

Interdisciplinary Note on Environmental and Occupational Risk Factors of Breast Cancer, and results based on three French studies (CECILE, E3N-Generations and CONSTANCES)

1. Introduction and Objectives

Breast cancer is a multifaceted disease and the leading cause of cancer-related mortality among women worldwide¹. With 2.3 million new cases and 685,000 deaths reported globally in 2020, the disease's burden continues to rise, particularly in high-income countries.¹ While advances in treatment and early detection have reduced mortality, changes in lifestyle and environmental exposures have driven an increase in incidence. Risk factors for breast cancer span genetic, hormonal, lifestyle, and environmental domains². Traditional risk factors include older age, family history, hormonal changes, and lifestyle behaviors like obesity, smoking, and alcohol consumption.² However, emerging evidence has highlighted the potential role of environmental exposures, such as artificial light at night (LAN) and night shift work, in disrupting circadian rhythms, which may elevate breast cancer risk¹. Circadian rhythms are endogenous 24-hour cycles regulating critical biological processes like sleep-wake patterns, metabolism, and hormone production³. Melatonin, a hormone that peaks at night, plays a key role in regulating circadian rhythms and exhibits cancer-protective properties³. Disruptions to this rhythm, whether due to LAN or irregular work schedules, diminish melatonin production and may create pathways for hormone-dependent cancer development⁴.

Despite a growing body of literature investigating the relationship between night shift work, light at night, and breast cancer risk, conclusive links have not yet been established due to various limitations and gaps in the available research. These limitations include inconsistencies in exposure assessment methods, inadequate control for confounding variables, and variability in study designs⁵. This thesis, therefore, aims to provide a comprehensive study on the effects of circadian disruption, through exposure to LAN and night shift work, and their associations with breast cancer risk in the French population.

The objectives of this thesis were:

1. To study the role of exposure to outdoor LAN in breast cancer risk in CECILE Study
2. To study the role of exposure to outdoor LAN in breast cancer risk in E3N-Generations cohort
3. To study the role of exposure to night shift work in breast cancer risk in CONSTANCES cohort

Methods and materials:

For the first objective we used data from the CECILE study – a population-based case-control study conducted in two departments in France between 2005 and 2007 involving 1185 breast cancer cases and 1214 controls. Face-to-face interviews using standardized questionnaires gathered detailed information on sociodemographic characteristics, medical and family history, reproductive and hormonal factors, lifestyle behaviors, and residential and occupational history. All the residential addresses over the 10 years preceding the diagnosis were geocoded using ArcGIS. To assess exposure to outdoor LAN, satellite images from the Defense Meteorological Satellite Program (DMSP) were utilized. These images were cross references with the geocoded locations of women to calculate the value of outdoor LAN exposure at the participants' residential addresses over the 10 years preceding their diagnosis of the cases or the reference date for the control group

For the second objective we used the data from a nested case-control study within the E3N-generation cohort, an ongoing national prospective study in France, which began in 1990, with women aged 40-65 primarily involved in teaching occupations. In the cohort, every 2-3 years self-administered questionnaires were sent to participants to collect information on sociodemographic information, medical and family history, reproductive and hormonal factors, lifestyle behaviors, and residential history. The nested case-control included all incident breast cancer cases (5222) from 1990 to 2011 and individually matched to controls (5222) was used in this thesis. All residential addresses were geocoded using ArcGIS. Exposure to outdoor LAN, which was also assessed using satellite images from the Defense Meteorological Satellite Program (DMSP) following similar methods as in the first objective.

