Abstract

BACKGROUND: With the unprecedented urbanization light pollution is a ubiquitous problem, with accumulating evidence on the links between exposure to light at night (LAN) and breast cancer risk. We conducted a systematic review and meta-analysis of published studies on the associations between LAN exposure and breast cancer risk.

METHODS: We included all observational human studies wherein the exposure variable was LAN measured in indoor and outdoor environments, and the outcome was breast cancer. We employed summary relative risks (SRR) for breast cancer by comparing highest versus lowest categories of LAN exposure within a random-effects model. The National Toxicology Program's (NTP) Office of Health Assessment and Translation (OHAT) risk of bias rating tool was adopted to assess the risk of bias in individual studies and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guideline was employed to assess confidence in the body of evidence.

RESULTS: A total 14 studies comprising four cohorts (13 155 cases among 414 000 exposed subjects), nine case-control and one case-referent studies of female subjects (39 757 cases and 21 541 controls) across seven countries and published between 2001-20 were included for review. Participants in the highest LAN exposure category were associated with higher risk of breast cancer in reference to those in the lowest (SRR: 1.12; 95% CI: 1.06-1.18; I^2 = 39% for outdoor LAN, and SRR: 1.13; 95%CI: 1.05-1.21; I^2 = 19% for indoor LAN). Pooled evidence identified relatively pronounced association of outdoor LAN exposure and breast cancer among women with estrogen receptor positive (ER+) tumor (SRR: 1.21; 95% CI: 1.04-1.40) and premenopausal status (SRR: 1.21; 95% CI: 1.06-1.37). The final rate of confidence in the body of evidence generated was graded as 'moderate' based on GRADE guideline.

DISCUSSION: LAN exposure was consistently associated with higher breast cancer risk corroborating NTP's recommendations which anticipates excessive LAN as *human carcinogen*.

Keywords: light pollution, light at night, breast cancer, melatonin, meta-analysis

Introduction

Breast cancer is the second most commonly diagnosed cancer in the world after lung cancer with more than 2 million new cases being diagnosed in 2018 (Bray et al., 2018). In women, it constitutes the most commonly diagnosed cancer accounting for one-fourth of all cancer cases and also the leading cause of cancer deaths in over 100 countries worldwide, accounting for 15% of deaths (Bray et al., 2018; Ghoncheh et al., 2016). Breast cancer is a heterogeneous and multifactorial disease caused by a broad range of risk factors including hereditary and genetic factors that account for 5 to 10% of cases (Bray et al., 2018) as well as hormonal milieu, such as early age at menarche, nulliparity and late menopause, which have all been positively associated with breast cancer incidence (Bray et al., 2004; Hankinson et al., 2004). The role of lifestyle-level risk factors, such as diet (Lu et al., 2016), smoking (Gaudet et al., 2013), air quality (Andersen et al., 2017), alcohol consumption (Scoccianti et al., 2014; Zhang et al., 2007) as well as socioeconomic status (Baquet and Commiskey, 2000; Hastert et al., 2015) have also been suggested.

Among the environmental factors, emerging evidence point to the links between light pollution and risk of breast cancer. The unprecedented urbanization rate (with nearly 70% of the global population estimated to reside in cities by 2050) has meant exposure to irregular light environments is ubiquitous (United Nations, 2019), with over 80% of the population being exposed to light-polluted skies at night (Falchi et al., 2016). Data from calibrated satellite radiometer has consistently shown that earth's outdoor artificial light at night (LAN) increased by 2.2% per year over the period 2012-2016, with a total annual increment of 1.8% in radiance levels (Kyba et al., 2017). Additionally, the transformations in urban lifestyles have exacerbated the problem, with significantly higher exposure to artificial LAN including those emitted by electronic devices like smartphones and tablets (Chang et al., 2015), and associated chronic disease risks (Lai et al., 2020). Besides the physiologic and genetic factors, exposure to LAN has emerged as one of the key understudied environmental risk factors for breast cancer (Cho et al., 2015). Specifically, it has been hypothesized that LAN exposure disrupts the circadian rhythms by suppressing the secretion of nocturnal pineal melatonin which is an active anti-cancer and anti-metastasis agent. Simultaneously, disruption of circadian rhythms also increases the level of estrogen which is an important risk factor of breast cancer (Blask et al., 2002; Cohen et al., 1978; Stevens, 1987; Su et al., 2017).

