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Evaluating the association between artificial light-at-night exposure and breast and prostate cancer risk in Spain (MCC-Spain study)

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Abstract:	Background. Night shift work, exposure to light-at-night and the consequent circadian disruption may increase the risk of hormone-dependent cancers. Objectives. We evaluated the association of exposure to artificial light at night (ALAN) during sleeping time with breast and prostate cancer in a multi-population based case-control study (MCC-Spain), among subjects who had never worked at night. We took into account chronotype, a characteristic that may relate to adaptation to light-at-night. Methods. We enrolled 1219 breast cancer cases, 1385 female controls, 623 prostate cancer cases and 879 male controls from 11 Spanish regions, 2008-2013. Indoor-ALAN information was obtained through questionnaires and outdoor-ALAN was analyzed using images from the International Space Station (ISS) available for Barcelona and Madrid, including data of remotely sensed upward light intensity and blue light spectrum information for each geocoded longest residence of each MCC-Spain subject. Results. Among participants with information on both internal and external ALAN, exposure to higher levels of blue light spectrum (outdoor-ALAN) was associated with an increased risk of breast (adjusted odds ratio OR=1.54, 95%CI 1.0-2.4) and prostate cancer (OR=1.90, 95%CI 1.2-2.9) cancers. Overall light intensity (outdoor-ALAN) was not associated with cancer risk. Those sleeping in more illuminated bedrooms (indoor-ALAN) had a higher risk of prostate cancer [OR=2.82, 95%CI 1.5-5.3] while there was no clear association for breast cancer (OR=1.19, 95%CI 0.6-2.6). Evening types tended to have slightly higher prostate cancer risks. Conclusion. Both indoor and outdoor ALAN and particularly blue enriched light spectrum were associated with an increased risk of breast and prostate cancer.
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Evaluating the association between artificial light-at-night exposure and breast and prostate cancer risk in Spain (MCC-Spain study)

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Short title

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Conflict of interest

The authors declare that they have no conflict of interest.

ABSTRACT

Background. Night shift work, exposure to light-at-night and the consequent circadian disruption may increase the risk of hormone-dependent cancers.

Objectives. We evaluated the association of exposure to artificial light at night (ALAN) during sleeping time with breast and prostate cancer in a population based multicase-control study (MCC-Spain), among subjects who had never worked at night. We took into account chronotype, a characteristic that may relate to adaptation to light-at-night.

Methods. We enrolled 1219 breast cancer cases, 1385 female controls, 623 prostate cancer cases and 879 male controls from 11 Spanish regions, 2008-2013. Indoor-ALAN information was obtained through questionnaires and outdoor-ALAN was analyzed using images from the International Space Station (ISS) available for Barcelona and Madrid, including data of remotely sensed upward light intensity and blue light spectrum information for each geocoded longest residence of each MCC-Spain subject.

Results. Among participants with information on both indoor and outdoor ALAN, exposure to higher levels of blue light spectrum (outdoor-ALAN) was associated with an increased risk of breast (adjusted odds ratio OR=1.54, 95%CI 1.0-2.4) and prostate cancer (OR=1.90, 95%CI 1.2-2.9). Overall light intensity (outdoor-ALAN) was not associated with cancer risk. Those sleeping in more illuminated bedrooms (indoor-ALAN) had a higher risk of prostate cancer [OR=2.82, 95%CI 1.5-5.3] while there was no clear association for breast cancer (OR=1.19, 95%CI 0.6-2.6). Evening types tended to have slightly higher prostate cancer risks.

Conclusion. Both indoor and outdoor ALAN and particularly blue enriched light spectrum were associated with an increased risk of breast and prostate cancer.

INTRODUCTION

The increase of artificial light at night (ALAN) in cities has altered the natural light levels in the nocturnal environment and extended human activities into the usually dark hours (Falchi et al. 2011). It has been estimated that more than 80% of the world population (99% of the population from USA and Europe) and almost one-fifth of the world terrain is under light polluted skies (Cinzano et al. 2001, Falchi et al. 2011, Falchi et al. 2016).

Depending on light intensity and wavelength, exposure to ALAN may affect human health by decreasing the production and secretion of pineal melatonin (N-acetyl-5-methoxytriptamine), which is a hormone normally produced in the dark phase of the 24h cycle (Brainard et al. 2001; Chang et al. 2014; Escofet and Bará 2015; Thapan et al. 2013). Melatonin may be involved in epigenetic regulation of limiting cancer initiation and progression by reducing severe DNA damage that is a consequence of unstable oxygen and nitrogen-based reactants (Korkmaz and Reiter 2011).

Those mechanisms led the International Agency for Research on Cancer (IARC) to conclude that shift work which involves circadian disruption is "probably carcinogenic to humans" (IARC, 2007). Differences between day and night shift workers and circadian variation of melatonin production and light exposure have been evaluated showing the lower melatonin levels in night workers.

Moreover, the genetic background of each individual can affect the ability to have a preferential day or night profile (chronotype), the adaptation to night work and changes in sleep and wake schedules, and can define groups more or less susceptible to effects of circadian cycle disruption. For instance, Papantoniou et al (2014) identified the lowest

142 melatonin levels among night shift workers with morning preference chronotype, an
143 individual characteristic that may relate to night shift work adaptation.

144 Furthermore, genetic (and epigenetic) mechanisms of cycle regulation are well
145 described and include negative auto regulated transcription models of genes (Chellappa
146 et al. 2011). For instance, melatonin suppresses both estrogen receptor positive (ERα)
147 mRNA expression and estrogen induced transcriptional activity of the ERα in (ERα+)
148 human breast cancer cells (Hill et al. 2015).

