National Toxicology Program
U.S. Department of Health and Human Services

# Draft Report on Carcinogens Monograph on Light at Night

## Peer Review Draft

**Running title: Draft RoC Monograph on Night Shift Work and Light at Night**

# Appendix C: Transmeridian Travel and Breast Cancer

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## List of Tables

# Appendix C. Light at Night (LAN) and Transmeridian Travel and Breast Cancer – Quality rankings and results.

Appendix C includes the rationales for quality rankings of studies of breast cancer and light at night reported in Section 3.3, Table 3-9. The rationales for the quality ratings of indoor and outdoor studies of breast cancer and light at night are shown in Tables C-1a-f. Results for the indoor and outdoor studies of breast cancer and light at night are shown in Appendix C: Table 2.

Appendix C also includes rationales for quality rankings of studies of breast cancer and transmeridian travel reported in Section 3.4, Table 3-13. The rationales for these rankings are shown in Appendix C: Table C-5. Results of the breast cancer and transmeridian travel studies are shown in Appendix C: Table C-6.

**Table C-1a: Breast cancer and lighting at night (LAN) – Indoor and Outdoor: Selection bias rationale**

| Reference | Selection bias rating |
|---|---|
| **Indoor lighting** | |
| Davis *et al.* 2001a | +++ ⬌<br>Cases and controls were selected from the same population by similar methods and criteria. No evidence that selection of the subjects was related to both exposure and disease. |
| Fritschi *et al.* 2013 | ++ ⬌<br>Cases and controls selected from same population with similar criteria. No evidence that selection was related to both exposure and disease. However, due to low response rates, sensitivity analyses were conducted to examine what level of selection bias (Lash 2009) would hide a real effect of 1.5 for ever working nights, resulting in that conclusion that it is unlikely that such bias could account for this size effect. There were some differences in age and residential remoteness between those who participated and those who did not for cases and differences in age for controls. If LAN is related to environmental light, differences in cases and controls in environmental light may be unmeasured. |
| Garcia-Saenz *et al.* 2018 | ++ ⬌<br>Cases and controls were selected from the same underlying population to ensure that they were comparable. There is no evidence that selection of the subjects was related to both exposure and disease; however, attrition bias is possible since recruitment differed between cases and controls with only 52% of the controls responding. Calls were made repeatedly at different times during the day to avoid missing night shift workers. |
| Hurley *et al.* 2014 | +++ ⬇<br>The cohort is clearly defined and includes the relevant eposed and nonexposed for a specific period/location with no evidence that follow-up differed between exposed and non-exposed subjects. No discussion of healthy worker effect/healthy worker survival effect (HWE/HWSE), however, residential light and light in the sleeping area are not likely to be related to employment. |
| Johns *et al.* 2018 | +++ ⬌<br>The cohort is clearly defined and includes the relevant exposed, non-exposed for a specific time period/location, with no evidence that follow-up differed between exposed and non-exposed. No evidence of HWE. |

| Reference | Selection bias rating |
|---|---|
| Keshet-Sitton *et al.* 2016 | + ⬆<br>Cases and controls might not have been selected from the same population. Slightly more controls lived in rural areas and significantly more were non-native born than cases. "For neighborhood (friend) controls to satisfy the study base principle, one must consider the base as divided into geographically defined strata, with controls representing the entire person-time of the area from which cases arise. Use of neighborhood controls in a study with a secondary base may not satisfy the principle" (Wacholder S 1992). There is not enough information about the criteria for selection of controls in terms of their residences; controls were matched to cases after their "selection." That more cases were native Israelis spoke to the issue that there may be cultural differences in exposure preferences or residential preference in areas with bright lights at night. For example, if cases lived in areas with more light than controls, or for various reasons used more/brighter light at night in their homes than immigrant controls, the odds ratio (OR) would be biased away from the null. |
| Kloog *et al.* 2011 | ++ ⬌<br>Cases and controls were selected from the same population by similar criteria. No evidence that selection of the subjects was related to both exposure and disease. Evidence of attrition bias due to low response rates in the controls. |
| Li *et al.* 2010 | +++ ⬌<br>Cases and controls selected from the same population by similar methods and criteria. No evidence that selection of subjects related to both exposure and disease. |
| O'Leary *et al.* 2006 | ++ ⬌<br>Cases and controls were initially selected from the same population by similar methods and criteria. There is no evidence that selection of the subjects was related to both exposure and disease. The second set of cases and controls were selected from the first based on their residential stability. These cases and controls differed from the full set of cases and controls – they were older, postmenopausal, white, parous, heavier, ever users of alcohol and hormone replacement therapy (HRT), and less likely to have more than a high school degree or to have breastfed. Cases and controls in the study subset were interviewed twice – the first time with participants in the larger study, then for a second time, on average 202-239 days later, focusing on questions involving light at night and shift work. While no data are available to determine how lighting differs between the two populations because these questions were only asked in the second interview, there is little reason to believe that differential selection bias would be introduced. Because of the two-phase study design, attrition particularly in the controls was significant suggesting some selection bias in an unknown direction. |
| White *et al.* 2017 | +++ ⬌<br>The cohort is clearly defined (e.g., includes the relevant exposed, nonexposed, or referent group for a specific time period/location), with no evidence that follow-up differed between exposed and non-exposed subjects. There is no evidence of HWE or HWSE as this is not an occupational cohort and women currently working shifts were excluded from the analysis. The mean age of the cohort is about 55 making it somewhat "older," and questions about LAN at baseline were asked in relation to habits in the past year. Six blind women were excluded. |

| Reference | Selection bias rating |
|---|---|
| **Outdoor lighting** | |
| Bauer *et al.* 2013 | + ⬇<br>It is not clear that lung cancer cases are the appropriate comparison group, as 5 studies have found lung cancer related to shift work (Kwon (2015), Gu (2014), Yong M (2014), Schernhammer 2013, Parent 2012); two of the studies were in females. If so, the estimate could be biased towards the null. Also, almost 20% of addresses were removed because of non-geocodable addresses which are more likely in rural areas. For the black/white analysis, there are many rural Georgia counties with > 50% blacks, and if they have less precise addresses, a bias towards the null would be likely particularly in the black/white analysis. These counties may also have fewer diagnosed cases as they are far from urban centers. |
| Garcia-Saenz *et al.* 2018 | ++ ⬌<br>Cases and controls were selected from the same underlying population to ensure that they were comparable. There is no evidence that selection of the subjects was related to both exposure and disease; however, attrition bias is possible since recruitment differed between cases and controls with only 52% of the controls responding. Calls were made repeatedly at different times during the day to avoid missing night shift workers. |
| Hurley *et al.* 2014 | +++⬇<br>The cohort is clearly defined and includes the relevant eposed and nonexposed for a specific period/location with no evidence that follow-up differed between exposed and non-exposed subjects. No discussion of HWE/HWSE; however, residential light and light in the sleeping area are not likely to be related to employment. |
| James *et al.* 2017 | +++ ⬌<br>The cohort is clearly defined (e.g., includes the relevant exposed, nonexposed, or referent group for a specific time period/location), with no evidence that follow-up differed between exposed and non-exposed subjects. Minimal HWSE, as young women were recruited into the cohort. Small amount of missing information from the cohort; but as only 85% of addresses could be geocoded, there was a loss of some addresses of some nurses which may differ in urban/nonurban characteristics and LAN exposure; likely to have a small impact. |
| Keshet-Sitton *et al.* 2016 | + ⬆<br>Cases and controls might not have been selected from the same population. Slightly More controls lived in rural areas and significantly more were non-native born than cases. "For neighborhood (friend) controls to satisfy the study base principle, one must consider the base as divided into geographically defined strata, with controls representing the entire person-time of the area from which cases arise. Use of neighborhood controls in a study with a secondary base may not satisfy the principle" (Wacholder S 1992). There is not enough information about the criteria for selection of controls in terms of their residences; controls were matched to cases after their "selection." That more cases were native Israelis spoke to the issue that there may be cultural differences in exposure preferences or residential preference in areas with bright lights at night. For example, if cases lived in areas with more light than controls, or for various reasons used more/brighter light at night in their homes than immigrant controls, the OR would be biased away from the null. |

**Table C-1b: Breast cancer and lighting at night (LAN) – Indoor and Outdoor: Exposure assessment rationale**

| Reference | Exposure Assessment rating |
|---|---|
| **Indoor lighting** | |
| Davis *et al.* 2001a | ++ ⬇<br>Exposure assessment methods have ability to distinguish women based on their own subjective assessment with high, medium, or low exposure to light in the residential area, and % of night with light on. No other information about light exposure from outside sources, and the "unexposed" may not be truly unexposed. Recall bias likely to be minimal as the hypothesis for light at night and cancer was not well publicized at the time of the study. |
| Fritschi *et al.* 2013 | + ⬇<br>Exposure assessment methods go beyond shiftwork studies by ascertaining level of light at the workplace. However, those with medium and high exposure were contrasted with those with unknown LAN work exposure, but who sleep in lighted rooms during the day, which calls into question the actual contrast. Unclear how different light levels at different jobs was handled. Exposure assessment methods have ability to distinguish women with high or low exposure to light from lighting in the workplace only, but not exposure from other sources, including use of electronic devices, TV, outside lighting, daylight, or residential lighting at home, nor information on amount, spectrum, timing or duration of lighting. Qualitative measures of ability to read, etc. are insufficient to classify exposure. Recall bias in this case-control study cannot be completely excluded, even though shift work and light were not the focus of the interview. |
| Garcia-Saenz *et al.* 2018 | ++ ⬇<br>The exposure assessment methods have moderate sensitivity and specificity with respect to level of exposure. Allows for discrimination between exposed and unexposed. However, no measure of direct light. |
| Hurley *et al.* 2014 | ++ ⬇<br>Exposure assessment methods for indoor light are sensitive and specific for exposure in the year before diagnosis as both frequency and duration of bright light in the sleeping area was assessed. No information on other sources of indoor light was collected (e.g., TV, electronic devices), nor any information on intensity, wavelength, and timing in the evening. |
| Johns *et al.* 2018 | + ⬇<br>The exposure assessment methods have low sensitivity and specificity with respect to ever-exposure, exposure level, timing, or other metrics of light at night. The question of the alignment of definitions used and lighting levels sufficient for circadian disruption and cancer are questionable. For some, the quality of recall about exposure at age 20 may have been 60+ years ago, and would be questionable. |
| Keshet-Sitton *et al.* 2016 | ++ ⬇<br>Self-reported exposure to light 10–15 years ago may be susceptible to non-differential memory bias; type of light was measured using pictures for reference which helps provide information about the intensity of lighting. Several different proxies included which allowed for assessment of various levels of light. |
| Kloog *et al.* 2011 | ++ ⬆<br>Exposure assessment methods have moderate sensitivity and specificity; includes information about levels of light and light from multiple sources at night. |