Previously, a series of human epidemiological studies have examined the links between night shift work and breast cancer. Besides being an occupational risk factor, night shift work mostly acted as a surrogate of LAN with the assumption that night shift workers are likely to be exposed to higher levels of LAN as compared to those who are not night shift workers, notwithstanding, with no direct evidence (Megdal et al., 2005; Schernhammer and Schulmeister, 2004; Ward et al., 2019). Simultaneously, direct evidence of links between LAN exposure and breast cancer had emerged first from experimental animal studies (Anisimov et al., 2004; Kettner et al., 2016), and subsequently from several human studies. It has been suggested that the overall estimate of breast cancer risk reported in the studies involving shift work might have been overestimated on account of the simultaneous effects of other detrimental occupational hazards prevalent in the occupational environment and hence the need for direct evidence (Keshet-Sitton et al., 2016). Furthermore, in many of the studies thus far, LAN has been assessed within the indoor environment using questionnaires and only recently, there has also been a proliferation of metrics of outdoor LAN derived from satellite data. Given the emerging direct evidences linking LAN exposures with breast cancer, and the emergence of studies measuring outdoor LAN, we aim to conduct a comprehensive systematic review and meta-analysis to objectively answer the question: 'among the general population, what is the effect of the highest LAN exposure compared to the lowest exposure category on breast cancer risk as evident from observational studies?', with a clearly framed Population-Exposure-Comparator-Outcome-Study Design (PECOS) statement (Morgan et al., 2016) (Appendix A).

Methods

Study protocol and eligibility criteria

We followed the modified Preferred reporting items for systematic review and meta-analysis (PRISMA) checklist (Moher et al., 2009) (Appendix B) to report our findings. The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (Registration number: CRD42019150864) to minimize bias and duplication and ensure validity of the protocol.

In the present review, studies were eligible for inclusion if: (a) the independent exposure variable was nightlight exposure; (b) the outcome variable included breast cancer; (c) the study adopted an observational design, such as case-control or cohort studies and (d) the study was English in

language. Studies were excluded if they were: (a) non-human, (b) reviews, conference proceedings, editorials or commentaries, (c) of laboratory-based experimental design, and (d) ecological in design (on account of ecological fallacy and the consequent individual-level confounding).

Search strategy, study selection and accuracy

We searched MEDLINE (EBSCO), Academic Search Complete (EBSCO), CINAHL Plus (EBSCO) and PubMed for peer-reviewed articles published up to May 8, 2020, using search terms linked to nightlight exposures coupled with breast cancer risk (Appendix C). The choice of search engines was supported by literature analyzing the characteristics of search engines and other relevant review articles (Appendix D). The search terms, initially created by combining keywords as specified within our PECOS statement with additional iterative modifications and supplementations on the basis of prior literature and websites (Appendix E), were employed in both titles and abstracts without any filtering. Reference lists of selected studies and related review articles were also screened for potential inclusion. Upon removal of duplicates, records were further excluded based on titles and abstracts following with a full-text assessment for eligibility. Two investigators of the study team (KYL and CS) had independently assessed the eligibility of studies, evaluated the study quality, and extracted all the data to ensure data accuracy. Any discrepancies were resolved by a third arbiter investigator (LWTC). A list of data items as specified in Appendix F were extracted for each of the chosen study and inputted in a predefined table with the use of Excel. A brief summary table including lead author, year of publication, geographical setting, definition of breast cancer, definition of exposure, age, follow-up year (only for cohort studies), population size (N), and estimates (see below for more details) was also provided.

Statistical analysis

Random-effects meta-analysis model, allowing heterogeneity in the true effect sizes across studies, was employed to synthesize the estimates of the risk of breast cancer with LAN exposure (Borenstein et al., 2010). All analyses were conducted using the '*metafor*' package of R (Viechtbauer, 2010). Summary relative risk (SRRs) estimates were reported. The analyses were

conducted independently for self-reported indoor and satellite-derived outdoor LAN. In order to estimate the risk of breast cancer associated with the highest LAN exposure category in reference to the lowest, hazard ratios (HRs) or odds ratios (ORs) with their 95% confidence interval (95% CI) for the breast cancer risk in relation to light exposure were extracted. For studies that included both indoor and outdoor LAN measures, both the estimates were extracted. For studies that included outdoor measures, we included the estimates associated with the highest category of LAN exposure in reference to the lowest. Similar strategy was also applied to studies with self-reported indoor LAN that categorized exposures into three or more categories of light intensity or frequency. In cases where more than a single type of LAN exposure was available, estimates of exposure to a light source, in particular nightlight being switched on during sleep were extracted for analysis. When results were available for several degrees of adjustments for confounding, estimates in the full-adjusted model with the highest number of confounding were pooled. In cases where analytical results for both the total population and a specific sub-group of population (e.g., non-shift-workers only) were provided, the former estimate was pooled for calculation of risk estimation, while the latter was also employed in sensitivity analysis (further details were shown below), given that all confounding factors available were adjusted. To examine the consistency of evidence between studies, we estimated the heterogeneity between studies using the I^2 statistic (Higgins et al., 2003) (see Appendix G for interpretation of I^2). In order to visualize heterogeneity on account of publication bias, we produced funnel plots of logarithms of relative risk (RR) estimates against the inverse of standard errors (1/SE). We performed linear regression test for funnel plot asymmetry for the main summary estimates (Egger et al., 1997).