149 Nevertheless, the IARC evaluation examined occupational rather than environmental
150 exposures and only few studies, most of them based on ecological comparisons, have
151 measured the direct impact of ALAN in cities on circadian rhythms and hormone-
152 dependent cancers. Nighttime satellite photometry, collected in the framework of the
153 U.S. Air Force Defense Meteorological Satellite Program—Operational Linescan
154 System (DMSP-OLS), has been used for mapping sky brightness and built surfaces
155 (Cinzano et al. 2000). Even though data obtained from satellite images are only able to
156 detect the intensity of light but not to measure the spectrum of nighttime lighting
157 emissions, different studies used this source of information to link the ALAN intensities
158 captured by DMSP-OLS with incidence rates of breast and prostate cancer and found a
159 significant positive association (Kloog et al. 2009, 2010). Furthermore, Rybnikova et
160 al. (2015, 2016), reanalyzed Kloog and co-authors work, using GLOBOCAN, US-
161 DMSP and World Bank's 2002 and 2012 databases, controlling for several country-
162 level predictors, including birth rates, percent of urban population, per capita GDP and
163 electricity consumption. They found a significant positive breast and prostate cancer-
164 ALAN association once the data were reorganized in geographic clusters of similarly
165 developed countries. Additionally, further studies (Bauer et al. 2013; Hurley et al.,
166 2014; Keshet-Shitton et al. 2015; Kloog et al. 2011) combined Indoor ALAN estimates,

based on questionnaire data regarding sleep habits and use of night time lighting, with estimates of outdoor ALAN obtained from DMSP-OLS or also from questionnaires, to evaluate the association with breast cancer, concluding that decreasing nighttime light exposure diminished breast cancer risk. All studies cited above used DMSP-OLS satellite data that are blind to the blue content of ALAN because of a lack of sensor sensitivity in that part of the visible spectrum.

We have recently shown in a population based case-control study in Spain (MCC-Spain) an overall higher risk of breast and prostate cancer among night shift workers (Papantoniou et al. 2015a, Papantoniou et al. 2015b). In the present analysis, we evaluated in the same study among non-night shift workers, the association of breast cancer and prostate cancer risk with the level of reported indoor ALAN during sleeping time and with remotely sensed levels of outdoor ALAN light intensity and colour (spectral content), individually assigned to geocoded addresses of study participants.

MATERIALS AND METHODS

Study population

The MCC-Spain is a population based multicase-control study (www.mccspain.org) on frequent tumours in Spain that includes 23 hospitals in 12 regions and assesses 5 types of cancer (breast, colorectal, prostate and stomach cancers and chronic lymphocytic leukaemia) using the same series of population controls for all cases (Castaño-Vinyals et al. 2015). In this analysis we focus only on breast and prostate cancer which are hormone-regulated type of cancers previously reported to be linked with ALAN exposures in the literature.

Recruitment of incident cancer cases and population controls aged 20-85 took place from 2008 to 2013. We recruited cases with an incident histologically confirmed

diagnosis of cancer, living in the catchment area of each selected hospital for at least 6 months. Controls were randomly selected from the Primary Health Centres (PHC) located in the same catchment area as cases with no history of cancer and were frequency matched to cases by sex, age in 5-year age groups and study area. They were contacted on behalf of their General Practitioner and invited to participate in the study. Excluded subjects included those incapable of participating in the interview due to communication difficulties (i.e. mental or speaking problems) and/or excess impairment of physical ability. Response rates varied by centre with an average 72% response rate among cases and a 52% among controls with valid telephone numbers in the PHC rosters.

Data collection

Data was collected through face-to-face interviews performed by trained personnel including lifetime residential and occupational history. Information on other risk factors for breast or prostate cancer was collected such as age, educational level, family socioeconomic level, race, body mass index (BMI), family history of cancer, smoking status, and in women age of menarche, parity, age at the first birth, menopausal status, oral contraceptive use and history of hormonal replacement therapy. Leisure time physical activity information (type, frequency and duration) was available for all activities held over lifetime. Current sleep duration and sleep problems (waking up during the night, problems falling asleep, use of sleep medication) that persisted for at least 1 year were also assessed. Diet habits as well as current and past (at 30-40 years of age) alcohol consumption was reported for all cases and controls through a self-administered diet questionnaire. Individual chronotype was assessed through a follow-up phone interview and the use of the Munich Chronotype Questionnaire (MCTQ). Chronotype (MSF_{corr}) was estimated as the mid-sleep time on free days [MSF=(sleep

onset on free day+sleep duration on free day)/2)], corrected for oversleep on free days compared to working days [MSF_{corr}=MSF – (sleep duration on free day-sleep duration on a working day)/2]. Chronotype was assessed using categorical variables with 3 categories: morning type (corresponding to MSF<04:00 hr); intermediate/neither type (MSF=04:01–05:00 h; and evening type MSF>05:00 hr (Papantoniou et al. 2015abc).

The MCC-Spain study followed the national and international directives namely the deontological code and declaration of Helsinki and the Spanish law on confidentiality of data (Ley Organica 15/1999 de 13 Diciembre de Proteccion de Datos de carácter personal -LOPD). All subjects that agreed to participate and fulfilled the eligibility criteria signed an informed consent form before participating in the study. The corresponding ethics committees of the participating centres and hospitals reviewed the protocol of the study.