| Reference | Exposure Assessment rating |
|---|---|
| Li *et al.* 2010 | + ⬇<br>Exposure assessment methods were limited to measuring residential lighting at night or while sleeping and do not refer to other sources of light, e.g., lighting at work. For residential exposure the assessment method allows for some discrimination between exposed and non-exposed as electronic sources and use of shades from street lighting is incorporated. No attempt was made to combine exposures to all of these sources of light at night. |
| O'Leary *et al.* 2006 | + ⬇<br>Exposure assessment methods have ability to distinguish women with high or low exposure to light from lighting in the residential area only, but not exposure from other sources, including electronic devices, TV, outside lighting, daylight, or shiftwork, nor information on amount, spectrum, timing or duration of lighting. Because LAN was defined so narrowly, it is not known whether the "unexposed" were truly unexposed. Recall bias may be possible given this subset of subjects was selected for a second interview for electromagnetic measurements and light at night which took place on average 200 days later. |
| White *et al.* 2017 | + ⬇<br>The exposure assessment methods have poor sensitivity and specificity for classifying overall exposure to light at night and are limited to light in the sleeping area at night with no information on exposure or duration of exposure to light prior to bedtime or during sleep. There is no information regarding outdoor lighting exposure. |
| **Outdoor lighting** | |
| Bauer *et al.* 2013 | + ⬇<br>Exposure assessment methods have strengths and weaknesses: the validation substudy suggests that the Defense Meteorological Satellite Program-Operation Linescan System (DMSP-OLS) satellite images are highly correlated with daysimeter readings which measure circadian relevant light; however, the personal exposure to measured light is ill-defined outside of the residential address. No additional information about where subjects may have spent most of their time during the day or evening is provided. In addition, no information on length of residency at the address that was geocoded, meaning exposure is not certain. |
| Garcia-Saenz *et al.* 2018 | +++ ⬇<br>The exposure assessment methods have good sensitivity and specificity with respect to level of exposure, allowing for discrimination between exposed and unexposed along relevant axis (melatonin suppression). |
| Hurley *et al.* 2014 | ++ ⬇<br>Exposure assessment methods for outdoor light; the satellite imagery used was the best available at the time, however, the available images for just one year (2006) were not congruent with baseline addresses (1995–1996). an examination of the low-dynamic range data showed that light levels were relatively similar. Also, data from other addresses of individuals who moved was not incorporated into the overall analysis, although sensitivity analyses were performed limiting analysis to those who were residentially stable. In addition, there is disagreement over whether satellite images measure light relevant for circadian disruption (CD). |

| Reference | Exposure Assessment rating |
|---|---|
| James *et al.* 2017 | ++ ⬇<br>The exposure assessment methods have good relative sensitivity and specificity, leading to reliable classification (or discrimination) as all addresses starting at baseline throughout follow-up were incorporated. Broad range of exposure levels compared to previous studies (48 states); that is, highest levels are much higher than in other studies. Past addresses were not geocoded, so if early exposure to outdoor LAN is associated with breast cancer, this wouldn't have been captured. Also, shift workers, who have the most extreme light at night, were included in the analysis to capture indoor light at night at work. However, DMSP output from the satellite may not strictly correlate with the restricted portion of the spectrum that is circadian disruptive, thus while the exposure assessment was superior to many, it is still a question of whether this is the appropriate exposure proxy (as these images capture only a fraction of the light from the earth, but represent relative levels of nighttime illumination at ground level (Hsu et al. 2015). In addition, details about other indoor light exposures were not measured. |
| Keshet-Sitton *et al.* 2016 | + ⬇<br>Self-reported exposure to light 10–15 years ago may be susceptible to non-differential memory bias; exposure to strong outdoor source of LAN does not account for type of LAN or source. |

Table C-1c: Breast cancer and lighting at night (LAN) – Indoor and Outdoor: Outcome assessment rationale

| Reference | Outcome assessment rating |
|---|---|
| **Indoor lighting** | |
| Davis *et al.* 2001a | ++ ⬌<br>Outcome methods clearly distinguish between diseased and non-diseased subjects. Diagnoses were conducted independent of exposure status. No cancer subtypes analyzed. |
| Fritschi *et al.* 2013 | +++ ⬌<br>Outcome methods clearly distinguish between diseased and non-diseased subjects. Diagnoses were conducted independent of exposure status. |
| Garcia-Saenz *et al.* 2018 | +++ ⬌<br>Diagnoses appear to have been conducted independent of exposure assessment; cases were histologically verified. |
| Hurley *et al.* 2014 | +++ ⬌<br>Outcome methods clearly distinguish between diseased and non-diseased subjects; follow-up and diagnosis were conducted independent of exposure status. Subtypes also evaluated, although small numbers of exposed precluded analysis of subtypes. |
| Johns *et al.* 2018 | +++ ⬌<br>Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnosis were conducted independent of exposure status. |
| Keshet-Sitton *et al.* 2016 | + ⬇<br>Outcome methods were not sufficiently detailed to determine how breast cancer cases were defined (e.g., ICD codes); whether they are prevalent or incident cases; and if these included breast cancer *in situ*. No diagnostic criteria described |
| Kloog *et al.* 2011 | ++ ⬇<br>Cases could be included if breast cancer in non-index breast, meaning that some of the "controls" were in fact cases. Thus, outcome methods did not clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status. While there was information on human epidermal growth factor receptor 2 (HER2) status, this was not included in analysis. |
| Li *et al.* 2010 | +++ ⬌<br>Outcome methods clearly distinguish between diseased and non-diseased subjects. Histologically confirmed cases and potential non-cases from surgeries performed. Estrogen receptor/progesterone receptor (ER/PR) status was also determined. |
| O'Leary *et al.* 2006 | +++ ⬌<br>Outcome methods clearly distinguish between diseased and non-diseased subjects. Diagnosis was conducted independent of exposure assessment. |
| White *et al.* 2017 | ++ ⬇<br>Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status; not all cases were verified by pathology. |
| **Outdoor lighting** | |
| Bauer *et al.* 2013 | +++ ⬇<br>Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status. However, use of lung cancer cases as controls may bias results towards the null if LAN is related to lung cancer. |

| Reference | Outcome assessment rating |
|---|---|
| Garcia-Saenz *et al.* 2018 | +++ ⬌<br>Diagnoses appear to have been conducted independent of exposure assessment. Cases were histologically verified. |
| Hurley *et al.* 2014 | +++ ⬌<br>Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnosis were conducted independent of exposure status. Subtypes also evaluated, although small numbers of exposed precluded analysis of subtypes. |
| James *et al.* 2017 | +++ ⬌<br>Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status. |
| Keshet-Sitton *et al.* 2016 | + ⬇<br>Outcome methods are not sufficiently detailed to determine how breast cancer cases were defined (e.g., ICD codes); whether they are prevalent or incident cases; and if these included breast cancer *in situ*. No diagnostic criteria described |

Table C-1d: Breast cancer and lighting at night (LAN) – Indoor and outdoor: Sensitivity rationale

| Reference | Sensitivity rating |
|---|---|
| **Indoor lighting** | |
| Davis *et al.* 2001a | ++ ⬇<br>Sufficient numbers of exposed cases; exposure levels were able to distinguish women at various levels of light exposure, but not to other sources of light. Whether LAN in the 10 years prior to diagnosis is the relevant window of exposure is not known; no lagged analyses were performed. |
| Fritschi *et al.* 2013 | ++ ⬇<br>The study does not have enough information on all sources of exposure to light determine who actually had "high" or "low" exposure to light. Authors conducted lagged analyses to exposure that occurred in the windows of time > 30 years, 20–30 years, 10–20 years, and ≤ 10 years before recruitment compared with those who were unexposed during each window of time. |
| Garcia-Saenz *et al.* 2018 | ++ ⬇<br>The study has an adequate number of exposed subjects (N = 211 including both dim light and quite illuminated); but small numbers (31 cases) for highest level of illumination. |
| Hurley *et al.* 2014 | ++ ⬇<br>The study has ability to distinguish levels of exposure, but there is a small number of exposed subjects with high indoor bright light exposure at night. There is adequate duration of follow-up. WIndow of exposure (past year) may not be adequate to assess exposure. |
| Johns *et al.* 2018 | + ⬇<br>Substantial numbers of exposed, but questions did not categorize individuals into groups which may have been highly exposed to circadian effective light. |
| Keshet-Sitton *et al.* 2016 | ++ ⬇<br>The study has a small number of cases. The window of exposure is reasonable. Some information available to assess levels of light. |
| Kloog *et al.* 2011 | ++ ⬇<br>The study has adequate number of exposed subjects at high levels as defined by this protocol. As exposure is considered "current" there is no accounting for latency period, and assumes that the most recent, current exposure is the relevant window of exposure. No consideration that cases may change their behaviors with respect to night lighting, thereby violating the temporality criteria. |
| Li *et al.* 2010 | + ⬇<br>Small to adequate number of exposed subjects with poorly defined exposure levels; no information on duration, and window of exposure is set *a priori* (past 10 years). Given that cases (72%) and controls (60%) are primarily over the age of 50, if this exposure period (10 years prior) is not relevant, it may not be possible to detect an effect. |
| O'Leary *et al.* 2006 | + ⬇<br>The study had an adequate number of exposed subjects with substantial exposure as defined in this study to light in the sleeping area at night; however, because the definition of exposure was so limited, it is not clear that these individuals were highly exposed, or that unexposed were truly unexposed. Also, the window of exposure may not have been adequate as only the last 5 years prior to the reference date was measured in this older population. No analyses of night workers and light was possible given the small number of night workers; and analyses by cancer subtypes were not possible given the small numbers. |

| Reference | Sensitivity rating |
|---|---|
| White *et al.* 2017 | + ⬇<br>If LAN in the sleeping area at a particular time in life is related to breast cancer, this study would not capture early exposures, either in adolescence or in young adulthood. Light at night prior to sleeping not captured; duration of light being on not captured. No outside LAN captured. |
| **Outdoor lighting** | |
| Bauer *et al.* 2013 | + ⬇<br>Limited exposure range and highest levels are quite low in Georgia compared to other similar studies. Window of exposure variable for each woman. |
| Garcia-Saenz *et al.* 2018 | ++ ⬌<br>The study has an adequate number of exposed subjects in the third tertile (N = 126 for visual light; N =138 for dim light). However, the very top 5%–10% were not noted. LAN not measured/relevant for younger ages. |
| Hurley *et al.* 2014 | + ⬇<br>Window of early exposure was excluded as data were only examined for the follow-up period when the average age was older. the available images (2006) were not congruent with baseline addresses (1995–1996), although limiting analysis to those who did not move did not change results, and ranking of LAN values were stable over the time in the study area. |
| James *et al.* 2017 | ++ ⬇<br>Missing window of exposure prior to about age 33 in this young cohort of women may decrease sensitivity if early LAN exposure is the most relevant. |
| Keshet-Sitton *et al.* 2016 | ++ ⬇<br>The study has a small number of cases. The window of exposure is reasonable. Can't separate highly and lower exposed individuals by source or other characteristics of LAN. |