As a part of sensitivity analyses, we performed sub-group analysis to extract stratified summary estimates by tumor status, menopausal status, breast cancer conditions, LAN source, LAN type, geographical settings and study type if two or more estimates were available.

We further conducted 14 independent sensitivity tests for the identified set of studies involving both indoor and outdoor LAN exposures. These included rerunning the meta-analyses by excluding from the analyses the study with the a) highest weight; b) highest effect estimate; c) excluding studies with shift workers. To further test for the rigour of the included studies in terms of adjustments for confounding, we conducted sub-group analyses by including studies

adjusting for specific key confounding variables. These included studies adjusting for d) race or ethnicity, as a modifying factor in relation to racial or ethnic difference; e) body mass index (BMI) and physical activity, a potential precursor and protector for breast cancer respectively; f) family history of breast cancer, as a potential genetic factor. Secondly, given previous literature reporting on the importance of reproductive risks factors in breast cancer etiology (Anderson et al., 2014), we ran our analyses by including studies adjusting for key reproductive risk factors of (g) oral contraceptive use, and (h) age at menarche; (i) number of births/livebirths; (j) age at first birth/first full term pregnancy; (k) breast feeding history; (l) hormone replacement therapy use; and (m) menopausal status/age at menopause as key reproductive risk factors of breast cancer. Lastly, we reran our analyses by n) including the effect estimates from the second highest exposure category in reference to the lowest (only including studies reporting three or more LAN exposure categories).

We further conducted a dose-response meta-analysis of multiple studies to estimate the trends of the risks of breast cancer across outdoor LAN exposure profiles using the *dosresmeta* (Crippa and Orsini, 2016) and the *rms* (Harrell, 2015) packages in R. We modelled the log-relative risk against LAN exposure by conducting the restricted cubic spline regression analysis using equidistant Harrell's knots placed at 10, 50 and 90 percentiles of exposure (Harrell, 2015). Restricted maximum likelihood method with the covariance approximation method was employed (Greenland and Longnecker, 1992; Orsini et al., 2012).

Assessment of quality confidence in the body of evidence

We adopted the National Toxicology Program (NTP)'s Office of Health Assessment and Translation (OHAT) risk of bias rating tool (Appendix H) to assess the risk of bias in the chosen individual studies examining carcinogenicity of LAN (Achilleos et al., 2017; Rooney et al., 2014). The results of the overall risk of bias assessment comprised seven bias domains pertaining to selection, confounding, attrition/exclusion, detection biases for both exposure and outcome, selective reporting and other biases, as prescribed in the OHAT risk of bias rating tool (National Toxicology Program, 2015) (Appendix I).

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guideline to assess confidence in the body of evidence (Guyatt et al., 2008) (Appendix J). GRADE systematically assesses the overall confidence in the evidence generated from meta-

analysis by examining eight study dimensions namely, risk of bias, indirectness, inconsistency, imprecision, publication bias, large magnitude of effect, dose response and confounding effect and rates the quality of evidence as either 'high', 'moderate', 'low' or 'very low' based on the reviewers' overall judgement.

Results

A total of 753 records were retrieved from initial searches, including 289 from MEDLINE (EBSCO), 182 from Academic Search Complete (EBSCO), 76 from CINAHL Plus (EBSCO), 206 from PubMed database; the reference lists of selected studies are illustrated in Fig. 1. We excluded 397 records due to duplications. Of the 356 records screened, 328 studies were excluded based on title and abstract according to the eligibility criteria outlined in methodology. We further excluded 13 ecological studies after full text review. One additional study was excluded for employing the same data source as another study (Keshet-Sitton et al., 2016) with only stratified results (see Appendix K for the excluded records).