Tumour subphenotypes

Breast cancer cases were subclassified into 3 subtypes based on local pathology reports: (1) ER/PR+ tumours with luminal human epidermal growth factor receptor 2 negative (HER2-) and oestrogen receptor positive (ER+) or progesterone receptor positive (PR+); (2) HER2+ tumours with luminal human epidermal growth factor receptor 2 positive (HER2+) irrespective of oestrogen or progesterone receptor results; (3) TN (triple-negative) tumours with ER-, PR- and HER2-.

Prostate cancer cases were evaluated by degree of differentiation/grade using the prostate biopsy Gleason score (7 or lower: well or moderately differentiated; 8 or above poorly differentiated- more aggressive).

240 **Artificial light-at-night (ALAN) exposures**

241 To evaluate the effect of indoor-ALAN exposure, study cases and controls from breast
242 and prostate cancer were selected from 11 MCC-Spain participating areas (Asturias,
243 Barcelona, Cantabria, Girona, Granada, Guipúzcoa, Huelva, León, Madrid, Navarra and
244 Valencia). In order to analyze the effect of ALAN during sleeping time, we excluded
245 subjects who had ever worked in night-shift (i.e. working schedule that involved
246 working partly or entirely between 00:00 and 06:00h, at least three times per month).
247 Due to this condition we excluded 224 breast cases, 208 female controls, 327 prostate
248 cases and 353 male controls.

249 We evaluated indoor-ALAN through the MCC-Spain questionnaire where it was
250 defined as the level of light in the bedroom during sleeping time when the participants
251 were at 40 years of age. This was a subjective measure requested during the face-to-face
252 interview using a four digit Likert scale. The scale used four values: (1) Total darkness;
253 (2) Almost dark; (3) Dim light; and (4) Quite illuminated.

254 For the evaluation of outdoor-ALAN we used images of Madrid (Figure 1) and
255 Barcelona (Figure 2), taken by astronauts aboard the ISS in 2012 (ISS030-E-82053) and
256 2013 (ISS045-E-120336), respectively. The images were downloaded from the Earth
257 Science and Remote Sensing Unit, NASA Johnson Space Centre (url:
258 https://eol.jsc.nasa.gov). Those images were taken with commercial Digital Single-Lens
259 Reflex (DSLR) cameras providing image information in three spectral bands, in the
260 visual range (red (R), green (G), blue (B); i.e. RGB) and with the European Space
261 Agency NightPod system (installed in 2012). These instruments may provide ground
262 level resolutions of less than 10 meters (Kyba et al. 2016) but in the images included in
263 the present analysis the spatial resolution was about 30 meters. The images were

calibrated applying the procedure described in Sánchez de Miguel (2015), by using existing databases of standard typical emission spectra of known types of outdoor lighting (white LED, low pressure sodium, metal halide, etc) and inferring the observed lighting type from the RGB signature (Sánchez de Miguel et al. 2007; Sánchez de Miguel 2014). More specifically, we used the G/R ratio, to proceed to the classification of the ground level spectral type of the lamps and then we used a lamp spectral database to estimate the ground based spectrum of the light emissions (Figure 3). In the estimation we assume the atmospheric transfer function and the ground reflectance to not affect much the classification process.

An estimate of the visual light was done using a relationship between the ratio of the photopic visual light over the green band fluxes detected from the ISS ($V(\lambda)/G$) to the ratio of the green to the red bands (G/R). This relationship has been determined for a variety of lighting technologies by Sánchez de Miguel (2015) (Figure 4).

We also calculated an index of outdoor blue light spectrum using an approach described in Aubé et al. (2013) to calculate the melatonin suppression index (MSI) at each pixel of the image. The MSI is related to exposure to blue light and is a metric designed to scale the spectral interaction between a given light spectrum and the published measurements of the melatonin suppression action spectrum (MSAS) (Brainard et al. 2001; Thapan et al. 2001). The MSI has been designed to separate the effect of the shape of a spectrum from its averaged luminous intensity by making use of the MSAS. The MSI determinations were done for the house location of each participant involved in the study and derived as a number generally ranging from 0 to 1. The MSI represents to what extent the spectrum shape of different lights are efficient to suppress the melatonin production compared to the spectrum shape of the CIE's illuminant D65 that has been arbitrarily set to the highest value (one). The International Commission on Illumination

289 (CIE) Standard Illuminant D65 corresponds approximately to the average midday
290 sunlight in Western and Northern Europe.

291 Therefore, two quantitative indices of outdoor-ALAN were estimated from space based
292 colour imagery: (1) outdoor visual-ALAN, as a proxy for luminance and (2) Melatonin
293 Suppression Index (MSI), which is highly linked to blue light spectrum and MSAS.

294 A geographic information system (GIS), QGIS (QGIS Development Team, 2015) was
295 used to assign outdoor-ALAN levels of visual light (outdoor visual-ALAN) and MSI to
296 each individual cases and controls locations from MCC-Spain study, selecting the
297 geocoded residence with the longest duration for each participant.

298 **Statistical analysis**

299 We used generalized additive models (GAMs) to examine the shape of the dose-
300 response relationship between indoor/outdoor ALAN exposure and risk of cancer. We
301 applied unconditional logistic regression and calculated adjusted ORs and 95% CIs in
302 separate and combined models of indoor and/or outdoor ALAN exposures for each of
303 the two cancers. In order to be able to include both indoor and outdoor ALAN
304 information in the same model, we selected those participants from Barcelona and
305 Madrid which were 40 years of age by the time they were living in their longest
306 residence.