Table C-1e: Breast cancer and lighting at night (LAN) – Indoor and outdoor: Confounding rationale

| Reference | Confounding rating |
|---|---|
| **Indoor lighting** | |
| Davis *et al.* 2001a | Breast: ++ ↑<br>Did not control for socioeconomic status (SES); shift work was not taken into consideration in analysis (6% of population had a history of night work). |
| Fritschi *et al.* 2013 | Breast: +++ ↔<br>The study measured all relevant potential confounders and used appropriate analyses to address them. |
| Garcia-Saenz *et al.* 2018 | Breast: +++ ↔<br>The study models were adjusted *a priori* for base level variables and an additional set. Reproductive variables not included in final model. |
| Hurley *et al.* 2014 | Breast: ++ ↓<br>Variables in the pathway and family history of breast cancer, breastfeeding, physical activity, were unrelated to indoor LAN and including them in the final model is likely to have lowered the risk estimate; no information was included on shift work. |
| Johns *et al.* 2018 | Breast: ++ ↓<br>Variables in the pathway were included in the model and were likely to have lowered the risk estimate. |
| Keshet-Sitton *et al.* 2016 | Breast: ++ ↓<br>The study measured relevant potential confounders and used appropriate analyses to address them. Addition of variables in the pathway and unrelated to LAN in the model, however, was likely to bias results towards the null. |
| Kloog *et al.* 2011 | Breast: ++ ↔<br>The study measured relevant potential confounders, and included them in models, but did not show differences in alcohol, education, ethnicity, or parity by case-control status. |
| Li *et al.* 2010 | Breast: ++ ↑<br>SES not controlled. |
| O'Leary *et al.* 2006 | Breast: ++ ↑<br>Did not take 7.6% of shift workers into account in this analysis, even though the authors had data on both shift work and LAN. |
| White *et al.* 2017 | Breast: +++ ↔<br>None |
| **Outdoor lighting** | |
| Bauer *et al.* 2013 | Breast: + ↑<br>The study measured relevant potential confounders on an individual or county-wide basis with the exception of alcohol consumption, but it is likely there is residual confounding remaining as a result of the lack of individual level data for parity and education. |
| Garcia-Saenz *et al.* 2018 | Breast: +++ ↔<br>Models were adjusted *a priori* for base level variables and an additional set. None included reproductive variables. |
| Hurley *et al.* 2014 | Breast: ++ ↓<br>Variables in the pathway, family history of breast cancer, breastfeeding history, physical activity, were unrelated to outdoor LAN and including them is likely to have lowered the risk estimate; no information on shift work. |

| Reference | Confounding rating |
|---|---|
| James *et al.* 2017 | Breast: ++ ↔<br>Other factors associated with outdoor LAN may not be fully controlled by population density and air pollution and could explain the relationship between LAN and breast cancer; alternatively, factors unrelated to LAN but included in the model may reduce the estimates of the effect. |
| Keshet-Sitton *et al.* 2016 | Breast: ++ ↓<br>The study measured relevant potential confounders and used appropriate analyses to address them. Addition of variables in the pathway and unrelated to LAN in the model, however, was likely to bias results towards the null. |

Table C-1f: Breast cancer and lighting at night (LAN) – Indoor and outdoor: Analysis and selective reporting rationale

| Reference | Analysis rating | Selective reporting rating |
|---|---|---|
| **Indoor lighting** | | |
| Davis *et al.* 2001a | +++ ⬌<br>Study used relevant data and appropriate assumptions and methods of analysis. | +++ ⬌<br>No evidence that reporting of the data or analyses were limited to only a subset of the data that were collected. |
| Fritschi *et al.* 2013 | ++ ⬌<br>The study used relevant data and appropriate assumptions and methods of analysis. Amount of light was controlled for; and lagged analyses were conducted. However, for the LAN analysis, restricting the questions only to shiftworkers limited the utility of this information. | +++ ⬌<br>No evidence that selective reporting of data or analyses compromised the interpretation of the study. |
| Garcia-Saenz *et al.* 2018 | +++ ⬌<br>The study used relevant data and appropriate assumptions and methods of analysis | +++ ⬌<br>No evidence that reporting of data or analyses were limited to only a subset of the data collected |
| Hurley *et al.* 2014 | +++ ⬌<br>The study used relevant data and appropriate assumptions and methods of analysis. | +++ ⬌<br>No evidence that reporting of the data or analyses were limited to only a subset of the data collected. |
| Johns *et al.* 2018 | +++ ⬌<br>The study used relevant data and appropriate assumptions and methods of analysis. | +++ ⬌<br>No evidence that reporting of data or analyses were limited to only a subset of the data collected |
| Keshet-Sitton *et al.* 2016 | +++ ⬌<br>The study used relevant data and methods. | ++ ⬌<br>Reporting of the data were limited to statistical results, and no numbers of exposed cases or controls were reported. |
| Kloog *et al.* 2011 | ++ ⬌<br>The analysis did not use relevant available data in their methods; that is, it was not possible to determine results for different levels of light notwithstanding the fact that data were available. Relevant data would have included information on time periods or duration, but these variables were not available. | ++ ⬌<br>Reporting didn't clearly indicate number of cases or relationships between covariates or levels of lighting effect even though they had the data. |
| Li *et al.* 2010 | ++ ⬇<br>The study used relevant data and appropriate assumptions and methods of analysis, but stopped short of combining various indices of light at night exposure. | +++ ⬌<br>No evidence that reporting of the data or analyses were limited to only a subset of the data collected. |

| Reference | Analysis rating | Selective reporting rating |
|---|---|---|
| O'Leary *et al.* 2006 | +++ ⬌<br>The study used relevant data and appropriate assumptions and methods of analysis. | +++ ⬌<br>No evidence that reporting of the data or analyses were limited to only a subset of the data collected. |
| White *et al.* 2017 | +++ ⬌<br>The study used relevant data and appropriate assumptions and methods of analysis. | +++ ⬌<br>There is no evidence that reporting of the data or analyses were limited to only a subset of the data that were collected. |
| **Outdoor lighting** | | |
| Bauer *et al.* 2013 | +++ ⬌<br>The study used relevant data and appropriate assumptions and methods of analysis. | +++ ⬌<br>No evidence that reporting of data or analyses were limited to only a subset of the data that were collected. |
| Garcia-Saenz *et al.* 2018 | +++ ⬌<br>The study used relevant data and appropriate assumptions and methods of analysis. | +++ ⬌<br>No evidence that reporting of data or analyses were limited to only a subset of the data collected. |
| Hurley *et al.* 2014 | +++ ⬌<br>The study used relevant data and appropriate assumptions and methods of analysis. | +++ ⬌<br>No evidence that reporting of the data or analyses were limited to only a subset of the data collected. |
| James *et al.* 2017 | +++ ⬌<br>The study used relevant data and appropriate assumptions and methods of analysis. In particular, LAN analyses were both controlled for and stratified by shift work. | +++ ⬌<br>There is no evidence that reporting of the data or analyses were limited to only a subset of the data that were collected. |
| Keshet-Sitton *et al.* 2016 | +++ ⬌<br>The study used relevant data and methods. | ++ ⬌<br>Reporting of the data was limited to statistical results, and no numbers of exposed cases or controls were reported. |