A total of 14 studies (Appendix L) published over the period 2001 to 2020 were included in the present review. These included four (28.5%) prospective cohort studies (Hurley et al., 2014; James et al., 2017; Johns et al., 2018; White et al., 2017), nine (64.3%) case-control (Davis et al., 2001; Fritschi et al., 2013; Garcia-Saenz et al., 2018; Keshet-Sitton et al., 2016; Kloog et al., 2011; Li et al., 2010; Oleary et al., 2006; Ritonja et al., 2020; Yang et al., 2019) and one (7.1%) case-referent study (Bauer et al., 2013) (Tables 1-2 shows the Study Profile after complete data extraction). The four prospective cohort studies comprised 414 000 participants with 13 155 diagnosed breast cancer cases having a follow-up of 6.1 to 22 years (mean follow-up of 12.5 years). The remaining ten case-control/case-referent studies comprised 39 757 breast cancer cases and 21 541 controls. All the studies included only female subjects aged 15 years and above. Stratifying by country, seven studies were conducted in the US (Bauer et al., 2013; Davis et al., 2001; Hurley et al., 2014; James et al., 2017; Li et al., 2010; Oleary et al., 2006; White et al., 2017), two in Israel (Keshet-Sitton et al., 2016; Kloog et al., 2011), and one each in Australia (Fritschi et al., 2013), Canada (Ritonja et al., 2020), Spain (Garcia-Saenz et al., 2018), the UK (Johns et al., 2018) and China (Yang et al., 2019).

In terms of the outcome variable, four studies regarded cases as both ductal carcinoma *in situ* (DCIS; non-invasive breast cancer) and invasive breast cancer (Johns et al., 2018; Oleary et al., 2006; Ritonja et al., 2020; White et al., 2017), while seven studies included only invasive breast cancer cases (Bauer et al., 2013; Davis et al., 2001; Fritschi et al., 2013; Hurley et al., 2014; James et al., 2017; Li et al., 2010; Yang et al., 2019). The remaining three studies lacked information pertaining to breast cancer conditions (Garcia-Saenz et al., 2018; Keshet-Sitton et al., 2016; Kloog et al., 2011).

Heterogeneity was observed in the methodologies employed for exposure assessment across the selected studies. There were two (14.3%) studies employing both self-reported indoor and satellite-derived outdoor LAN exposure measurements (Garcia-Saenz et al., 2018; Hurley et al., 2014). Nine (64.3%) studies exclusively adopted questionnaire-based self-reported indoor LAN (Davis et al., 2001; Fritschi et al., 2013; Johns et al., 2018; Keshet-Sitton et al., 2016; Kloog et al., 2011; Li et al., 2010; Oleary et al., 2006; White et al., 2017; Yang et al., 2019), while the remaining three (21.4%) adopted only outdoor LAN exposures (Bauer et al., 2013; James et al., 2017; Ritonja et al., 2020).

Of the five studies using outdoor LAN exposures, three employed remotely sensed images sourced only from the U.S. Defense Meteorological Satellite Program's (DMSP's) Operational Linescan System (OLS) (Bauer et al., 2013; Hurley et al., 2014; James et al., 2017; Ritonja et al., 2020), one used data sourced from the International Space Station (ISS) (Garcia-Saenz et al., 2018). Another employed data derived from both DMSP and the Visible Infrared Imaging Radiometer Suite Day-Night Band (Ritonja et al., 2020). One study adopted the cumulative average outdoor LAN for each questionnaire response accounting for changes of LAN exposure and address over time (James et al., 2017). Another employed 15-year time-series satellite images to measure average LAN exposure until the year of breast cancer diagnosis, assigned to subjects' residential addresses at diagnosis (Bauer et al., 2013).

Of the eleven studies which measured self-reported indoor LAN exposure, four reported on the types of light exposure in the bedroom (Keshet-Sitton et al., 2016; Kloog et al., 2011; Li et al., 2010; White et al., 2017), another four used questionnaire-based proxy of intensity of LAN exposure (Davis et al., 2001; Garcia-Saenz et al., 2018; Johns et al., 2018; Yang et al., 2019) and two employed questionnaire-based assessment of the frequency of light use at night (Hurley et

al., 2014; Oleary et al., 2006). The remaining one asked participants if they were exposed to LAN (Fritschi et al., 2013). With regard to the duration of measurement, three studies measured LAN exposure in 10 to 15 years before diagnosis (Davis et al., 2001; Keshet-Sitton et al., 2016; Li et al., 2010), two in 5 years before diagnosis (Oleary et al., 2006; Yang et al., 2019), one in 1 year before the baseline survey (Hurley et al., 2014), three at baseline (Fritschi et al., 2013; Kloog et al., 2011; White et al., 2017), one measured LAN over the years prior to recruitment (Johns et al., 2018) and the remaining one measured LAN when the participants were at age 40 years or at the age of diagnosis or interview (Garcia-Saenz et al., 2018).