307 Models were adjusted a priori (basic adjustment) for age, centre (participant cities) and
308 educational level (less than primary school; primary school; secondary school and
309 university); breast cancer models included also adjustment for menopausal status. A
310 further adjustment was also carried out including the previous variables and also: body
311 mass index (BMI) treated as a categorical variable: normal weight (0 to <25),
312 overweight (25 to 30) and obese (≥30); urban vulnerability to measure socioeconomic

status at area level coded from 0 to 1; family history of breast/prostate cancer; alcohol intake at age 40 (gr/day); smoking habits (ever smoked at least 100 cigarettes or 360 gr of tobacco vs. none) and chronotype information (morning, evening vs. intermediate).

We analyzed effects on subphenotypes of the diseases using multinomial logistic regression applying the basic adjustment for breast and prostate cancer. Chronotype was also examined in a stratified analysis.

All statistical analyses were performed using DeduceR package (Fellows, 2012) within R software environment (R core team, 2016).

RESULTS

Study population

A total of 1219 cases and 1385 controls for breast cancer and 623 cases and 879 controls for prostate cancer were the initially selected population from MCC-Spain study, including information of indoor ALAN exposures, after excluding participants who had worked as night shift workers. The distribution of potential breast and prostate cancer risk factors among selected participants for indoor-ALAN model are shown in Table 1 and 2, respectively.

From the initially selected population, around 30% of female population and 50% of male population had a BMI of 25-30. Female cases were slightly younger than controls (55.8; SD 11.8 vs 58.8; SD 12.6 years), less often postmenopausal (63.8 vs 71.7 %), reported more frequently family history of breast cancer (14.8 vs 9.3 %) compared to controls, and consumed more alcohol (6.2 vs 5.2 gr/day). Male cases also reported more frequently family history of prostate cancer than controls (16.5 vs 6.5%) and consumed a higher amount of alcohol compared to controls (31.9 vs 28.7 gr/day). A total of 2578

females and 1475 males completed the chronotype questionnaire. Additionally, clinical information from medical records analyzed for 412 breast cancer cases, including tumour hormonal receptor status, and for 433 prostate cases with information of Gleason score.

For the outdoor-ALAN model, we selected a total of 446 cases and 568 controls of breast cancer and 438 cases and 660 controls for prostate cancer, living in Madrid and Barcelona from MCC-Spain study. The study characteristics and distribution of risk factors for the subsample, for which environmental outdoor-ALAN estimates were available, are also shown in Table 1 and 2. For nearly all variables, distributions are very similar for the main population and the subsample.

Indoor and outdoor ALAN models

The associations between indoor-ALAN exposure models, evaluated in the whole Spanish study population, for breast and prostate cancer are shown in Table 3. Results were very similar for basic and further adjustments. We observed an OR of 2.56 (CI 95%: 1.57, 4.17) for prostate cancer cases exposed to the highest level of indoor illumination during bedtime, reported as "quite illuminated" compared to those reporting sleeping "in total darkness". No association was found for breast cancer (OR=0.95, CI 95%: 0.64, 1.42).

We could only evaluate the joint effect of indoor and outdoor ALAN for the population in Barcelona and Madrid. Outdoor-ALAN variables were included into the models as categorical variables using tertiles of exposure. Original values were used for the GAM models. Visual light data (units proportional to the luminance, a quantity generally expressed in units of Cd/m^2) had an average of 0.065 (SD: 0.034; Min: 0.009; Max: 0.225) for breast cancer and an average of 0.066 (SD: 0.034; Min: 0.002; Max: 0.225)

for prostate cancer. Values of MSI had an average of 0.152 (SD: 0.046; Min: 0.041; Max: 0.407) for breast cancer and an average of 0.151 (SD: 0.047; Min: 0.017; Max: 0.412) for prostate cancer. No correlation was found between indoor-ALAN and outdoor-ALAN either for MSI or visual, in the subsample population of Barcelona and Madrid.

In GAM models (Figure 5), we observed a non-linear relationship in prostate cancer both for visual light (outdoor ALAN) and for MSI- blue light (outdoor ALAN) with p-values for departure from linearity of p=0.031 and p=0.062 respectively. There was no significant departure from linearity for breast cancer. All subsequent analyses are based on tertiles of exposure.

In further adjustment models (Table 4)., also mutually adjusted for outdoor and indoor ALAN, we found that those sleeping in more illuminated bedrooms (indoor-ALAN) had a higher risk of prostate cancer [OR=2.82, 95%CI 1.5-5.3] while there was only a slight increased risk for breast cancer (OR=1.19, 95%CI 0.6-2.6). Exposure to higher levels of blue light spectrum (outdoor-ALAN; highest tertile of MSI) was associated with an increased risk of both breast (adjusted odds ratio OR=1.54, 95%CI 1.0-2.4) and prostate cancer (OR=1.90, 95%CI 1.2-2.9) cancers. Overall visual light (outdoor-ALAN) was not associated with cancer risk.

Chronotype and tumour subphenotypes

For stratified analyses by chronotype and tumour subphenotypes we present results for the basic adjustment models so as to have a larger population sample size. However risk estimates were of similar direction for fully adjusted models.

Exposure to higher levels of blue light spectrum (outdoor-ALAN; highest tertile of MSI) was associated with slightly higher risks for estrogen or progestagen positive receptor breast cancer tumours (OR=1.27, 0.87, 1.85) but differences with Her+ positive and triple negative tumours were not marked (Table 5). For prostate cancer exposure to blue light (outdoor-ALAN; highest tertile of MSI) indicated similar risks in more aggressive cancers with a Gleason scores of 7 or higher (OR=1.70; CI 95%: 1.05, 2.53) and in less aggressive tumour with Gleason below 7 (OR=1.57, 1.05- 2.34) (Table 5).