**Table C-2: Breast cancer and light at night (LAN) study results – Indoor and outdoor**

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| **Indoor lighting studies** | | | | | |
| Davis *et al.* 2001b<br>Case-control<br>Seattle, WA<br>**Enrollment or follow-up:**<br>1992–1995 | **Population:**<br>Cases: 813; Controls: 793<br>**Exposure assessment method:** questionnaire | **OR Ambient light levels** | | Parity, family history of breast cancer, oral contraceptive (OC) use, sse of hormone replacement therapy (HRT) discontinued < 5 years, age. | **Exposure information:**<br>Bedroom light: self-reported ambient light level of bedroom at night, number of times per night turning on light, and percentage of night light was on. Non-peak sleep (not sleeping during nocturnal melatonin peak (going to sleep after 2:00 AM, rising before 1:00 AM, not sleeping): ever non-peak sleep, number nights/week, or number of years of non-peak sleep during 10 years prior to diagnosis.<br>**Strengths:**<br>Population-based case-control study with good response rates; early study conducted prior to concerns about light at night and breast cancer likely to introduce little recall bias; exposure assessment good for nonpeak sleep and adequate for light in the sleeping area.<br>**Limitations:**<br>Other sources of light in the sleeping area or prior to bedtime are not known; likely that unexposed were not completely unexposed.<br>**Additional results:**<br>-<br>**Confidence in evidence:**<br>Strong to moderate evidence (highest self-reported ambient light level (elevated, but not significant); frequent non-peak sleep. |
| | | Darkest | 1; 94 | | |
| | | Some light | 1 (0.7–1.4); 633 | | |
| | | Lightest | 1.4 (0.8–2.6); 35 | | |
| | | Continuous levels of light | 1.1 (0.9–1.2); 762 | | |
| | | **OR Frequency (# times/night) of light turned on during night** | | Same as above | |
| | | Reference | 1; 429 | | |
| | | < 0.3 | 0.8 (0.6–1.2); 67 | | |
| | | 0.3–0.8 | 1.1 (0.8–1.5); 94 | | |
| | | 0.8–1.3 | 1.1 (0.8–1.6); 93 | | |
| | | ≥ 1.3 | 1 (0.7–1.4); 80 | | |
| | | Continuous number of times | 1.03 (0.9–1.18); 763 | | |
| | | **OR Percentage of night with light on** | | Same as above | |
| | | Reference | 1; 435 | | |
| | | < 0.4 | 1 (0.7–1.4); 86 | | |
| | | 0.4–0.9 | 0.9 (0.6–1.2); 76 | | |
| | | 0.9–2.9 | 1 (0.7–1.4); 79 | | |
| | | ≥ 2.9 | 1 (0.7–1.4); 86 | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| | | Continuous percentage | 0.99 (0.97–1.02); 762 | | |
| | | **OR Frequency (nights/week) of non-peak sleep** | | Same as above | |
| | | Reference | 1; 665 | | |
| | | < 0.6 | 1 (0.5–1.8); 22 | | |
| | | 0.6–1.2 | 1.1 (0.6–2.1); 23 | | |
| | | 1.2–2.6 | 1 (0.5–1.9); 20 | | |
| | | ≥ 2.6 | 1.7 (1–3.1); 33 | | |
| | | Continuous nights per week | 1.14 (1.01–1.28); 763 | | |
| | | Trend-test *P*-value = 0.03 | | | |
| | | **OR Ever or duration (years) of non-peak sleep ≥ 3 nights/wk** | | Same as above | |
| | | No | 1; 682 | | |
| | | Yes | 1.4 (1–2); 81 | | |
| | | < 1 | 1.2 (0.6–2.3); 19 | | |
| | | 1.0–3.0 | 1.4 (0.7–2.8); 20 | | |
| | | 3.0–4.6 | 0.6 (0.3–1.5); 9 | | |
| | | ≥ 4.6 | 2.3 (1.2–4.2); 33 | | |
| | | Continuous number of years | 1.09 (1.02–1.18); 763 | | |
| | | Trend-test P-value = 0.01 | | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| Fritschi *et al.* 2013<br>Case-control<br>Western Australia<br>**Enrollment or follow-up:**<br>May 2009 – January 2011 | **Population:**<br>Cases: 1,202; Controls: 1,785<br>**Exposure assessment method:** questionnaire | **OR LAN during night shift work: level of exposure** | | Age | **Exposure information:**<br>Self-reported levels of light at work or while sleeping during the day; number of years exposed to high (enough light to read) or medium (enough light to see but not enough to read) light.<br>**Strengths:**<br>Large population based-study which measured self-reported LAN during night work.<br>**Limitations:**<br>Low response rate, particularly among controls. Exposure limited and non-exposure ill-defined. Potential for attrition bias.<br>**Additional results:**<br>-<br>**Confidence in evidence:**<br>Some evidence (reading easily at night at work [elevated, not significant]; < 10 or 10–19 years sleeping with medium/high light [elevated, not significant]). |
| | | Never exposed | 1; 947 | | |
| | | Ever exposed | 1.15 (0.96–1.38); 253 | | |
| | | Low levels | 0; 0 | | |
| | | Medium levels | 1.06 (0.82–1.37); 110 | | |
| | | High levels | 1.25 (0.98–1.59); 143 | | |
| | | < 10 years (medium/high levels) | 1.25 (0.99–1.57); 153 | | |
| | | 10–19 years (medium/high levels) | 1.21 (0.86–1.7); 65 | | |
| | | ≥ 20 years (medium/high levels) | 0.84 (0.55–1.28); 35 | | |
| | | Premenopausal | 1.1 (0.78–1.55); 92 | | |
| | | Postmenopausal | 1.17 (0.94–1.45); 196 | | |
| Garcia-Saenz *et al.* 2018<br>Case-control<br>Spain<br>**Enrollment or follow-up:**<br>2008–2013 | **Population:**<br>Cases: 380; Controls: 490<br>**Exposure assessment method:** Interview | **OR Indoor LAN (base model)** | | Age, center, educational level, menopausal status | **Exposure information:**<br>4 levels of self-reported LAN in the bedroom while sleeping atatat the age of 40: total darkness, almost dark, dim light, and quite illuminated.<br>**Strengths:**<br>Strong design and analysis.<br>**Limitations:**<br>Potential selection bias due to attrition in controls; exposure assessment restricted to self-reported data on light levels in the sleeping area based on one self-reported measurement at the age of 40.<br>**Additional results:** |
| | | Total darkness | - | | |
| | | Almost dark | 0.88 (0.55–1.41); 119 | | |
| | | Dim light | 1.26 (0.78–2.03); 180 | | |
| | | Quite illuminated | 1.08 (0.57–2.02); 31 | | |
| | | **OR Indoor LAN (fully adjusted model)** | | Age, center, educational level, menopausal status, socioeconomic status (SES), body mass | |
| | | Total darkness | - | | |
| | | Almost dark | 0.73 (0.44–1.21); 118 | | |
| | | Dim light | 1.01 (0.6–1.69); 178 | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| | | Quite illuminated | 0.77 (0.39–1.51); 31 | index (BMI), tobacco, family history of breast cancer, chronotype, adjustment for outdoor LAN, urban vulnerability index (UVI) | Fully adjusted model point estimates for exposure levels were null and non-significant. Chronotype showed no clear pattern; no correlation found between indoor and outdoor ALAN values; nor between outdoor ALAN visual and melatonin index.<br>**Confidence in evidence:**<br>No evidence |
| | | **OR Indoor LAN (base model) and morning chronotype** | | Age, center, educational level, menopausal status | |
| | | Total darkness | 1; 17 | | |
| | | Dim light | 1.67 (0.8–3.46); 85 | | |
| | | Quite illuminated | 1.29 (0.47–3.53); 11 | | |
| | | **OR Indoor LAN (base model) and evening chronotype** | | Age, center, educational level, menopausal status | |
| | | Total darkness | 1; 10 | | |
| | | Dim light | 0.65 (0.17–2.55); 27 | | |
| | | Quite illuminated | 1.2 (0.23–6.28); 7 | | |
| Hurley *et al*. 2014<br>Cohort<br>California<br>**Enrollment or follow-up:**<br>1995–1996 | **Population:**<br>California Teachers Study<br>106,731<br>**Exposure assessment method:**<br>questionnaire | **HR Use of Indoor LAN: Combined hrs/ night, frequency (night/wk) and duration (months)** | | Age, race/birthplace, family history of breast cancer, age at menarche, pregnancy history, breastfeeding history, physical activity, strenuous, BMI, alcohol | **Exposure information:**<br>Indoor users of LAN: heavy users (≥ 10 months for ≥ 5 days/week/≥ 7 hours/night); light users (0–-3 months, 1–3 days/week/1–2 hours/night); medium users: all other combinations of duration/frequency.<br>**Strengths:**<br>Large defined cohort of teachers with well-defined |
| | | No use of LAN | 1; 4,869 | | |
| | | Any use of LAN | 1.03 (0.9–1.18); 226 | | |
| | | Light user | 1.17 (0.87–1.57); 45 | | |
| | | Medium user | 0.99 (0.82–1.2); 109 | | |
| | | Heavy user | 1.13 (0.84–1.52); 44 | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| | | Trend-test *P*-value = 0.53 | | consumption, menopausal status + hormone replacement therapy, smoking status, smoking pack years, neighborhood SES, urbanization. | information on covariates; specific information on frequency and duration of bright light at night in the sleeping area.<br>**Limitations:**<br>Limited data on sources of LAN in the indoor environment leading to potential misclassification of exposure; window of most relevant exposure may not be adequate.<br>**Additional results:**<br>-<br>**Confidence in evidence:**<br>Some evidence (highest self-reported ambient level of light [not significant]). |
| Johns *et al.* 2018<br>Cohort<br>United Kingdom<br>**Enrollment or follow-up:**<br>2003–2012 | **Population:**<br>UK Generations Study<br>105,866<br>**Exposure assessment method:**<br>questionnaire | **HR LAN and Night waking, All women, year before recruitment** | | Age, benign breast disease, family history of breast cancer, SES score, age at menarche, age at first birth, parity, breastfeeding duration, OC use, HRT, menopausal status, age at menopause, BMI-premenopausal, BMI-post-menopausal, alcohol consumption, smoking, physical activity. | **Exposure information:**<br>Self-reported LAN in the sleeping area: light enough to read (high), light enough to see across room but not read (medium) and too dark to see your hand or wear a mask (low ) during year prior to recruitment and at age 20.<br>**Strengths:**<br>Large national prospective study, comprehensive assessment of breast cancer risk factors, high follow-up rates.<br>**Limitations:**<br>Limited exposure assessment in relation to LAN metrics, and precision of metric chosen. Concern as to whether "high" light represents light sufficient to result in circadian disruption and cancer.<br>**Additional results:**<br>-<br>**Confidence in evidence:** |
| | | Low | 1; 416 | | |
| | | Medium | 1 (0.89–1.12); 847 | | |
| | | High | 1.01 (0.88–1.15); 512 | | |
| | | No night waking | 1; 939 | | |
| | | Yes night waking | 1.01 (0.92–1.12); 674 | | |
| | | **HR LAN and Night Waking, Post-menopausal women, year before recruitment** | | Age, benign breast disease, family history of breast | |
| | | Low | 1; 271 | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| | | Medium | 1.05 (0.91–1.22); 521 | cancer, SES score, age at menarche, age at first birth, parity, breastfeeding duration, OC use, HRT, menopausal status, age at menopausse, BMI, premenopausal, BMI, post-menopausal, alcohol consumption, smoking, physical activity. | No evidence |
| | | High | 1 (0.85–1.18); 293 | | |
| | | No night waking | 1; 527 | | |
| | | Night waking | 0.96 (0.85–1.1); 427 | | |
| | | **HR LAN and Night Waking, Premenopausal women, year before recruitment** | | Age, benign breast disease, family history of breast cancer, SES score, age at menarche, age at first birth, parity, breastfeeding duration, OC use, HRT, BMI-premenopausal, alcohol consumption, smoking, physical activity. | |
| | | Low | 1; 145 | | |
| | | Medium | 0.91 (0.74–1.1); 326 | | |
| | | High | 1 (0.81–1.24); 219 | | |
| | | No night waking | 1; 412 | | |
| | | Night waking | 1.1 (0.93–1.29); 247 | | |
| | | **HR LAN and night waking, All women, age 20** | | Age, benign breast disease, family history of breast cancer, SES score, age at menarche, age at first birth, parity, | |
| | | Low | 1; 452 | | |
| | | Medium | 1.02 (0.9–1.16); 846 | | |
| | | High | 1 (0.88–1.15); 540 | | |
| | | No night waking | 1; 1450 | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| | | Night waking | 0.85 (0.7–1.04); 103 | breastfeeding duration, OC use, HRT, BMI-premenopausal, alcohol consumption, smoking, physical activity, BMI- post-menopausal, menopausal status, age at menopause | |
| | | **HR LAN and Night Waking, Post-menopausal women, age 20** | | Age, benign breast disease, family history of breast cancer, SES score, age at menarche, age at first birth, parity, breastfeeding duration, OC use, HRT, BMI-premenopausal, alcohol consumption, smoking, physical activity, BMI-post-menopausal, menopausal status, age at menopause | |
| | | Low | 1; 227 | | |
| | | Medium | 1.11 (0.95–1.29); 525 | | |
| | | High | 1.04 (0.88–1.24); 302 | | |
| | | No night waking | 1; 857 | | |
| | | Night waking | 0.96 (0.73–1.27); 53 | | |
| | | **HR LAN and Night Waking, Pre-menopausal women, age 20** | | Age, benign breast disease, family history of breast cancer, SES score, age at menarche, age at first birth, parity, | |
| | | Low | 1; 125 | | |
| | | Medium | 0.88 (0.71–1.08); 321 | | |
| | | High | 0.91 (0.73–1.13); 238 | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| | | No night waking | 1; 593 | breastfeeding duration, OC use, HRT, BMI-premenopausal, alcohol consumption, smoking, physical activity | |