The summary results of the random effects models examining associations between outdoor and indoor LAN exposures and breast cancer risk are presented in table 3. The participants in the highest outdoor LAN exposure category had 12% higher risk of breast cancer (SRR: 1.12; 95% CI: 1.06-1.18 in reference to those in the lowest exposure category) with a moderate level heterogeneity (I^2 = 38.97%). With respect to study design, the association remained significant in prospective cohort studies (SRR: 1.13; 95% CI: 1.04-1.23), but not in case-control studies (SRR: 1.09; 95% CI: 0.83-1.43). Moderate level of heterogeneity was observed in case-control studies (I^2 = 68.75%) only (see Appendix M). The results of our pooled analysis indicate significant positive effects remained in the US studies. The associations remained significant only in cases with estrogen receptor positive (ER+) tumor (SRR: 1.21; 95% CI: 1.04-1.40), premenopausal status (SRR: 1.21; 95% CI: 1.06-1.37), but not in cases with estrogen receptor negative (ER-) tumor (SRR: 0.91; 95% CI: 0.68-1.24) and postmenopausal status (SRR: 1.00; 95%CI: 0.90-1.11). Seven out of fourteen sensitivity tests produced significant results with low-to-moderate levels of heterogeneity (I^2 = 0-54%) (Appendix N). Specifically, sensitivity analyses with reproductive risk factors of breast cancer produced significant results in studies that adjusted for menopausal status/age at menopause, the associations being slightly attenuated (SRR: 1.11; 95%CI: 1.03-1.20).

Consistently, participants in the highest indoor LAN exposure category reported significantly higher risk of breast cancer (SRR: 1.13; 95%CI: 1.05-1.21 in reference to those in the lowest exposure category) with low level of heterogeneity (I^2 = 18.80%) (Fig. 2b). The pooled associations remained significant in studies conducted in Israel and case-control studies, but not in studies conducted in the US or Europe, and prospective cohort studies. The associations

between breast cancer risk and indoor LAN exposure were reported to be insignificant across tumor status (ER+: SRR: 1.07; 95% CI: 0.91-1.26; ER-: SRR: 1.11, 95% CI 0.86-1.41), menopausal status (premenopausal: SRR: 1.02; 95% CI: 0.84-1.24; postmanopausal: SRR: 1.04; 95% CI: 0.90-1.21), breast cancer conditions (both DCIS and invasive: SRR: 1.05; 95% CI: 0.95-1.16; invasive only: SRR: 1.05; 95% CI: 0.97-1.14) and LAN type. The results for the stratified analyses generally showed null heterogeneity (I^2 = 0%), except the two combining estimates of studies assessing nightlight on while sleeping (I^2 = 69.25%) and Israeli studies (I^2 =38.63%), in which moderate level of heterogeneity was evident. Three out of 14 sensitivity tests indicated significant positive associations between a higher levels of indoor LAN exposure and breast cancer risk low heterogeneity (I^2 = 0-25%) (Appendix N), except one synthesizing estimates that excluded shift workers (I^2 = 46.54%). Among the reproductive risk factors, studies adjusting for number of births/livebirths remained significant (SRR: 1.13; 95%CI: 1.02-1.24).

We further pooled two large prospective cohort studies comprising 249 909 participants with 8 644 breast cancer cases to estimate the dose-response curve showing the trajectory of breast cancer risk across the continuum of outdoor LAN adjusting for all other factors (Hurley et al., 2014; James et al., 2017). Increased dose of LAN exposure was consistently associated with a higher risk of breast cancer, with the result being significant only beyond the cut-point of approximately 50 nW/cm^2/sr being significantly associated with a 9-15% higher risk for breast cancer over the exposure range of 50-114 nW/cm^2/sr (Appendix O).