The highest prostate cancer risk for exposure to indoor-ALAN during sleep time was observed in participants with evening chronotype (OR=6.2; CI 95%: 2.01, 19.21) (Supplemental Material, Table S1); risk for morning types was also elevated but lower (OR=1.74, 1.0-3.2). No differences were observed by chronotype and indoor ALAN for breast cancer (Supplemental, Table S1). There were no marked differences by morning, intermediate or evening chronotypes in relation to risk associated with levels of blue light spectrum (outdoor-ALAN; MSI), neither for prostate nor for breast cancer (Supplemental Material, Table S2). However, for prostate cancer ORs tended to be higher in evening compared to morning or intermediate chronotypes.

DISCUSSION

We evaluated the association between exposure to indoors and outdoors artificial light-at-night (ALAN) during sleep time and breast and prostate cancer risk, two cancers that have been associated with circadian disruption. We found that outdoor light at night and specifically exposure to blue light that has been shown to reduce melatonin levels was associated with an increased risk of both prostate and breast cancer. Indoor-ALAN was associated with an increased risk of prostate cancer. Evening types tended to have slightly higher risk but overall we did not find a clear pattern of risk with chronotype.

406 Even though we applied in this study more accurate methods for the evaluation of light
407 exposure compared to previous studies, exposure assessment remains a key issue when
408 examining the potential health effects of artificial light-at-night in human studies.

409 Exposure to ALAN is ubiquitous and a public health issue is whether the spread of
410 exposure to ALAN may increase cancer risk and how could this be prevented. Exposure
411 to short wavelength light colour during the hours before bedtime has been shown to
412 suppress nocturnal melatonin production in the pineal gland which, in turn, has been
413 associated with an increased risk of hormone-dependent type of cancers such as breast
414 and prostate cancer (Cajochen et al. 2005; Chang et al. 2014; Gringras et al. 2015;
415 Keshet-Shitton et al. 2015; Papantoniou et al. 2014; Stevens et al. 2015).

416 Artificial night time lighting is especially widespread and changing rapidly and most
417 countries across Europe are experiencing marked increases in night time brightness
418 (Bennie et al. 2014), especially with the massive arrival and exponential growth of
419 Light Emitting Diodes (LED) in the way of replacing the incandescent and high
420 pressure sodium lamps (Sanchez de Miguel et al. 2017). Moreover, the increase in
421 ALAN exposure has been widely recognized to be an ecological problem (Gaston et al.
422 2015). Even though different measures can be implemented to reduce ALAN exposure
423 indoors, it is more complex to deal with the inappropriate and unshielded outdoor
424 lighting (Escofet and Bará 2015).

425 Existing studies examining ALAN exposures and cancer risk rates have relied almost
426 exclusively on satellite data, primarily from the Defense Meteorological Satellite
427 Program/Operational Linescan System (DMSP/OLS; e.g. Cinzano et al. 2001, Bennie et
428 al. 2014), and more recently the Visible Infrared Imaging Radiometer Suite (VIIRS)
429 with its Day-Night Band camera onboard the Suomi National Polar-Orbiting

Partnership (Suomi NPP) satellite (e.g. Baugh et al. 2013). In particular, the satellite sensors from which the data have been obtained are effectively 'colour blind', able to detect the intensity of light integrated across a range of wavelengths but not to measure the spectrum of night time lighting emissions. Moreover both satellite platforms are insensitive to the blue content of the light. As a consequence, very little is known about the spatial and temporal dynamics of the spectrum of artificial night time lighting systems (Gaston et al. 2015). This is critical for at least two reasons. First, almost all known environmental impacts of artificial night time lighting are sensitive to the spectrum of that lighting including melatonin production (Aubé et al. 2013); second, these changes in physiological parameters may in turn influence circadian rhythms and hence timing of sleep, blood pressure regulation, seasonal reproduction and the role of melatonin as an antioxidant (Korkmaz and Reiter, 2011), with consequences for the prevalence of some kinds of cancer (e.g. Cajochen et al. 2005).

We applied new methods available that make it feasible to convert International Space Station (ISS) images with simple three-band spectral information into ecological risk maps, using known spectral responses of key physiological and ecological processes with a higher spatial resolution (up to 10 meters), rather than those images obtained from the VIIRS/DNB platform (750 m) or DMSP/OLS (3.5 km). In common with other remotely sensed data on artificial light at night, the maps we produced also represent light emitted or reflected upwards towards the sensor assuming that this is a good proxy for the intensity and density of light sources at ground level. It would be interesting in further studies to include information about the aerosol content of the atmosphere in order to correct the ISS images by differential atmospheric absorption.

The methodology we used provides information on the spatial distribution and on the temporal evolution of the luminance next to the participant houses, depending on the

455 available ISS images. Note that when a change in the spectral technology is made (e.g.
456 when changing High Pressure Sodium (HPS) lamps for white LEDs), illuminances are
457 usually maintained constant on the street level. But in some cases a change in the
458 lateral photometry of the light fixtures can result in a significant change of the
459 luminance entering the bedroom windows even if the street illuminance is maintained.
460 The ISS data cannot identify such an effect and there is inevitably an unquantifiable
461 error when determining the window level luminance.