| | | Night waking | 0.74 (0.55–0.99); 50 | | |
| | | **HR ER positive tumor, High LAN or waking at night** | | Age, benign breast disease, family history of breast cancer, SES score, age at menarche, age at first birth, parity, breastfeeding duration, OC use, HRT, BMI-premenopausal, alcohol consumption, smoking, physical activity. | |
| | | All, high LAN, year before recruitment | 0.98 (0.84–1.14); 391 | | |
| | | All, waking, year before recruitment | 1.01 (0.9–1.13); 524 | | |
| | | All  high LAN, at age 20 | 1 (0.86–1.17); 409 | | |
| | | All, waking, at age 20 | 0.82 (0.65–1.04); 77 | | |
| | | Postmenopausal, high LAN, year before recruitment | 0.97 (0.81–1.17); 226 | | |
| | | Postmenopausal, waking, year before recruitment | 0.96 (0.83–1.11); 336 | | |
| | | Postmenopausal, high LAN, at age 20 | 1 (0.82–1.22); 224 | | |
| | | Postmenopausal, waking, at age 20 | 0.95 (0.69–1.3); 41 | | |
| | | Premenopausal, high LAN, year before recruit | 0.97 (0.76–1.24); 165 | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| | | Premenopausal, waking, year before recruitment | 1.09 (0.91–1.31); 188 | | |
| | | Premenopausal, high LAN, at age 20 | 0.97 (0.76–1.25); 185 | | |
| | | Premenopausal, waking, at age 20 | 0.69 (0.49–0.97); 36 | | |
| | | **HR ER negative tumor, High LAN or waking at night** | | Age, benign breast disease, family history of breast cancer, SES score, age at menarche, age at first birth, parity, breastfeeding duration, OC use, HRT, BMI-premenopausal, alcohol consumption, smoking, physical activity. | |
| | | All, high LAN, year before recruitment | 1.16 (0.82–1.65); 77 | | |
| | | All, waking, year before recruitment | 1.01 (0.78–1.32); 100 | | |
| | | All, high LAN, at age 20 | 0.94 (0.67–1.32); 84 | | |
| | | All, waking, at age 20 | 0.82 (0.49–1.4); 15 | | |
| | | Postmenopausal, high LAN, year before recruitment | 1.23 (0.79–1.92); 46 | | |
| | | Postmenopausal, waking, year before recruitment | 0.9 (0.64–1.26); 61 | | |
| | | Postmenopausal, high LAN, at age 20 | 1.17 (0.76–1.8); 53 | | |
| | | Postmenopausal, waking, at age 20 | 0.72 (0.32–1.63); 6 | | |
| | | Premenopausal, high LAN, year before recruitment | 1.04 (0.59–1.85); 31 | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| | | Premenopausal, waking, year before recruitment | 1.24 (0.82–1.86); 39 | | |
| | | Premenopausal, high LAN, at age 20 | 0.64 (0.37–1.11); 31 | | |
| | | Premenopausal, waking, at age 20 | 0.91 (0.45–1.82); 9 | | |
| Keshet-Sitton *et al.* 2016<br>Case-control<br>Israel<br>**Enrollment or follow-up:**<br>2010–2014 | **Population:**<br>Cases: 93; Controls: 185<br>**Exposure assessment method:**<br>Questionnaire | **OR Light before sleep** | | | **Exposure information:**<br>Self-reported light intensity, light use before or during sleep, light from outside.<br>**Strengths:**<br>Multiple metrics of exposure to light at night<br>**Limitations:**<br>Potential selection bias in this case-control study supported by the fact that breast cancer risk factors were unrelated to case-status; likely non-differential exposure misclassification, lack of information on numbers of participants at different levels of exposure.<br>**Additional results:**<br>-<br>**Confidence in evidence:**<br>Some evidence (subjective level of lighting, continuous [not significant]). |
| | | Reading with bed light | 0.81 (0.67–0.97); NR | | |
| | | Reading with room light | 0.96; NR | | |
| | | **OR LAN (indoor) use during sleep in bedroom** | | | |
| | | Turning lights on | 0.88; NR | | |
| | | Dim light | 0.89; NR | | |
| | | Sleep with light on (reading intensity) | 0.96; NR | | |
| | | TV on most of night | 1.26; NR | | |
| | | Falling asleep with TV on | 0.84; NR | | |
| | | **OR LAN levels and type of light** | | | |
| | | Subjective light intensity | 1.21; NR | | |
| | | Bedroom illumination LWL/SWL | 1.35; NR | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| | | Bed light illumination long-wavelength light (LWL)/short-wavelength light (SWL) | 1.56; NR | | |
| Kloog *et al.* 2011<br>Case-control<br>Israel<br>**Enrollment or follow-up:**<br>2006–2008 | **Population:**<br>Cases: 794; Controls: 885<br>**Exposure assessment method:**<br>questionnaire | **OR Sources of light during sleep hours** | | Education, ethnicity, parity, alcohol consumption | **Exposure information:**<br>Presence of several inside sources of lighting (e.g., bedlight, TV). Self-reported levels of light in the sleeping area (dark, low, average, and high (all lights on))<br>**Strengths:**<br>Large, population-based study of breast cancer. Multiple exposure metrics and ability to differentiate high and low exposed individuals.<br>**Limitations:**<br>Low response rates in controls; exposure assessment is limited to current time period which may violate temporality criteria that exposure precede disease; no data to assess latency, and assumes that current exposure is the relevant time window.<br>**Additional results:**<br>-<br>**Confidence in evidence:**<br>Evidence (subjective level of lighting, continuous) |
| | | Bedroom light intensity (1-4) | 1.22 (1.118–1.311); 425 | | |
| | | Bedroom shutters, open | 0.818 (0.663–1.008); 527 | | |
| | | TV on while sleeping | 0.914 (0.725–1.151); 180 | | |
| | | Trend-test *P*-value = 0.001 | | | |
| Li *et al.* 2010<br>Case-control<br>Connecticut, U.S.A.<br>**Enrollment or follow-up:** | **Population:**<br>Cases: 363; Controls: 356<br>**Exposure assessment method:**<br>Questionnaire | **OR Premenopausal women: Indoor LAN during sleep** | | Age, race, BMI, age at menarche, family history of breast cancer, age at first birth, breastfeeding duration, cigarette | **Exposure information:**<br>LAN in the sleeping area at night (e.g., keeping light on while sleeping, sleeping during night or day, clock radio, TV, hall light)<br>**Strengths:**<br>Well-conducted population-based case-control |
| | | No lights | 1; 67 | | |
| | | Lights on | 1.1 (0.4–3.6); 7 | | |
| | | No other light sources | 1; 13 | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| 1994–1997 | | Other light sources (e.g TV, hall light) | 1.1 (0.5–2.5); 61 | smoking, alcohol drinking. | study of breast cancer with information on subtypes.<br><br>**Limitations:**<br>Small sample size, weak exposure assessment limited to broad questions about bedroom lighting and sleeping during the day/night. Assumes current exposure is relevant window of exposure.<br>**Additional results:**<br>-<br>**Confidence in evidence:**<br>Evidence (turns on light when waking; daylight or sleeping during the day); some evidence among post-menopausal women (light from outside (shades up) while sleeping) |
| | | **OR Premenopausal women: Timing of sleep** | | Same as above | |
| | | Night | 1; 71 | | |
| | | Day | 0.9 (0.2–3.9); 3 | | |
| | | **OR Premenopausal women: Outdoor LAN during sleep** | | Same as above | |
| | | Shades down | 1; 62 | | |
| | | Shades up | 0.7 (0.3–1.5); 12 | | |
| | | No street/exterior light | 1; 42 | | |
| | | Street or exterior lighting | 1 (0.5–1.8); 32 | | |
| | | **OR Post menopausal women: Indoor LAN during sleep** | | Same as above | |
| | | No lights | 1; 263 | | |
| | | Lights on | 1.4 (0.7–2.7); 26 | | |
| | | No other light sources | 1; 45 | | |
| | | Other LAN sources (e.g., TV) | 1.1 (0.6–1.7); 244 | | |
| | | **OR Post menopausal women: Timing of sleep** | | Same as above | |
| | | Night | 1; 280 | | |
| | | Day | 1.4 (0.5–4.3); 9 | | |
| | | **OR Post menopausal women: Outdoor LAN during sleep** | | Same as above | |
| | | Shades down | 1; 215 | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| | | Shades up | 1.2 (0.8–1.9); 74 | | |
| | | No outside street or exterior lighting | 1; 180 | | |
| | | Street or exterior lighting | 1.1 (0.8–1.7); 109 | | |
| O'Leary *et al.* 2006<br>Case-control<br>Long Island, NY<br>**Enrollment or follow-up:**<br>August 1996–June 1997 | **Population:**<br>Electromagnetic fields and breast cancer on Long Island study<br>Cases: 487; Controls: 509<br>**Exposure assessment method:**<br>Questionnaire | **OR Frequency of lights on during sleep hours** | | Parity, family history of breast cancer, education, benign breast disease, age at reference date | **Exposure information:**<br>Frequency of turning lights on during sleep hours per night and per week.<br>**Strengths:**<br>Overall large sample size and analytic control for potential confounders.<br>**Limitations:**<br>Highly selected population-based on long-term residence; retrospective assessment of exposure in a delayed second interview creating opportunities for recall bias; exposure to light at night was limited to the past 5 years in this somewhat older subset of participants.<br>**Additional results:**<br>-<br>**Confidence in evidence:**<br>Strong to moderate evidence (waking ≥ 2/week and turning on light ≥ 2/night; and waking ≥ 1/week and turning on light ≥ 2/night (not significant). |
| | | < 1/mo or never | 1; 311 | | |
| | | 1–3/mo | 0.98 (0.66–1.44); 66 | | |
| | | 1/wk | 0.71 (0.43–1.16); 31 | | |
| | | 2–4/wk | 0.99 (0.67–1.48); 63 | | |
| | | ≥ 5/wk | 1.12 (0.8–1.57); 105 | | |
| | | **OR Frequency of lights on when waking: Highly exposed (lights ≥ 1 or 2 per week)** | | Parity, family history of breast cancer, education, benign breast disease, age at reference date | |
| | | 1–3/mo or never (ref) | 1; 377 | | |
| | | 1/wk: 1/night | 0.88 (0.67–1.16); 145 | | |
| | | 1/wk: ≥ 2/night | 1.46 (0.92–2.32); 53 | | |
| | | 2/wk: 1/night | 0.91 (0.67–1.24); 116 | | |
| | | 2/wk: ≥ 2/night | 1.65 (1.02–2.69); 51 | | |
| | | **Non-peak sleep: OR** | | Parity, family history of breast cancer, education, benign breast disease, age at reference date | |
| | | No | 1; 556 | | |
| | | Yes | 0.83 (0.44–1.57); 19 | | |
| White *et al.* 2017 | **Population:** | **HR Sleep: Frequency of waking up** | | Race, education, | **Exposure information:** |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| Cohort<br>Continental U.S.A. and Puerto Rico<br>**Enrollment or follow-up:**<br>2003–2009 | The Sister Study<br>50,884<br>**Exposure assessment method:** questionnaire | < 1 month | 1; 151 | income, marital status, HRT use, OC use, alcohol consumption, age at menarche, parity, age at first birth, age at menopause, pack years of smoking, physical activity | Frequency of waking (daily, weekly); and yes/no about turning on light/TV in sleeping area<br>**Strengths:**<br>Large sample size allowed consideration of ER status, excluded shift workers<br>**Limitations:**<br>Light at night prior to sleeping and duration of time that lights are on not captured. Assumes window of exposure is the relevant time window.<br>**Additional results:**<br>-<br>**Confidence in evidence:**<br>No evidence |
| | | 1–3 days/month | 0.98 (0.78–1.23); 163 | | |
| | | ≥ 1 / week | 0.92 (0.76–1.1); 612 | | |
| | | Most or every night | 1.05 (0.88–1.24); 1809 | | |
| | | **HR Sleep: Number of times waking up/night** | | Same as above | |
| | | Never | 1; 50 | | |
| | | 1 | 1.08 (0.81–1.44); 1538 | | |
| | | 2 | 1.14 (0.85–1.53); 743 | | |
| | | ≥ 3 | 1.13 (0.83–1.53); 400 | | |
| | | **HR LAN during sleep: All women** | | Same as above | |
| | | No LAN | 1; 486 | | |
| | | Daylight | 0.87 (0.66–1.15); 65 | | |
| | | Light/TV in room | 1.09 (0.93–1.26); 336 | | |
| | | Light outside room | 1.01 (0.9–1.13); 936 | | |
| | | Nightlight | 0.97 (0.87–1.08); 1762 | | |
| | | **HR LAN during sleep: ER+** | | Same as above | |
| | | No LAN | 1; 264 | | |
| | | Daylight | 1.05 (0.74–1.5); 41 | | |
| | | Light/TV in room | 1.2 (0.97–1.47); 178 | | |
| | | Light outside room | 1.11 (0.96–1.3); 543 | | |
| | | Nightlight | 1.07 (0.93–1.23); 1028 | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| | | **HR Turns lights on when waking up** | | Same as above | |
| | | No | 1; NR | | |
| | | Turn lights on | 1.07 (0.95–1.21); 320 | | |
| | | Lights already on | 0.86 (0.52–1.4); 18 | | |
| **Outdoor lighting studies** | | | | | |
| Bauer *et al.* 2013<br>Case-control<br>Georgia, U.S.A.<br>**Enrollment or follow-up:**<br>2000–2007 | **Population:**<br>Cases: 33,503; Lung cancer controls: 14,314<br>**Exposure assessment method:**<br>Environmental monitoring | **OR Outdoor LAN level** | | Race, tumor grade and stage, year of diagnosis, age at diagnosis, Metropolitan Statistical Area (MSA) (county level), MSA population mobility (county level), birth/1,000 women ages 15–50 (county level), prevalence of cigarette smoking at county level | **Exposure information:**<br>Range of LAN levels = 0 to 63 watts per steradian $cm^2$. Low = 0–20 watts per steradian $cm^2$; medium = 21–41 watts per steradian $cm^2$; and high = 41-63 watts per steradian $cm^2$.<br>**Strengths:**<br>Large population-based study of LAN; satellite measurements of LAN and cancer registry data based on individual level data. A substudy validation of ground level measurements of circadian-relevant light spectrum and satellite images strengthens this study.<br>**Limitations:**<br>Lung cancer controls may not be an appropriate choice as LAN has been found to be related to lung cancer in some studies. Potential selection bias due to large percentage of non-geocodable addresses; window of exposure varies for each woman; and changes of addresses over time are not incorporated. Further, DMSP data is the low-intensity data so range of exposure is narrow and low. County level covariates rather than individual level covariates increased likelihood of uncontrolled confounding. |