The OHAT risk of bias rating tool assessed the risk of bias in each study on the basis of criteria applicable to cohort (Appendix P) and case-control studies (Appendix Q) with results in table 3 and details summarized in Appendix R. Risk of biases regarding confounding, exposure measures, selective reporting and other bias were rated as ‘probably low’ in all the five studies that measured outdoor LAN (100%). 4/5 studies measuring outdoor LAN incorporated low risks for selection and exclusion biases (80%), whereas one presenting ‘probably high’ risk due to recruiting patients with lung cancer as referents and excluding considerable proportion of participants without precise geocoding respectively (Bauer et al., 2013). Detection bias for outcome was rated as ‘probably low’ in most cases (80%), except one lacking information regarding breast cancer conditions (Garcia-Saenz et al., 2018). Among the 11 studies measuring indoor LAN, risk of biases with respect to exclusion criteria, selective reporting and other bias

were rated as ‘probably low’ (100%). Selection bias rating of ‘probably low’ was found in 8/11 (73%) studies measuring indoor LAN, while a rate of ‘probably high’ was associated with the remaining studies owing to drawing controls from a population greatly dissimilar than cases including random digit dialing (Davis et al., 2001; Li et al., 2010; Oleary et al., 2006). Confounding bias rating of ‘probably low’ was also identified in 8/11 studies (73%), while the remaining were rated as ‘probably high’ for either adjusting for a large number of confounders with a small sample size (Yang et al., 2019) or failing to adjust for potential key confounders (Fritschi et al., 2013; Kloog et al., 2011). The detection bias for outcome was rated as ‘probably low’ in 8/11 studies (73%) with sufficient information regarding breast cancer conditions. Detection bias for exposure was rated as ‘probably high’ in studies employing self-reported LAN exposures.

The assessment of confidence in the body of evidence of the association between LAN exposure and risk of breast cancer performed following the GRADE guidelines has been summarized in Appendix S. Based on the above risk of bias assessment, detection bias for exposure was observed in studies employing indoor LAN measures. Several studies also showed biases with respect to selection, confounding, attrition/exclusion and outcome. Therefore, we judged that confidence in the results was weakened with sufficient evidence of risk of bias, producing a grade of -1 for such dimension. A grade of 0 was assigned to the remaining four downgrading domains, indicating that the cumulative evidence being affected by indirectness, inconsistency, imprecision and publication bias tend to be minimal. Confidence to the exposure-outcome association was strengthened by the dose-response curve, yielding a grade of +1 in the dose-response domain. The two upgrading domains including effect magnitude and confounding did not permit a judgement of upgrading, resulting in a grade of 0. The final rate of the overall confidence in the body of evidence remained at the level of ‘moderate’ based on the combined judgements of the reviewers in consideration of all the GRADE domains.

Discussion

Our systematic review and meta-analysis of 14 human observational studies published over the past two decades reported a positive association between higher LAN exposure level and risk of breast cancer. 80% (4/5) of studies employing satellite-derived outdoor LAN produced significant findings, reporting an overall 12% higher risk among participants in highest exposure

category in reference to the lowest, with moderate heterogeneity. Seven out of 14 sensitivity tests showed consistent results. Among the studies employing indoor LAN, 18.2% (2/11) of studies reported significant findings with a 13% higher risk of breast cancer in elevated LAN exposure category in reference to the lowest with moderate level of heterogeneity between the included studies. Three out of 14 sensitivity tests showed significant results. Dose-response analysis identified a threshold LAN value of 50 $nW/cm^2/sr$ beyond which exposures were significantly associated with higher risks of breast cancer. These are important findings, given the evidenced increasing LAN levels and its variability in major cities across the world, thereby constituting a significant risk factor of breast cancer (Falchi et al., 2019). The observed positive association between LAN exposure and breast cancer incidence was also consistent with a few other ecological studies (not included in our analyses) conducted in Israel (Keshet-Sitton et al., 2017), Korea (Kim et al., 2015) and the US (Portnov et al., 2016). The rate of confidence in the body of evidence generated from the included studies was considered 'moderate' as per the GRADE guideline. The evidence of the association between LAN exposure and breast cancer compliments the recommendations of the NTP which has reported that: "excessive LAN exposure combined with insufficient daylight exposure — that cause circadian disruption are *reasonably anticipated to be a human carcinogen*" (p. 196) (National Toxicology Program, 2018).

We additionally found that independent of shift work, exposure to LAN was associated with increased risk for breast cancer, although the result remained significant in studies involving outdoor LAN. Prior studies have employed shift work as a surrogate for LAN exposure, nonetheless, breast cancer risk of night shift workers can plausibly be attributed to other risk factors related to occupational exposures such as altered eating habit, greater alcohol consumption as well as hazardous environmental risks (Dorrian et al., 2017; Wong et al., 2010). As evidenced by our analysis, LAN exposure should not be considered solely as a kind of occupational exposure in order to overcoming confounding due to other risk factors prevalent in work environments.

Accurate case ascertainment is important for methodological rigor. The cumulative evidence may potentially be biased from the varying classifications of breast cancer conditions in different studies. In our meta-analysis, 3/14 studies lacked relevant information on breast cancer

condition. We suggest that future studies should specify explicitly the inclusion criteria for breast cancer cases to ensure standardization across studies with respect to stage/severity and transparency of reporting.