462 Results of the present study showed a higher risk association between exposure to
463 outdoor- blue-light spectrum (MSI), independently from outdoor visual-ALAN (i.e.
464 luminance), for prostate and breast cancer. Visual light estimates are based on what the
465 cameras detect from space while there is a part of the light emitted that might never
466 enter the houses. Moreover, the luminance at the window level is linked in a complex
467 way to ground-based light emissions while taking into account atmospheric-induced
468 optical distortion as well as spectral and geometrical transformations from the
469 underlying ground surfaces and obstacles (Aubé 2015). In other words, the light output
470 pattern of the light fixtures cannot be assessed from space and it is possible that the
471 upward light remains weakly correlated to the horizontal light that enters the houses.
472 There is less of this problem with MSI. The only variation on the spectrum can come
473 from different combinations of direct and reflected lights as a function of the angle but
474 generally the most important contribution to the light entering a window is the direct
475 light and for that component MSI does not depend on the angle. Visual response that we
476 and others have used to evaluate the outdoor visual-ALAN is poorly correlated to the
477 blue light. Assessments that have only used visual response are probably missing the
478 part of the light (blue) which is likely to be important when evaluating biological
479 responses related to cancer.

We did not find clear evidences of a differential effect of chronotype, with only a higher risk of prostate cancer among evening types, who may be subjects getting too much light in the wrong hours. Previous studies on night shift workers and breast or prostate cancer have not shown a consistent pattern of risk by chronotype although overall prostate cancer risk was also higher among subjects with an evening chronotype (Papantoniou 2015b). Although chronotype is related to preference for morningness or eveningness, the direct association with long term cancer risk is still unknown.

We found a higher risk of prostate cancer, and slightly similar trend for breast cancer, among participants with a more illuminated bedroom at night (indoor-ALAN). There was no association between outdoor visual-ALAN and indoor-ALAN. This lack of correlation could be due to the use of shutters at night among subjects with high outdoor visual ALAN, or perhaps a lack of relationship between the light reaching the ISS and the light reaching the house's windows. Similar results were described in a previous study carried out by Rea et al (2011) concluding that satellite-measured sky brightness (visual light) was unrelated to personal light exposures. Additionally, most human made surfaces are less reflective in the blue part of the spectrum and the MSI parameters can be underestimated even though, the results showed a higher correlation with prostate cancer. Indoor-ALAN measurements are very important to complement outdoor visual-ALAN impact on hormone-dependent cancers in countries like Spain, where the use of closed curtains or shutters is extended. In addition, other sources rather than street light might be contributing to indoor-ALAN exposures like light coming from neighbours, or the use of portable electronic devices with self-luminous displays and energy-efficient lighting (LEDs). The use of such devices is increasing and has a significant effect on decreasing melatonin production if they are used before bedtime (Bonmati-Carrion et al. 2014; Chang et al. 2014).

In further studies it will be interesting to measure indoor light levels rather than using only questionnaire-based methodology which is more subjective although may be capturing a longer time span of exposure. Improvements in modelling exposure such as the inclusion of the height of the building-residences and of different obstacles in the street like trees or other buildings which could protect from the received outdoor light, would have been advantageous but also should be validated with light measurements. Such approaches could help explain our observations where outdoor visual-ALAN (i.e. luminance) was associated with no or a negative effect that is opposite to that observed for blue light (MSI index), which might still penetrate the curtains or shutters (Aubé et al. 2013).

Summarizing, in this study we used modelled images provided by the International Space Station (ISS) to map the spatial variation of artificial night time lighting exposure including blue light spectrum combined with data from questionnaires on exposure to indoor light at night, and related this information with the risk of developing the two most common hormone dependent cancers (breast and prostate). The main strengths of this study are the use of individual information rather than relying on ecological comparisons as most other studies and the possibility therefore of developing personal estimates of exposure and adjusting for potential confounding factors. In addition we used new methods for the evaluation of blue light spectrum. The main limitation of the study is exposure misclassification since we used proxy estimates for the evaluation of both indoor-ALAN and for outdoor visual-ALAN exposure (although not for MSI), although it is unlikely that this would result to differential misclassification between cases and controls.

CONCLUSIONS

This is the first large study using individual information on the two cancers most strongly associated with circadian disruption and light-at-night during shift work, and provides some evidence of the importance of artificial light-at-night (ALAN) for the development of cancer in the general population. Exposure to both indoor and outdoor ALAN was associated with a higher risk of prostate cancer while findings were less consistent overall for breast cancer. The strongest findings for both breast and prostate cancer were for exposure to outdoor blue-light spectrum that is probably the most biologically relevant exposure.

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711 **TABLES**

712

713 **Table 1.** Distribution of potential breast cancer risk factors among MCC-Spain
714 participants included in the indoor-ALAN and outdoor-ALAN models (only for Madrid
715 and Barcelona).