For the third objective, we used the data from C3-Nuit study, a nested case-control study within the CONSTANCES cohort of French adults aged 18-69, who were invited to a health examination and completed detailed questionnaires at baseline and during follow-up, where information on sociodemographic information, personal and medical history, occupational and environmental factors were collected. The C3-Nuit study specifically designed to investigate the association between night shift work and the risk of breast, prostate, and colorectal cancers, while this thesis only included breast cancer cases and their controls. Data collection for the C3-Nuit study involved a specific questionnaire administered via telephone interviews, collecting detailed information on participants' employment history, night shift work schedules, sleep patterns, and meal schedules. Cases were identified through self-reporting and using the SNDS database. The study involved 674 breast cancer cases and 1,024 controls. Night shift work was defined as working for at least 3 hours between midnight and 5 AM. Participants were categorized as fixed, alternating, or irregular night shift workers based on their work schedules. Several exposure metrics were assessed, including the frequency of night shifts, the duration of night shift work, the length of each shift, and the cumulative number of nights worked.

Logistic regression models were applied to estimate the odds ratios and corresponding 95% CI for the association between outdoor LAN and breast cancer risk while adjusting for multiple possible confounders including socio-demographic factors such as age, urbanization education, multiple reproductive and hormonal factors, lifestyle related factors and environmental factors such as air pollution (measured by NO₂, PM_{2.5}, and PM₁₀ levels) and residential greenness (measured using the Normalized Difference Vegetation Index, NDVI).

2. Results

In the CECILE study, in the basic adjustment model (adjusted for age, department, and urbanization), the ORs were moderately elevated in second tertile 1.11 (95% CI: 0.86-1.41) and third tertile 1.25 (95% CI: 0.95-1.63), of outdoor LAN exposure compared to first. The OR for one interquartile range (IQR = 159.9 nW/cm²/sr) increase in LAN exposure was 1.09 (95% CI: 0.96-1.24). Further adjustment for reproductive and lifestyle-related factors reduced the ORs in T2 and T3 and as well as for per IQR increase in LAN. Additional adjustment for NO₂ used as a marker of traffic-related air pollution resulted in further reduction of the ORs in T2 (1.05; 95% CI: 0.81-1.37) and T3 (1.10; 95% CI: 0.78-1.56) as well as for one IQR increase in LAN to 0.98 (95% CI: 0.81-1.52). Alternative adjustments for PM_{2.5} or PM₁₀ instead of also reduced the ORs, although only a minor reduction was observed for PM₁₀.

In the nested case-control study within E3N-generation cohort, the basic model conditioned for the matching factors, exhibited a regular increase in the ORs in the 2nd, 3rd, and 4th quartiles of outdoor LAN exposure with reference to the lowest quartile, with an OR in the 4th quartile of 1.20 (95% CI: 1.06-1.37). Adjustment for reproductive, hormonal, and lifestyle-related factors and education resulted in a reduction in the ORs. No further reduction of the ORs was observed on further adjustment for NO₂. Alternative adjustments for PM_{2.5} and PM₁₀ resulted in negligible changes in the estimates. On adjustment for residential greenness instead of air pollution, a negligible reduction in the estimates was observed across the quartiles. We also adjusted for both NO₂ and residential greenness (NDVI) together and observed no changes in the estimates. The ORs per one IQR increase in outdoor LAN exposure remained significantly elevated after adjusted for NO₂ (1.11, 95% CI: 1.04-1.18) as well as after adjusting for NO₂ and NDVI (1.12, 95% CI: 1.03-1.21).

In the C3-Nuit study, basic adjustment models showed no association between night shift work and breast cancer risk was observed (All types, OR: 1.08, 95% CI: 0.81-1.45). Further adjustment on reproductive and hormonal factors and lifestyle-related factors and education used as a proxy for socio-economic status brought negligible change in the OR: 1.06 (95% CI: 0.78-1.43). Among women who ever worked alternating night shift work compared to non-night shift workers, OR was notably higher (1.36, 95% CI: 0.85-2.27) than fixed or irregular night shift or all types combined. The ORs associated with other several features of night shift work such as duration, frequency, length of shift, total nights worked in life time, did not reveal a clear association. However, regardless of the exposure metrics use, ORs were found to be increased for alternating night shift work than for fixed or irregular night shifts, especially when working less than 3 consecutive nights with alternating schedule (OR: 2.73, 95% CI: 1.24-5.99). We also found a positive association for women who started alternating night shifts regardless of before the first pregnancy (OR: 1.99, 95% CI: 1.10-3.59).