Systematic and rigorous assessment of LAN exposure is important for robust evidence and overall, our analysis reported a 'probably high' risk of bias in 9/14 included studies on account of the studies employing only self-reported questionnaire-based measures of indoor LAN exposure which may potentially be associated with recall bias (Kyba and Spitschan, 2018) and resulting exposure misclassification. We suggest future studies should appraise the validity of the self-reported instruments, especially the temporal gap between outcomes assessment and exposure measurement (duration of recall in retrospectively assessed indoor LAN). With the evolving technology, the application of more objective measures of bedroom LAN such as with sensors and light meters is of value (Kyba and Spitschan, 2018).

The application of remote sensing-derived metrics of outdoor LAN has certain advantages given objectivity associated with such measures, the ability to automate such measures at a large scale as well as the potential to employ standardized exposure metrics across studies. 4/5 studies retrieved nightlight satellite data from the DMSP which provides an objective measure of LAN exposure, while one used employed ISS data, which employs nighttime photographs taken by astronauts at relatively high spatial resolution of around 10m/pixel (Kotarba and Aleksandrowicz, 2016). Remotely-sensed satellite data have traditionally been employed for exposure assessment in epidemiological studies such as those measuring greenspace (Rojas-Rueda et al., 2019). The application of remotely sensed data of validated spatial and temporal resolution to estimate outdoor LAN has inherent strengths in terms of objectivity, nonetheless, it is imperative to model potential ground-level distortions in LAN, especially in high density urban landscapes by accounting for factors such as terrain, building height, tree cover, etc. Another challenge in employing satellite-derived LAN emerges from the saturation of luminosity values in highly urbanized areas resulting in same DN values and consequent lower differentiation in LAN in urban cores. Future studies employing DMSP data should mitigate such saturation effects in highly urbanized areas by accounting for land surface features (Li and Zhou, 2017; Zhang et al., 2013).

It is noteworthy to mention that indoor LAN exposure is a more important risk factor of breast cancer in terms of dosage, given most people spend significant amount of time at night in their homes with the potential to be directly absorbed by the retina and perturbing circadian rhythm. Additionally, it may be plausible that the impacts of outdoor LAN are likely to attenuate if micro-level factors such as the use of orientation of window, use of blinds, eye masks etc are not accounted for. There has thus far been no study examining the effect of indoor LAN on risk of breast cancer using objective measurements. With the evolution of sensor technology as well as cloud-based data sharing platforms, this is a possibility to be explored in future studies. A greater rigour in LAN assessment will entail accounting for both indoor and outdoor LAN. It has been evidenced that satellite derived metrices of LAN may not act as a good proxy for personal indoor LAN exposure, plausibly attributed to the modifying effects of micro-level factors such as window orientation, use of curtains, masks etc (Huss et al., 2019).

Future studies should also account for temporal incongruence between the actual LAN exposure measurements and the time of breast cancer incidence and diagnosis as has been reported in some of the studies pooled together. As in any observational study, selection bias emerging from neighbourhood self-selection and migration exist. Similarly, future studies must also take account of the change of address over the years before cancer diagnosis to reliably capture exposures. Thus far, studies have tended to assign LAN value to the address according to their own selection, either residence at cancer diagnosis (Bauer et al., 2013), residence at baseline (Hurley et al., 2014) or residence with the longest duration (Garcia-Saenz et al., 2018). Only two studies have thus far adopted a detailed design, one measuring the cumulative average outdoor LAN for each questionnaire response and accounted for changes of LAN and address changes over the entire duration of the study (1996-2013) (James et al., 2017) and another one measuring the mean outdoor LAN taken into account participants' residential histories from 5 to 20 years before study entry (Ritonja et al., 2020).

As in any observational study, the issue of residual confounding is an important factor impeding causal inference and in our analyses of 3/10 case-control/case-referent studies reported 'probably high' confounding bias. It is important to account for micro-environmental factors that may lead to exposure misclassification distorting individual-level LAN exposures, such as subjects using blackout curtains or eye masks during bedtime as well as usage of short-wavelength light-

emitting electronic devices at night (Cajochen et al., 2011) that may potentially induce melatonin suppression (Higuchi et al., 2003; Lockley et al., 2003).