716

Breast	Indoor ALAN		Outdoor-Visual	
Factors	**Controls N=1385 N (%)**	**Cases N=1219 N (%)**	**Controls n=568 n (%)**	**Cases n=446 n (%)**
Age (years); mean (SD)	58.82(12.6)	55.78(11.8)	59.73(12.5)	55.11(12.2)
Educational level				
Less than Primary school	211 (15.3)	157 (12.9)	124 (21.8)	73 (16.4)
Primary school	438 (31.5)	410 (33.6)	178 (31.3)	145 (32.5)
Secondary school	447 (32.2)	418 (34.3)	163 (28.7)	147 (33.0)
University	289 (20.8)	234 (19.2)	103 (18.1)	81 (18.2)
Urban vulnerability; mean (SD)	0.46 (0.1)	0.49 (0.1)	0.46 (0.2)	0.49 (0.1)
BMI				
<25	694 (50.1)	590 (48.4)	266 (46.8)	203 (45.5)
25-30	440 (31.7)	409 (33.5)	187 (32.9)	162 (36.3)
>=30	251 (18.0)	220 (18.1)	115 (20.2)	81 (18.2)
Smoking (ever)				
Yes	578 (41.7)	547 (44.9)	212 (37.4)	199 (44.6)
No	807 (58.2)	671 (55.1)	355 (62.6)	247 (55.4)
Family History				
No	1257 (90.6)	1040 (85.3)	513 (90.3)	368 (85.5)
Yes	130 (9.3)	180 (14.8)	55 (9.7)	78 (17.5)
Alcohol consumption; mean(SD)	5.24 (8.6)	6.19 (11.3)	5.05 (8.11)	6.32 (10.6)
Chronotype				
Morning	529(38.5)	442(36.6)	231 (47.7)	165 (43.5)
Intermediate	555(40.3)	474(39.2)	186 (38.4)	152 (40.1)
Evening	290(21.1)	291(24.1)	67 (13.8)	62 (16.4)
Menopause				
Premenopausal	391(28.2)	441 (36.2)	118 (20.8)	156 (35.1)
Postmenopause	994(71.7)	778 (63.8)	448 (79.2)	289 (65.9)

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723 **Table 2**. Distribution of potential prostate cancer risk factors among MCC-Spain
724 participants included in the indoor-ALAN and outdoor-ALAN models (only for Madrid
725 and Barcelona).

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Prostate	Indoor ALAN		Outdoor-Visual	
Factors	**Controls N=879 N (%)**	**Cases N=623 N (%)**	**Controls n=660 n (%)**	**Cases n=438 n (%)**
Age (years); mean (SD)	66.09(8.3)	65.59(6.9)	66.02 (8.4)	65.22 (6.9)
Educational level				
Less than Primary school	125 (14.2)	111 (17.8)	109 (16.5)	85 (19.4)
Primary school	259 (29.5)	249 (40.0)	199 (30.2)	165 (37.7)
Secondary school	268 (30.5)	146 (23.4)	189 (28.6)	101 (23.1)
University	227 (25.8)	117 (18.8)	163 (24.7)	87 (19.9)
Urban vulnerability; mean (SD)	0.49 (0.2)	0.51 (0.1)	0.46 (0.2)	0.50 (0.1)
BMI				
<25	234 (26.6)	161 (25.8)	175 (26.5)	115 (26.3)
25-30	448 (50.8)	324 (52.0)	346 (52.4)	224 (51.1)
>=30	197 (22.4)	138 (22.2)	139 (21.1)	99 (22.6)
Smoking (ever)				
Yes	644 (73.3)	467 (75.0)	499 (75.6)	324 (74.0)
No	235 (26.7)	156 (25.0)	161 (24.4)	114 (26.0)
Family History				
No	822 (93.5)	520 (83.5)	616 (93.3)	367 (83.8)
Yes	57 (6.5)	103 (16.5)	44 (6.7)	71 (16.2)
Alcohol consumption; mean(SD)	28.72 (32.0)	31.89 (35.4)	29.40 (32.8)	30.15 (33.5)
Chronotype				
Morning	430 (50.4)	311 (50.1)	294 (55.6)	198 (54.9)
Intermediate	316 (37.0)	231 (37.2)	174 (32.9)	120 (33.2)
Evening	108 (12.6)	79 (12.7)	61 (11.5)	43 (11.9)

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Table 3. Association of Indoor artificial light-at-night (ALAN) when sleeping, with breast and prostate cancer in the total MCC-Spain population (OR: odds ratio; 95% CI: 95% confidence interval)

	Controls/Cases N (%)	ORs (95%CI)	Controls/Cases N(%)	ORs (95%CI)
Basic adjustment[a]	**Breast Cancer (N=2604)**		**Prostate Cancer (N=1502)**	
Indoor ALAN				
Ref= Total darkness	196(14.1)/168(13.8)	1.0	151(17.2)/ 91(14.6)	1.0
Almost dark	534(38.6)/448(36.7)	1.05(0.8, 1.4)	369(42.0)/ 218(35.0)	0.96(0.7, 1.3)
Dim light	434(31.4)/415(34.1)	1.30(0.9, 1.7)	266(30.3)/ 209(33.5)	1.21(0.9, 1.7)
Quite illuminated	221(15.9)/188(15.4)	1.02(0.8, 1.4)	93(10.6)/ 105(17.0)	1.90(1.3, 2.9)
Further adjustment[b]	**Breast Cancer (N=1590)**		**Prostate Cancer (N=1096)**	
Indoor ALAN				
Ref= Total darkness	126(13.5)/83(11.1)	1.0	125(18.9)/ 74(17.1)	1.0
Almost dark	360(38.6)/235(37.6)	1.00(0.7, 1.4)	275(41.5)/ 135(31.1)	0.86(0.6, 1.3)
Dim light	303(32.5)/246(37.6)	1.27(0.9, 1.8)	207(31.3)/ 146(33.6)	1.12(0.7, 1.7)
Quite illuminated	144(15.4)/93(13.6)	0.95(0.6, 1.4)	55(8.3)/ 79(18.2)	2.56(1.6, 4.2)

a. Basic adjustment: age, centre, educational level and menopausal status (in breast cancer).

b. Further adjustment: age, centre, educational level, urban vulnerability, body mass index (BMI), alcohol, tobacco, family history of breast/prostate cancer and chronotype. Menopausal status (only breast cancer).

Table 4. Association of indoor and outdoor artificial light-at-night (ALAN) when sleeping, with breast and prostate cancer. Subjects from Barcelona and Madrid, MCC-Spain. MSI (blue light) and Visual light were divided into tertiles of exposure [a,b] and first tertile was the reference level (OR: odds ratio; 95% CI: 95% confidence interval).