3. Interdisciplinarity of the thesis

This thesis exemplifies the interdisciplinary nature of research aimed at understanding the associations between circadian disruption, environmental and occupational exposures, and breast cancer risk. By integrating perspectives from epidemiology, chronobiology, public health, urban planning, occupational health, and environmental health, it provides a comprehensive framework for addressing these complex relationships. The thesis integrates perspectives from environmental science, occupational health, and epidemiology to inform public health strategies aimed at mitigating breast cancer risk associated with circadian disruption.

3.1. Epidemiology and biostatistics

Epidemiological methods form the backbone of this research, utilizing robust designs such as case-control study, and nested case control study to quantify risks associated with environmental and occupational exposures. By systematically assessing the association of artificial light at night (LAN) and night shift work with breast cancer, the study follows the principles of epidemiology to uncover the nature of associations between these exposures and the outcome. Adjustments for confounders such as air pollution and socioeconomic factors ensure that findings are both credible and are realizable in the real life. The thesis also applies standard statistical procedures and follows the best practices in epidemiology and biostatistics in the calculation of effect estimate as well as in the interpretation and

generalization of the results. The thesis also acknowledges the possible methodological limitations and possible biases in the risk estimates and displays a methodological rigor.

3.2. Occupational Health

Night shift work is a critical occupational exposure that has been studied for decades in regard to its risk breast cancer. Night shift work has also been categorized as a “probable carcinogen” by International Agency on Cancer Research (IARC)⁶. A considerable proportion of population is exposed to night shift work as a result of modernization and expansion in global work force. This thesis studies exposure to night shift work and breast cancer risk with an attempt to fill a longstanding gap in the existing literature through a comprehensive exposure assessment allowing to capture multiple features of night shift work. The finding of this thesis emphasizes on the need of rigorous exposure assessment as night shift work is a complex occupational exposure, which is frequently studied but without a complete exposure assessment. The findings of increased risk associated with alternating night shift work points towards the need of optimizing work schedules to minimize alternating or irregular shifts and thus to reduce the potential role in breast cancer .

3.3. Environmental Health

Increasing prevalence of exposure to outdoor LAN has multiple effects on human health. Out of numerous environmental exposures, outdoor LAN is gaining interests from scientific community following the results from studies on night shift work and its evaluation by IARC⁶. The environmental exposure to LAN and its interaction with other urban exposures, such as air pollution, noise pollution and urban greenness, as a public health concern is an important aspect of this thesis. The findings highlight the need for an integrated environmental health strategy to address the growing urban exposures in order to mitigate the possible risk of breast cancer.

3.4. Chronobiology

Insights from chronobiology highlight the biological mechanisms underlying the observed associations. Circadian rhythms, regulated by melatonin secretion, are disrupted by LAN and night work schedules. Melatonin suppression, a key mechanism identified in this research, offers a plausible pathway linking circadian disruption to hormone-dependent cancers like breast cancer. This biological foundation strengthens the epidemiological findings, underscoring the importance of maintaining circadian health. This thesis thus brings together occupational and environmental exposure which are believed to increase the risk of breast cancer through the same underlying mechanism.

3.5. Methodological Innovations

The methodological approaches used in this thesis reflect significant advancements and limitations in studying environmental and occupational exposures. The use of satellite data for LAN exposure assessment represents a novel approach, offering large-scale exposure information. Satellite data, while innovative, is limited by low resolution and potential exposure misclassification. Future studies should employ high-resolution data, such as International Space Station imagery, to refine exposure assessment. In term s of night shift work, the detailed categorization in the CONSTANCES cohort advances prior methodologies by capturing nuanced exposure metrics. Retrospective exposure

assessment for night shift work introduces risks of recall bias, though meticulous classification efforts have minimized these biases.