The underlying mechanism from LAN exposure to the development of breast cancer has been evidenced to follow the melatonin pathway. Melatonin (N-acetyl-5methoxytryptamine), primarily synthesized in human pineal gland, acts as a chemical messenger translating the *light-dark* (L-D) cycle information to all the tissues in the body (Reiter, 1991). The Retinal Ganglion Cells (ipRGC), a special class of photoreceptors in the eyes sends out electrical impulses to the endogenous circadian clock − the suprachiasmatic nuclei (SCN) within the hypothalamus via the retino-hypothalamic tract for circadian photo-transduction (LeGates et al., 2014; Provencio et al., 2002; Stevens et al., 2007). This in turn synchronizes the rhythm of melatonin synthesis to the L-D cycle, with lower levels produced during day time and higher levels at night (Claustrat et al., 2005). It has been hypothesized that melatonin acts as an anticancer and anti-metastasis agent and breast cancer develops as a result of melatonin suppression attributed to higher exposure to LAN (Blask et al., 2002; Su et al., 2017). Melatonin inhibits cancer cell proliferation and telomerase activity as well as induces apoptotic cell death (Mediavilla et al., 2010). Mounting evidence also indicates the anti-metastasis functions of melatonin involve regulating expression of cell adhesion molecules associated with tight junctions and adherens junctions (Su et al., 2017).

It has also been hypothesized that LAN induced melatonin suppression may result in inadequate inhibition of estrogen, thereby increasing mammary carcinogenicity and stimulating development of breast cancer (Cohen et al., 1978; Schernhammer and Schulmeister, 2004; Stevens, 1987). Melatonin inhibits the growth of ER+ (estrogen responsive), but not ER- (estrogen-insensitive), breast cancer cell lines (Cos et al., 1998; Hill et al., 1992; Yuan et al., 2002). Estrogen has been known to promote breast cancer via induced changes in the expression of growth factors (such as TGF-α, TGF-β, IGF) or specific oncogenes (Dickson and Lippman, 1987). Consistently, in our meta-analyses, a higher breast cancer risk was found among ER+ subjects, as compared to that of ER-, though the result was only significant in studies measuring outdoor LAN.

Stratifying our meta-analysis by menopausal status produced an overall positive association between outdoor LAN exposure and breast cancer risk in subjects with premenopausal status, but

not among those with postmenopausal status. It is plausible that premenopausal status may act as a proxy of age effects upon lenticular transmittance and pupil diameter. As the lenticular transmittance at short-wavelengths as well as the pupil diameter attenuate with age (Charman, 2003), younger people are likely to be more susceptible to LAN exposure and associated melatonin suppression, leading to a higher breast cancer risk. Furthermore, nightlight may potentially shorten the length of menstrual cycle, which may impose further impact upon a higher breast cancer risk among subjects at premenopausal stage (Lin et al., 1990; Stevens and Rea, 2001). Our evidence corroborates a recent meta-analysis reporting relatively higher risk of breast cancer among premenopausal women engaged in night shift work of higher intensity and longer duration (Cordina-Duverger et al., 2018). Another potential factor is varying lifestyles between the young and the old with higher nighttime exposure to light-emitted devices in the former.

Conclusion

Breast cancer is a global public health challenge. Although its prevalence has been comparatively higher in high income countries, mortality from it is about 13% higher in lower and middle income countries (Tao et al., 2015). Our study found a positive association between exposure to LAN and breast cancer risk reporting a 12% and 13% higher risk in the top LAN exposure category (in reference to the bottom category), measured in outdoor and indoor environments respectively. Dose-response analysis also showed significant effects upon breast cancer risk beyond a threshold of 50 $nW/cm^2/sr$ LAN exposure. The degree of confidence in the body of evidence generated in the studies included in this meta-analysis was rated as 'moderate' as per the GRADE guideline.

With the increasing urbanization and the ubiquity of light pollution, exposure to LAN has emerged as an important public health issue. Following WHO's stress on the role of occupational environment in melatonin suppression and associated carcinogenicity in 2007 (Straif et al., 2007), NTP has recently identified LAN causing circadian disruption as a *human carcinogen* (National Toxicology Program, 2018). The accumulating scientific evidence of the carcinogenicity of LAN exposure, as presented in this study has important public health implications, especially in guiding regulations governing artificial light in cities as an upstream level preventive intervention, thereby minimizing the health burdens of cancer.

Contributors

KYL and CS evaluated the study quality, and extracted all the data to ensure accuracy and analyzed it. LWTC advised throughout on study selection and aspects related to breast cancer as well as acted as the third arbiter investigator. KYL produced the first draft of the manuscript. All the authors (KYL, CS, LWTC, CW, MYN, JG) contributed to data interpretation and remodifying the draft. Discrepancies were resolved by discussions and consensus.

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