| | | Low | 1; 27,121 | | |
| | | Medium | 1.06 (0.97–1.16); 5,974 | | |
| | | High | 1.12 (1.04–1.2); 9,659 | | |
| | | **OR Outdoor LAN level: White women** | | Same as above | |
| | | Low | 1; 8,367 | | |
| | | Medium | 1.07 (0.97–1.17); 4,912 | | |
| | | High | 1.13 (1.05–1.22); 18,359 | | |
| | | **OR Outdoor LAN level: Black women** | | Same as above | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| | | Low | 1; 1,240 | | **Additional results:**<br>-<br>**Confidence in evidence:**<br>Evidence |
| | | Medium | 1.04 (0.78–1.38); 991 | | |
| | | High | 1.02 (0.82–1.28); 8,230 | | |
| Garcia-Saenz *et al.* 2018<br>Case-control<br>Spain<br>**Enrollment or follow-up:**<br>2008-2013 | **Population:**<br>Cases: 380; Controls: 490<br>**Exposure assessment method:** environmental monitoring | **OR Outdoor LAN - visual light (base model)** | | Age, center, education, menopausal status | **Exposure information:**<br>LAN from photos with 3 spectral bands from the International Space Station (ISS) 2012–13. Visual light average for cases = 0.034; blue light average for cases = 0.155.<br>**Strengths:**<br>Strong design and analysis and exposure assessment.<br>**Limitations:**<br>Potential selection bias due to attrition in controls; exposure at young age not captured.<br>**Additional results:**<br>No correlation between outdoor and indoor lighting for breast cancer; also no correlation between blue light and visual spectrum light.<br>**Confidence in evidence:**<br>Strong to moderate evidence |
| | | 1st tertile: 0.009–0.046 (reference) | 1; 133 | | |
| | | 2nd tertile: 0.046–0.071 | 0.86 (0.6–1.21); 121 | | |
| | | 3rd tertile: 0.071–0.226 | 0.86 (0.59–1.26); 126 | | |
| | | **OR Outdoor LAN - visual light (adjusted model)** | | Age, center, education, menopausal status, SES, urban vulnerability index (UVI), BMI, tobacco, family history of breast cancer, chronotype, indoor light. | |
| | | 1st tertile: 0.009–0.046 (reference) | 1; 132 | | |
| | | 2nd tertile: 0.046–0.071 | 0.87 (0.6–1.24); 121 | | |
| | | 3rd tertile: 0.071–0.226 | 0.81 (0.54–1.2); 123 | | |
| | | **OR Outdoor LAN - blue light (base model)** | | Age, center, education, menopausal status. | |
| | | 1st tertile: 0.041–0.128 (reference) | 1; 126 | | |
| | | 2nd tertile: 0.128–0.163 | 0.8 (0.56–1.15); 116 | | |
| | | 3rd tertile: 0.163–0.407 | 1.16 (0.81–1.66); 138 | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| | | **OR Outdoor LAN - blue light (adjusted model)** | | Age, center, education, menopausal status, SES, urban vulnerability index (UVI), BMI, tobacco, family history of breast cancer, chronotype, indoor light. | |
| | | 1st tertile: 0.041–0.128 (reference) | 1; 124 | | |
| | | 2nd tertile: 0.128–0.163 | 0.91 (0.62–1.32); 114 | | |
| | | 3rd tertile: 0.163–0.407 | 1.47 (1–2.17); 138 | | |
| | | **OR Outdoor LAN - MSI, ER+ PR+ and HER2-** | | Age, center, education, menopausal status. | |
| | | 1st tertile | 1; 84 | | |
| | | 2nd tertile | 0.86 (0.6–1.28); 82 | | |
| | | 3rd tertile | 1.26 (0.8–1.88); 101 | | |
| | | **OR Outdoor LAN - MSI, HER2+** | | Age, center, education, menopausal status. | |
| | | 1st tertile | 1; 18 | | |
| | | 2nd tertile | 0.8 (0.4–1.65); 19 | | |
| | | 3rd tertile | 0.99 (0.5–2.07); 20 | | |
| | | **OR Outdoor LAN - MSI, Triple negative** | | Age, center, education, menopausal status. | |
| | | 1st tertile | 1; 13 | | |
| | | 2nd tertile | 0.59 (0.2–1.6); 7 | | |
| | | 3rd tertile | 0.64 (0.2–1.8); 6 | | |
| Hurley *et al.* 2014<br>Cohort<br>California<br>**Enrollment or follow-up:** | **Population:**<br>California Teachers Study<br>106,731<br>**Exposure assessment method:**<br>Environmental monitoring | **HR All women: outdoor light levels (quintiles)** | | Age, race/birthplace, family history of breast cancer, age at menarche, pregnancy history, breastfeeding | **Exposure information:**<br>Average annual 2006 DMSP satellite night time radiance value assigned to residence at baseline.<br>**Strengths:**<br>Large defined cohort of teachers with full |
| | | 1 (lowest) | 1; 1006 | | |
| | | 2 | 1.05 (0.95–1.16); 1029 | | |
| | | 3 | 1.06 (0.95–1.17); 1010 | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| 1995–1996 | | 4 | 1.05 (0.95–1.17); 1009 | history, physical activity (strenuous) BMI, alcohol consumption, menopausal status + HRT, smoking status, smoking pack years, neighborhood SES, urbanization | information on potential confounders. **Limitations:** Window of outdoor light exposure limited to older ages; potential misalignment of satellite data and residential addresses. **Additional results:** - **Confidence in evidence:** Some evidence |
| | | 5 (hightest) | 1.12 (1–1.26); 1041 | | |
| | | Trend-test *P*-value = .0.06 | | | |
| | | **HR Premenopausal women BMI < 25: Outdoor LAN levels (quintiles)** | | Same as above | |
| | | 1 (lowest) | 1; 142 | | |
| | | 2 | 1.33 (1.03–1.73); 175 | | |
| | | 3 | 1.37 (1.05–1.8); 167 | | |
| | | 4 | 1.3 (0.98–1.72); 151 | | |
| | | 5 (highest) | 1.56 (1.16–2.08); 167 | | |
| | | Trend-test *P*-value = 0.02 | | | |
| | | **HR Premenopausal women BMI ≥ 25: Quintiles of outdoor LAN** | | Same as above | |
| | | 1 (lowest) | 1; 87 | | |
| | | 2 | 0.94 (0.67–1.33); 86 | | |
| | | 3 | 0.92 (0.64–1.32); 83 | | |
| | | 4 | 0.91 (0.62–1.32); 80 | | |
| | | 5 (highest) | 1.06 (0.72–1.56); 98 | | |
| | | Trend-test *P*-value = 0.59 | | | |
| | | **HR Postmenopausal women BMI <25: Outdoor LAN (quintiles)** | | Same as above | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| | | 1(lowest) | 1; 341 | | |
| | | 2 | 0.94 (0.79–1.12); 322 | | |
| | | 3 | 0.95 (0.8–1.14); 324 | | |
| | | 4 | 1.03 (0.86–1.24); 352 | | |
| | | 5 (highest) | 0.98 (0.8–1.18); 326 | | |
| | | Trend-test *P*-value = 0.82 | | | |
| | | **HR Postmenopausal women BMI ≥ 25: Outdoor LAN (quintiles)** | | Same as above | |
| | | 1 (lowest) | 1; 271 | | |
| | | 2 | 1.06 (0.87–1.28); 273 | | |
| | | 3 | 1.07 (0.87–1.31); 277 | | |
| | | 4 | 1.02 (0.82–1.25); 272 | | |
| | | 5 (highest) | 1.11 (0.89–1.39); 295 | | |
| | | Trend-test *P*-value: 0.44 | | | |
| James *et al.* 2017<br>Cohort<br>48 states in continental U.S.A<br>**Enrollment or follow-up:**<br>1989–2013; followup 1989–2013 | **Population:**<br>Nurses Health Study II. 109,672<br>**Exposure assessment method:**<br>Environmental monitoring | **HR Cumulative average LAN: Quintiles (median nW/cm²/sr)** | | Benign breast disease, family history of breast cancer, age at menarche, parity and age at first birth, height, white race, BMI, BMI at age 18, OC use, mammography screening, menopausal status, | **Exposure information:**<br>Cumulative LAN exposure based on time-varying satellite data for a composite of persistent nighttime illumination at ~ 1 km2 scale for each residence during follow-up. Quintiles with medians 4.3, 12.4, 22.9, 37.2, and 64 nW/cm2/sr.<br>**Strengths:**<br>Large established cohort of young nurses with shift work exposure; examination of impact of shift work on LAN estimates; inclusion of time-varying information on addresses throughout follow-up. |
| | | Quintile 1 (4.3) | 1; 571 | | |
| | | Quintile 2 (12.4) | 1.05 (0.94–1.18); 715 | | |
| | | Quintile 3 (22.9) | 1.01 (0.9–1.13); 710 | | |
| | | Quintile 4 (37.2n) | 1.08 (0.97–1.22); 776 | | |
| | | Quintile 5 (64.0) | 1.14 (1.01–1.29); 777 | | |
| | | Continuous LAN (per interquartile range [IQR], 31.6, increase) | 1.05 (1–1.11); NR | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| | | Trend-test *P*-value = 0.02 | | smoking status, alternative healthy eating index (AHEI), physical activity, marital status, living alone, personal income, shift work after 1989, region, PM2.5, census-tract median home value, income, population density. | **Limitations:**<br>Satellite images of visual light may not be the most relevant proxy for circadian disruption; missing measurement of LAN during window of early exposure and from indoor sources. While air pollution and population density were controlled, cannot rule out the possibility that other factors correlated with outdoor LAN may explain the observed association of LAN and breast cancer risk; many variables included in model which may not be associated with LAN that may reduce the estimate of effect.<br>**Additional results:**<br>Continuous LAN 1.06 (95% CI = 0.99–1.13) for ER+; Continuous LAN 0.98 (95% CI = 0.85–1.13) for ER-; p for heterogeneity for ER+/ER-, *P* = 0.33.<br>**Confidence in evidence:**<br>Some evidence |
| | | **HR Cumulative average LAN: Premenopausal women** | | Same as above except menopausal status | |
| | | Quintile 1 | 1; 282 | | |
| | | Quintile 2 | 1.02 (0.87–1.19); 367 | | |
| | | Quintile 3 | 1.08 (0.92–1.26); 415 | | |
| | | Quintile 4 | 1.12 (0.96–1.31); 447 | | |
| | | Quintile 5 | 1.2 (1.02–1.41); 462 | | |
| | | Continuous LAN (per IQR increase) | 1.07 (1.01–1.14); NR | | |
| | | **HR Cumulative average LAN: Postmenopausal women** | | Same as above | |
| | | Quintile 1 | 1; 223 | | |
| | | Quintile 2 | 0.96 (0.8–1.16); 242 | | |
| | | Quintile 3 | 0.92 (0.77–1.11); 229 | | |
| | | Quintile 4 | 0.99 (0.82–1.19); 248 | | |
| | | Quintile 5 | 0.95 (0.78–1.15); 230 | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| | | Continuous LAN (per IQR increase) | 1 (0.91–1.09); NR | | |
| | | **HR No shift work since 1989** | | Same as above except shift work status, menopausal status. | |
| | | Quintile 1 | 1; 386 | | |
| | | Quintile 2 | 0.98 (0.86–1.13); 469 | | |
| | | Quintile 3 | 0.96 (0.84–1.1); 472 | | |
| | | Quintile 4 | 1.01 (0.88–1.16); 515 | | |
| | | Quintile 5 | 1.04 (0.9–1.2); 511 | | |
| | | Continuous LAN (per IQR increase) | 1.03 (0.97–1.09); NR | | |
| | | **HR Cumulative average: Any shift work since 1989** | | Same as above | |
| | | Quintile 1 | 1; 185 | | |
| | | Quintile 2 | 1.18 (0.98–1.43); 246 | | |
| | | Quintile 3 | 1.09 (0.9–1.32); 238 | | |
| | | Quintile 4 | 1.19 (0.98–1.44); 261 | | |
| | | Quintile 5 | 1.29 (1.06–1.56); 266 | | |
| | | Continuous LAN (per IQR increase) | 1.09 (1.01–1.18); NR | | |
| | | **HR ER positive tumor** | | Same as above | |
| | | Quintile 1 | 1; 325 | | |
| | | Quintile 2 | 1.13 (0.97–1.3); 434 | | |
| | | Quintile 3 | 1.08 (0.93–1.26); 433 | | |
| | | Quintile 4 | 1.16 (1–1.35); 476 | | |
| | | Quintile 5 | 1.2 (1.02–1.4); 469 | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| | | Continuous LAN (per IQR increase) | 1.06 (0.99–1.13); NR | | |
| | | Trend-test *P*-value = 0.06 | | | |
| | | **HR ER negative tumor** | | Same as above | |
| | | Quintile 1 | 1; 96 | | |
| | | Quintile 2 | 0.92 (0.69–1.23); 105 | | |
| | | Quintile 3 | 0.8 (0.59–1.08); 95 | | |
| | | Quintile 4 | 0.93 (0.7–1.25); 111 | | |
| | | Quintile 5 | 0.94 (0.69–1.29); 105 | | |
| | | Continuous LAN (per IQR increase) | 0.98 (0.85–1.13); NR | | |
| | | Trend-test *P*-value = 0.86 | | | |
| | | **HR Continuous cumulative average exposure (per IQR increase): smoking status** | | Same as above except smoking status, shift work after 1989. | |
| | | Non smokers | 1 (0.94–1.07); NR | | |
| | | Past smokers | 1.1 (1.01–1.19); NR | | |
| | | Current smokers | 1.21 (1.07–1.37); NR | | |
| Keshet-Sitton *et al.* 2016<br>Case-Control<br>Israel<br>**Enrollment or follow-up:** | **Population:**<br>Cases: 93; Controls: 185<br>**Exposure assessment method:** questionnaire | **OR Outdoor LAN sources** | | | **Exposure information:**<br>Strong residential LAN source near sleeping area<br>**Strengths:** Population-based case-control study with specific metric of exposure to light at night from external source.<br>**Limitations:** |
| | | Closed shutters during sleep | 0.82 (0.68–0.99); NR | | |
| | | Residing near strong LAN sources | 1.52 (1.1–2.12); NR | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| 2010-2014 | | Outdoor light penetrating during sleep | 0.96; NR | | Breast cancer risk factors were unrelated to case-status, supporting potential selection bias; likely non-differential exposure misclassification, lack of information on source of external light.<br>**Additional results:**<br>-<br>**Confidence in evidence:**<br>Some evidence - residing near strong ambient source of LAN. |