3.6. Prevention and Health Promotion

The findings underscore the need for targeted prevention and health promotion strategies to reduce the burden of breast cancer by addressing environmental and occupational risk factors:

3.6.1. Reducing Light Pollution:

- Design streetlights that minimize unnecessary brightness and blue light emissions, known to disrupt circadian rhythms and potentially increase breast cancer risk.
- Establish regulations to limit artificial lighting in public spaces and on billboards during nighttime hours.
- Raise community awareness about the health risks of excessive nighttime lighting and encourage participation in dark-sky initiatives to reduce overall light pollution.
- Enhance urban environments by incorporating green spaces, which can mitigate the negative effects of urbanization on health, including potential cancer risks.

3.6.2. Mitigating Night Shift Work Risks

- Limit the number of consecutive night shifts and ensure sufficient recovery time between shifts to reduce breast cancer risk associated with circadian disruption.
- Provide tailored interventions for vulnerable populations, including post-menopausal women and morning chronotypes, who may be at higher risk.
- Incorporate workplace lighting systems that minimize exposure to circadian-disruptive wavelengths of light, protecting workers from prolonged circadian disruption.

3.7. Public Health implication

The findings of this thesis hold significant implications for urban planning, occupational health, and environmental health. Each domain offers opportunities to translate research insights into effective public health interventions. The study's identification of modifiable exposures such as LAN and night shift work underscores its relevance to public health. Preventive strategies rooted in these findings can mitigate the risks associated with circadian disruption. For example, raising awareness about the health impacts of light pollution and irregular work schedules can empower individuals and organizations to adopt healthier practices. In addition, this thesis covers an important aspect of urban planning as these areas are characterized by higher LAN exposure, high levels of air pollution and less residential greenness. The results of this thesis carry significant public health implications across individual, organizational, and policy levels:

- i. Individual-Level Interventions: Behavioral changes, such as reducing exposure to artificial LAN, maintaining regular sleep patterns, and adopting healthy lifestyle habits, could mitigate potential risks.
- ii. Organizational Policies: Workplace interventions should optimize shift schedules, limit excessive rotations, and adopt lighting designs that minimize circadian disruption. Policies should also address support mechanisms for night shift workers to safeguard their health.

- iii. Policy Recommendations: Stricter regulations on public lighting, such as those implemented in major cities in France, can reduce unnecessary LAN exposure. Regulatory bodies like IARC should consider classifying LAN and night shift work as potential carcinogens, influencing global public health policies.

4. Conclusion and Future Directions

In conclusion, this thesis provides a comprehensive and interdisciplinary approach to understanding and addressing breast cancer risk associated with modern environmental and occupational exposures. The integration of epidemiological rigor, biological insights, and public health strategies offers a roadmap for preventive measures and policy interventions. Future research with advanced exposure assessments and interdisciplinary collaboration will further refine these findings and contribute to creating healthier environments and work practices, reducing the burden of circadian disruption-related health risks globally.

References

1. Łukasiewicz S, Czeczelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast cancer—epidemiology, risk factors, classification, prognostic markers, and current treatment strategies—An updated review. *Cancers (Basel)*. 2021;13(17). doi:10.3390/cancers13174287
2. Smolarz B, Zadrozna Nowak A, Romanowicz H. Breast Cancer—Epidemiology, Classification, Pathogenesis and Treatment (Review of Literature). *Cancers (Basel)*. 2022;14(10). doi:10.3390/CANCERS14102569
3. Stevens RG. Circadian disruption and breast cancer: From melatonin to clock genes. *Epidemiology*. 2005;16(2):254-258. doi:10.1097/01.EDE.0000152525.21924.54
4. Davis S, Mirick DK, Stevens RG. Night Shift Work, Light at Night, and Risk of Breast Cancer. *JNCI: Journal of the National Cancer Institute*. 2001;93(20):1557-1562. doi:10.1093/jnci/93.20.1557
5. Stevens RG, Hansen J, Costa G, et al. Considerations of circadian impact for defining “shift work” in cancer studies: IARC Working Group Report. *Occup Environ Med*. 2011;68(2):154-162. doi:10.1136/oem.2009.053512
6. IARC. *Night Shift Work Volume 124.*; 2020.