}$ (2000), and county with metropolitan area of ≥ 1 million people (RUCC 1993)

[e] Modeled as a continuous variable derived from the median of each exposure category

Table 2.

Quintiles of LAN (nW/cm^2/sr) stratified by body mass index (BMI) or menopause hormone therapy use and risk of primary epithelial endometrial cancer and endometrioid cancer[a]

			Primary endometrial cancer		Endometrioid adenocarcinoma	
Body mass index[b]	**Quintiles of LAN**	**N**	**Cases**	**HR 95%CI**	**Cases**	**HR 95%CI**
BMI <25, Normal[c]	0.65 – < 11.0	8575	93	REF	53	REF
	11.05 – < 23.1	9035	97	0.97 (0.73, 1.3)	55	0.95 (0.65, 1.4)
	23.08 – < 39.2	9183	83	0.81 (0.60, 1.1)	47	0.79 (0.53, 1.2)
	39.16 – < 62.0	8927	101	1.0 (0.75, 1.3)	60	1.0 (0.71, 1.5)
	61.98 – 220.7	8232	96	1.1 (0.81, 1.5)	51	1.0 (0.69, 1.5)
BMI 25-<30, Overweight	0.65 – < 11.0	6292	113	REF	62	REF
	11.05 – < 23.1	5935	88	0.82 (0.62, 1.1)	55	0.94 (0.65, 1.4)
	23.08 – < 39.2	5887	91	0.84 (0.64, 1.1)	50	0.86 (0.59, 1.2)
	39.16 – < 62.0	5953	94	0.87 (0.65, 1.1)	61	1.0 (0.72, 1.5)
	61.98 – 220.7	5932	98	0.90 (0.67, 1.2)	61	1.1 (0.74, 1.6)
BMI 30+, Obese	0.65 – < 11.0	4063	143	REF	81	REF
	11.05 – < 23.1	3991	129	0.90 (0.71, 1.1)	66	0.81 (0.59, 1.1)
	23.08 – < 39.2	3864	133	0.97 (0.76, 1.2)	84	1.1 (0.79, 1.5)
	39.16 – < 62.0	4002	138	0.98 (0.77, 1.2)	95	1.2 (0.87, 1.6)
	61.98 – 220.7	4520	128	0.84 (0.64, 1.1)	83	0.98 (0.70, 1.4)
				*p*interaction[d]=0.52		*p*interaction[d]=0.70
Menopause hormone therapy use[e]	**Quintiles of LAN**	**N**	**Cases**	**HR 95%CI**	**Cases**	**HR 95%CI**
Never	0.65 – < 11.0	6694	135	REF	70	REF
	11.05 – < 23.1	6553	95	0.71 (0.55, 0.93)	51	0.73 (0.51, 1.0)
	23.08 – < 39.2	6559	118	0.88 (0.68, 1.1)	72	1.0 (0.73, 1.4)
	39.16 – < 62.0	6494	118	0.89 (0.69, 1.2)	73	1.1 (0.76, 1.5)
	61.98 – 220.7	6700	126	0.96 (0.74, 1.2)	76	1.2 (0.83, 1.7)
Estrogen therapy only	0.65 – < 11.0	1055	26	REF	16	REF
	11.05 – < 23.1	926	18	0.82 (0.45, 1.5)	7	0.48 (0.19, 1.2)
	23.08 – < 39.2	896	13	0.59 (0.30, 1.2)	6	0.40 (0.16, 1.0)

	39.16 – < 62.0	901	13	0.56 (0.28, 1.1)	10	0.65 (0.29, 1.5)
	61.98 – 220.7	831	13	0.65 (0.32, 1.3)	7	0.57 (0.23, 1.4)
Sequential estrogen plus progestin	0.65 – < 11.0	1651	40	REF	27	REF
	11.05 – < 23.1	1693	34	0.81 (0.51, 1.3)	22	0.79 (0.45, 1.4)
	23.08 – < 39.2	1690	40	1.0 (0.64, 1.6)	28	1.0 (0.61, 1.8)
	39.16 – < 62.0	1702	38	0.94 (0.60, 1.5)	23	0.85 (0.48, 1.5)
	61.98 – 220.7	1333	37	1.2 (0.77, 2.0)	23	1.1 (0.62, 2.0)
Continuous estrogen plus progestin	0.65 – < 11.0	2867	39	REF	27	REF
	11.05 – < 23.1	2865	43	1.1 (0.71, 1.7)	28	1.0 (0.62, 1.8)
	23.08 – < 39.2	2992	32	0.77 (0.48, 1.2)	25	0.90 (0.52, 1.6)
	39.16 – < 62.0	2897	29	0.72 (0.44, 1.2)	18	0.68 (0.37, 1.2)
	61.98 – 220.7	2555	35	1.0 (0.62, 1.6)	17	0.75 (0.40, 1.4)
Incomplete	0.65 – < 11.0	6433	103	REF	54	REF
	11.05 – < 23.1	6640	111	1.0 (0.79, 1.4)	60	1.1 (0.73, 1.5)
	23.08 – < 39.2	6564	95	0.86 (0.65, 1.1)	49	0.83 (0.56, 1.2)
	39.16 – < 62.0	6778	118	1.0 (0.79, 1.4)	80	1.3 (0.92, 1.9)
	61.98 – 220.7	7287	116	0.89 (0.67, 1.2)	73	1.1 (0.74, 1.6)
				*p*interaction[d]=0.50		*p*interaction[d] =0.66

[a] Adjusted for age, race/ethnicity, % persons below poverty line, and state of residence

[b] Includes 94,391 women with non-missing BMI status

[c] Includes 1448 women who are underweight (BMI<18.5)

[d] Interaction terms: Exposure quintiles and BMI or hormone use categories

[e] Includes 93,556 women; excluded women who did not know their HRT status but completed the risk factor questionnaire (N= 4,121)