**Table C-3a. Breast cancer and transmeridian travel: Selection bias rationale**

| Reference | Selection bias rating |
|---|---|
| Linnersjö *et al.* 2003 | ++ ⬌<br>Cases and controls selected from the cohort based on similar criteria; this young cohort was well defined (age at start < 30 years of age) with 5% of person-years among 60+ year olds. SIR overall was 1.01 for women (95% CI = 0.78–1.24) indicating no healthy worker effect (HWE) (SIR for breast cancer was 1.3 (95% CI = 0.85–1.74)). 8% were lost due to migration. |
| Pinkerton *et al.* 2016 | ++ ⬇<br>The cohort from which this nested study was composed is clearly defined (e.g., includes the relevant exposed, nonexposed, or referent group for a specific time period/location); there is no evidence of HWE as participants had 37% increased breast cancer risk compared to U.S. population. The original cohort (9,617) was reduced to the analysis incidence cohort (6,093) or 64.4% of original mortality cohort. Proxies responding for deceased individuals had lower response rates (41%/46%), but participants had longer employment histories with Pan Am than the initial mortality cohort, thus the remaining women constitute a survivor cohort. |
| Pukkala *et al.* 2012 | +++ ⬌<br>Included most of the certified cabin crew in four countries; no incomplete follow-up. |
| Reynolds *et al.* 2002 | ++ ⬌<br>Union files only available for one year, thus age, sex, and residential distributions had to be estimated for earlier time periods based on data from a single time period and assumptions of workforce profile stability and no information on race/ethnicity on non-cases. SIRs and proportional incidence ratios (PIRs) were similar, suggesting that little bias was introduced as a result of having data from only one period of time. |
| Schubauer-Berigan *et al.* 2015 | ++ ⬇<br>The cohort is clearly defined (e.g., includes the relevant exposed, nonexposed, or referent group for a specific time period/location); there is no evidence of HWE as participants had 37% increased breast cancer risk compared to U.S. population. The original cohort (9,617) was reduced to the analysis incidence cohort (6,093) or 64.4% of original mortality cohort. Proxies responding for deceased individuals had lower response rates (41%/46%), but participants had longer employment histories with Pan Am than the initial mortality cohort, thus the remaining women are a survivor cohort. |

Table C-3b. Breast cancer and transmeridian travel: Exposure assessment rationale

| Reference | Exposure assessment rating |
|---|---|
| Linnersjö *et al.* 2003 | ++ ⬇<br>Exposure assessment methods have moderate sensitivity and specificity, leading to reliable discrimination between exposed and unexposed. Block hours in long-distance flights may or may not adequately estimate times zones crossed. |
| Pinkerton *et al.* 2016 | ++ ⬌<br>The exposure assessment methods have moderate sensitivity and specificity, leading to some misclassification with respect to circadian disruption (CD) exposure metrics. Not all members had individual flight records; no records were available to back up self-reported time zones or radiation so these may be quite imprecise which could result in non-differential misclassification, although in this retrospective analysis, recall bias should be considered. |
| Pukkala *et al.* 2012 | ++ ⬇<br>Exposure assessment methods have moderate sensitivity and specificity crossing time zones. Women classified as unexposed or less exposed may have been more exposed since transmeridian flights with stopovers were counted as separate segments. No information on turnover rates (long stayovers or short stayovers), repeated jet lags, irregular night shift work, and associated sleep loss. Assumptions of similar route distribution may have misclassified exposure, but likely in the null direction. |
| Reynolds *et al.* 2002 | ++ ⬇<br>The exposure assessment methods have moderate sensitivity to differentiate exposed and unexposed. However, union records were limited and flight information based on only one point in time. Transmeridian flights are not clearly defined, only international flights; however, duration and age at entry were available. |
| Schubauer-Berigan *et al.* 2015 | ++ ⬌<br>The exposure assessment methods have moderate sensitivity and specificity, leading to some misclassification with respect to CD exposure metrics. Not all members had individual flight records; no records to back up self-reported time zones or radiation so these may be quite imprecise and could result in non-differential misclassification, although in this retrospective analysis, recall bias should be considered. |

Table C-3c. Breast cancer and transmeridian travel: Outcome assessment rationale

| Reference | Outcome assessment rating |
|---|---|
| Linnersjö *et al.* 2003 | +++ ⬌<br>Outcome methods clearly distinguish between diseased and non-diseased subjects; follow-up and diagnoses are conducted independent of exposure. |
| Pinkerton *et al.* 2016 | ++ ⬇<br>Includes prevalent cases in the population denominator. |
| Pukkala *et al.* 2012 | +++ ⬌<br>Complete record linkage in 4 countries. Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status. |
| Reynolds *et al.* 2002 | +++ ⬌<br>Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status. |
| Schubauer-Berigan *et al.* 2015 | ++ ⬇<br>Prevalent cases in denominator and second primaries in numerator increased population rates by 3.5% which would introduce bias towards the null. |

Table C-3d. Breast cancer and transmeridian travel: Sensitivity rationale

| Reference | Sensitivity rating |
|---|---|
| Linnersjö *et al.* 2003 | ++ ⬇<br>The study has a moderate level of sensitivity in that it is not clear if those classified as highly exposed actually crossed time zones; small numbers of exposed cases decreased power to detect an effect. |
| Pinkerton *et al.* 2016 | ++ ⬇<br>The study has highly correlated exposure metrics, flight data (domicile averages applied to individuals) likely contributed to high correlations between metrics and inability to detect an effect (however in studies of pilots with individual level data on cumulative cosmic dose and times zones, high correlations also exist); small numbers in certain relevant analytic subsets; adequate duration of follow-up for latency. |
| Pukkala *et al.* 2012 | ++ ⬇<br>Adequate sensitivity as 40% had at least 150 flights across 6 or more time zones. |
| Reynolds *et al.* 2002 | ++ ⬇<br>Use of the three metrics allowed differentiation of those at risk; numbers were adequate and follow-up was adequate. |
| Schubauer-Berigan *et al.* 2015 | ++ ⬇<br>The study has highly correlated exposure metrics, flight data (domicile averages applied to individuals) likely contributed to high correlations between metrics and inability to detect an effect (however in studies of pilots with individual level data on cumulative cosmic dose and times zones, high correlations also exist); small numbers in certain relevant analytic subsets; adequate duration of follow-up for latency. |

Table C-3e. Breast cancer and transmeridian travel: Confounding rationale

| Reference | Confounding rating |
|---|---|
| Linnersjö *et al.* 2003 | Breast: + ↑<br>An external source of information about potential confounders (limited to reproductive variables parity and age at first full-term pregnancy) was used to estimate that an excess breast cancer incidence of 10% would be expected rather than 1.3 observed. In addition, alcohol, socioeconomic status (SES), were not controlled. |
| Pinkerton *et al.* 2016 | Breast: +++ ↑<br>Indirect adjustments for parity and age at first birth suggest that the two factors in combination could have explained the excess risk observed. No adjustments were made for SES or alcohol consumption. |
| Pukkala *et al.* 2012 | Breast: ++ ↑<br>The study did not control for all potential confounders including SES, age. |
| Reynolds *et al.* 2002 | Breast: + ↑<br>The study did not control for potential confounders including alcohol consumption, parity. No measures of radiation dose were evaluated. |
| Schubauer-Berigan *et al.* 2015 | Breast: ++ ↑<br>Indirect adjustments made for independent effects of parity and age at first birth suggest that the two factors in combination could have explained the excess risk observed. No adjustments were made for SES or alcohol consumption. |

Table C-3f. Breast cancer and transmeridian travel: Analysis and selective reporting rationale

| Reference | Analysis rating | Selective reporting rating |
|---|---|---|
| Linnersjö *et al.* 2003 | +++ ⬌<br>The study used relevant data and appropriate methods of analysis. | +++ ⬌<br>No evidence that selective reporting of the data or analyses was limited to a subset of the data. |
| Pinkerton *et al.* 2016 | +++ ⬌<br>The study used relevant data and appropriate assumptions and methods of analysis. Multiple sensitivity analyses performed: alternative lag periods were considered, exclusion of data from proxies, exclusion of those with multiple diagnostic x-rays or radiation prior to diagnosis; surgical menopause time dependent term. | +++ ⬌<br>No evidence that reporting of the data or analyses were limited to only a subset of the data that were collected. |
| Pukkala *et al.* 2012 | +++ ⬌<br>The study used relevant data and appropriate assumptions and methods of analysis. | ++ ⬌<br>No indication that reporting was selective; however, results were less than adequately presented so that the number of cases in various categories were not shown. |
| Reynolds *et al.* 2002 | +++ ⬌<br>The study used relevant data and appropriate assumptions and methods of analysis. | +++ ⬌<br>No evidence that reporting of the data or analyses were limited to only a subset of the data that were collected. |
| Schubauer-Berigan *et al.* 2015 | +++ ⬌<br>The study used relevant data and appropriate assumptions and methods of analysis. Conducted multiple analyses with different lag windows. | +++ ⬌<br>No evidence that reporting of the data or analyses were limited to only a subset of the data that were collected. |

**Table C-4. Breast cancer and transmeridian travel study results**

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| Linnersjö *et al.* 2003<br>Nested case-control<br>Sweden<br>**Enrollment or follow-up:**<br>1957–1994 | **Population:**<br>Crew from the Swedish Scandinavian Airline System (SAS)<br>Cases: 48; Controls: 174<br>**Exposure assessment method:**<br>Company records | **OR > 10,000 total block hours** | | | **Exposure information:**<br>10,000+ block hours; high altitutde, long-distance flight duty; and 5,000+ block hours in high altitude long distance flights.<br>**Strengths:**<br>Administrative flight records available particularly on types of high-altitude long-duration flights; young exposed population.<br>**Limitations:**<br>Exposure assessment does not clearly differentiate cases highly exposed to multiple time zones; and the small numbers of cases led to inadequate power to detect an effect; no control for alcohol.<br>**Additional results:**<br>Comparator is female Swedish population.<br>**Confidence in evidence:**<br>Some evidence (high altitude, long duration flights) |
| | | < 10,000 block hours | 1; NR | | |
| | | > 10,000 block hours | 1.14 (0.15–8.48); 3 | | |
| | | **OR High altitude, long distance flight duty** | | | |
| | | Never | 1; NR | | |
| | | Ever | 1.79 (0.31–10.45); 14 | | |
| | | **OR > 5,000 block hours in high altitude, long distance flights** | | | |
| | | Never | 1; NR | | |
| | | Ever | 3.27 (0.54–19.7); 5 | | |
| | | **SIR External evaluation - Employment duration (years)** | | | |
| | | < 10 yr | 1.36 (0.72–2.32); 13 | | |
| | | 10–19 yr | 1.26 (0.67–2.15); 13 | | |
| | | 20+ yr | 1.39 (0.56–2.86); 7 | | |
| Pinkerton *et al.* 2016<br>Nested case-control<br>U.S.A.<br>**Enrollment or follow-up:**<br>2002–2005 | **Population:**<br>Pan American World Airways (Pan Am) flight attendants<br>Cases: 344; Controls: 5,749<br>**Exposure assessment method:**<br>questionnaire | **eRR Excess RR for 10-year lagged cumulative standard sleep interval (SSI)** | | | **Exposure information:**<br>Absorbed dose 10 mGy increase; SSI 2,000 hour increase; time zones crossed (per 4,600 increase in zones crossed).<br>**Strengths:**<br>Largest cohort of flight attendants with individual self-reported data; long follow-up; evaluated working during the standard sleep interval or circadian night; medical record follow-back and registry linkage for diagnosis verification; use of objective external sources to derive exposure |
| | | Per 2,000 hour increase of SSI, parity 0,1,2 | -0.039 (-0.15–0.14); NR | | |
| | | Per 2,000 hour increase of SSI, Parity = 3+ | 0.99 (-0.041–4.3); NR | | |
| | | Trend-test *p*-value: .06 | | | |
| | | **eRR Excess RR for 10-year lagged cumulative time zones crossed** | | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| | | Per 4,600 increase of time zones crossed, Parity = 0, 1, 2 | -0.0017 (-0.12–0.18); NR | | metrics for time zones crossed. Detailed and sensitive analysis and treatment of potential confounding and effect modification.<br>**Limitations:**<br>Low cumulative exposure, potential exposure misclassification, potential recall bias, relatively low participation.<br>**Additional results:**<br><br>**Confidence in evidence:**<br>Some evidence based on women of 3+ parity |
| | | Per 4,600 increase of time zones crossed, Parity = 3+ | 1.5 (0.14–6.2); NR | | |
| | | Trend-test *P*-value = 0.02 | | | |
| Pinkerton *et al.* 2012<br>Cohort<br>U.S.A.<br>**Enrollment or follow-up:**<br>2002–2005 | **Population:**<br>Pan American World Airways (Pan Am) flight attendants<br>11,311<br>**Exposure assessment method:**<br>company records | **SRR Standard sleep interval (SSI) (hours)** | | | **Exposure information:**<br>Duration of employment; standard sleep interval; time zones crossed<br>**Strengths:**<br>Largest cohort of flight attendants with individual self-reported data; long follow-up; evaluated working during standard sleep interval or circadian night; medical record follow-back and registry linkage for diagnosis verification; use of objective external sources to derive exposure metrics for time zones crossed and working during the standard sleep interval.<br>**Limitations:**<br>Low sensitivity due to mortality outcome; limited duration of employment; likely that there is some exposure misclassification; highly correlated exposure metrics.<br>**Additional results:**<br>-<br>**Confidence in evidence:**<br>Supporting evidence |
| | | 0 to < 318 | 1; 69 | | |
| | | 318 to < 792 | 1 (0.69–1.45); 69 | | |
| | | 792 to < 1,435 | 1.41 (0.98–2.05); 67 | | |
| | | 1,435 to < 2,642 | 1.13 (0.78–1.63); 70 | | |
| | | ≥ 2,642 | 0.93 (0.64–1.36); 68 | | |
| | | **SRR Employment duration (days)** | | | |
| | | 0 to < 731 | 1; 68 | | |
| | | 731 to < 1,614 | 0.78 (0.54–1.12); 68 | | |
| | | 1614 to < 2,831 | 1.02 (0.71–1.48); 69 | | |
| | | 2,831 to < 5,369 | 0.96 (0.65–1.41); 70 | | |
| | | ≥ 5,369 | 0.74 (0.51–1.08); 68 | | |
| | | **SRR time zones crossed** | | | |
| | | 0 to < 724 | 1; 69 | | |
| | | 724 to < 1,716 | 0.94 (0.66–1.36); 70 | | |
| | | 1716 to < 3,201 | 1.17 (0.81–1.68); 67 | | |
| | | 3201 to < 6,399 | 1.01 (0.69–1.47); 68 | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| | | ≥ 6,399 | 0.87 (0.6–1.26); 69 | | |
| Pukkala *et al.* 2012<br>Nested case-control<br>Nordic countries<br>**Enrollment or follow-up:**<br>1953–2005 | **Population:**<br>Nordic airline cabin crew from Sweden, Norway, Finland, and Iceland.<br>**Exposure assessment method:**<br>Company records | **OR RIsk per 100 flights crossing 6+ times zones** | | Parity, age | **Exposure information:**<br>100+ flights crossing 6+ time zones.<br>**Strengths:**<br>Large study with decades of population-based registration of incident cancer. Exposure assessment based on time zones crossed.<br>**Limitations:**<br>Exposure assessment may have been diluted due to the nature of company records on flights.<br>**Additional results:**<br>Similar results for those crossing 4+ or 5+ time zones. Also adjusted for age at first live birth which was similar in cases and non-cases.<br>**Confidence in evidence:**<br>No evidence |
| | | Per 100 crossings of 6+ times zones | 0.92 (0.77–1.11); NR | | |
| Reynolds *et al.* 2002<br>Cohort<br>California, U.S.A.<br>**Enrollment or follow-up:**<br>1988–1995 | **Population:**<br>California flight attendants. 44,021<br>**Exposure assessment method:**<br>Company records | **SIR Domestic vs. International flights** | | | **Exposure information:**<br>Domestic vs. international assignments; age starting employment < 25; employment duration 15+ years.<br>**Strengths:**<br>Largest flight attendant union, and largest population-based cancer registry, PIR and SIRs similar in magnitude, information on employment duration, age started and assignment on international flights. |
| | | Domestic | 1.21 (0.8–1.75); 28 | | |
| | | International | 1.79 (1.21–2.54); 31 | | |
| | | **SIR Employment duration (years)** | | | |
| | | ≥ 15 yr | 1.57 (1.16–2.08); 49 | | |
| | | < 15 yr | 0.96 (0.48–1.73); 11 | | |
| | | **SIR Age at entry** | | | |
| | | < 25 yr of age | 1.72 (1.23–2.34); 41 | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| | | ≥ 25 yr of age | 1.09 (0.65–1.7); 19 | | **Limitations:**<br>No control for confounders; exposure assessment based on one point in time, and does not indicate transmeridian crossing, only international flights.<br>**Additional results:**<br>-<br>**Confidence in evidence:**<br>Evidence |
| Schubauer-Berigan *et al.* 2015<br>Cohort<br>U.S.A.<br>**Enrollment or follow-up:**<br>2002–2005 | **Population:**<br>Pan American World Airways (Pan Am) flight attendants<br>6,093<br>**Exposure assessment method:**<br>questionnaire | **SRR Standard sleep interval (SSI) (hours)** | | | **Exposure information:**<br>> 933.9 time zones crossed; > 395 hours working during standard sleep interval (night work) (Grajewski *et al.* 2003; Waters *et al.* 2009) based on all airline jobs; > 853 days employment duration.<br>**Strengths:**<br>Largest cohort of flight attendants with individual self-reported data; long follow-up; evaluated working at night; medical record follow-back and registry linkage for diagnosis verification; use of objective external sources to derive exposure metrics for time zones crossed.<br>**Limitations:**<br>Selected participants employed longer with company so likely survivor cohort; Correlated exposure metrics; no airline history of flights so time zone metrics were calculated; low cumulative exposure, potential exposure misclassification, potential recall bias, relatively low participation. Prevalent cases in population denominator. No direct control for potential confounders or effect modifiers. |
| | | 0 to < 318 | 1; 69 | | |
| | | 318 to < 792 | 1 (0.69–1.45); 69 | | |
| | | 792 to < 1,435 | 1.41 (0.98–2.05); 67 | | |
| | | 1435 to < 2,642 | 1.13 (0.78–1.63); 70 | | |
| | | ≥ 2,642 | 0.93 (0.64–1.36); 68 | | |
| | | **SRR Employment duration (days)** | | | |
| | | 0 to < 731 | 1; 68 | | |
| | | 731 to < 1,614 | 0.78 (0.54–1.12); 68 | | |
| | | 1,614 to < 2,831 | 1.02 (0.71–1.48); 69 | | |
| | | 2,831 to < 5,369 | 0.96 (0.65–1.41); 70 | | |
| | | ≥ 5,369 | 0.74 (0.51–1.08); 68 | | |
| | | **SRR time zones crossed** | | | |
| | | 0 to < 724 | 1; 69 | | |
| | | 724 to < 1,716 | 0.94 (0.66–1.36); 70 | | |
| | | 1716 to < 3,201 | 1.17 (0.81–1.68); 67 | | |
| | | 3201 to < 6,399 | 1.01 (0.69–1.47); 68 | | |

| Reference, study-design, location, and year | Population description & exposure assessment method | Exposure category or level | Risk estimate (95% CI); exposed cases | Co-variates controlled | Comments, strengths, and weaknesses |
|---|---|---|---|---|---|
| | | ≥ 6,399 | 0.87 (0.6–1.26); 69 | | **Additional results:**<br>-<br>**Confidence in evidence:**<br>Some evidence |

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