	Controls/Cases N (%)	ORs (95%CI)	Controls/Cases N(%)	ORs (95%CI)
Basic adjustment[c]	**Breast Cancer (N=705)**		**Prostate Cancer (N=738)**	
Indoor ALAN				
Ref= Total darkness	48(12.1)/37(12.0)	1.0	102(23.8)/64(20.6)	1.0
Almost dark	154(38.9)/96(31.1)	0.85(0.5, 1.4)	155(36.2)/74(23.9)	0.75(0.5, 1.2)
Dim light	163(41.2)/152(49.2)	1.34(0.8, 2.3)	142(33.2)/124(40.0)	1.36(0.9, 2.1)
Quite illuminated	31(7.8)/24(7.8)	1.06(0.5, 2.1)	29(6.7)/48(15.5)	2.88(1.6,5.1)
ALAN-Visual Light				
Ref=1st tertile (lowest)	122(30.8)/107(34.6)	1.0	130(30.4)/124(40.0)	1.0
2nd tertile	144(36.4)/104(33.7)	0.89(0.6, 1.3)	158(36.9)/96(31.0)	0.64(0.4, 1.0)
3rd tertile (highest)	130(32.8)/98(31.7)	0.91(0.6, 1.4)	140(32.7)/90(29.0)	0.64(0.43, 1.0)
ALAN-MSI				
Ref=1st tertile	136(27.4)/106(34.3)	1.0	157(36.7)/98(31.6)	1.01.18(0.8,
2nd tertile	236(47.6)/92(29.8)	0.9(0.6, 1.3)	151(35.3)/100(32.3)	1.7)
3rd tertile	124(25.0)/111(35.9)	1.23(0.8, 1.8)	120(28.0)/112(36.1)	1.79(1.2, 2.7)
Further adjustment[d]	**Breast Cancer (N=521)**		**Prostate Cancer (N=659)**	
Indoor ALAN				
Ref= Total darkness	43 (12.6)/32(12.0)	1.0	89(23.2)/61(22.2)	1.0
Almost dark	135(39.4)/82(31.0)	0.79(0.4, 1.4)	145(37.8)/64(23.3)	0.65(0.4, 1.1)
Dim light	138(40.4)/128(48.3)	1.18(0.7, 2.1)	125(32.5)/107(38.9)	1.24(0.8, 2.0)
Quite illuminated	26(7.6)/23(8.7)	1.19(0.6, 2.6)	25(6.5)/43(15.6)	2.82(1.5, 5.3)
ALAN- Visual Light				
Ref=1st tertile	107(31.2)/99(37.4)	1.0	123(32.0)/108(39.3)	1.0
2nd tertile	119(34.8)/87(32.8)	0.79(0.5, 1.2)	139(36.2)/85(30.9)	0.63(0.4, 1.0)
3rd tertile	116(34.0)/79(29.8)	0.72(0.4, 1.2)	122(31.8)/82(29.8)	0.60(0.4, 1.0)
ALAN- MSI				
Ref=1st tertile	117(34.2)/89(33.6)	1.0	141(36.7)/85(30.9)	1.0
2nd tertile	114(33.3)/80(30.2)	1.11(0.7, 1.7)	133(34.6)/92(33.5)	1.33(0.8, 2.0)
3rd tertile	111(32.5)/96(36.2)	1.54(1.0, 2.4)	110(28.7)/98(35.6)	1.90(1.2, 2.9)

a. Breast ALAN-Visual Light tertiles of exposure: 1st tertile=0.009-0.046; 2nd tertile= 0.047-0.071; 3rd tertile=0.072-0.225. Prostate ALAN- Visual Light tertiles of exposure: 1st tertile=0.002-0.047; 2nd tertile= 0.048-0.073; 3rd tertile=0.074-0.225.

b. Breast ALAN-MSI tertiles of exposure: 1st tertile=0.041-0.129; 2nd tertile= 0.130-0.164; 3rd tertile=0.164-0.407. Prostate ALAN-MSI tertiles of exposure: 1st tertile=0.017-0.128; 2nd tertile= 0.129-0.162; 3rd tertile=0.163-0.413

c. Basic adjustment: age, centre, educational level and menopausal status (in breast cancer).

d. Further adjustment: age, centre, educational level, urban vulnerability, body mass index (BMI), alcohol, tobacco, family history of breast/prostate cancer, chronotype, menopausal status (only breast cancer) and mutual adjustment for the three light exposure variables.

Table 5. Association of Outdoor ALAN-MSI (blue light) with breast and prostate cancer subphenotypes. Models with basic adjustment[a]. Relative risk ratios (RRR) for Outdoor ALAN-MSI exposures in tertiles[b].

Outdoor-ALAN-MSI	1st tertile		2nd tertile			3rd tertile		
Breast cancer	**N (%)**	**RRR**	**N (%)**	**RRR**	**95%CI**	**N (%)**	**RRR**	**95%CI**
Hormone receptors[c]	98 (31.7)	1.0	100 (32.4)	0.94	(0.7, 1.4)	111 (35.9)	1.27	(0.9, 1.9)
Erb 2+	23 (35.9)	1.0	20 (31.3)	0.69	(0.4, 1.4)	21 (32.8)	0.86	(0.4, 1.7)
Triple negative	17 (43.6)	1.0	13 (33.3)	0.78	(0.4, 1.7)	9 (23.1)	0.7	(0.3, 1.8)
Controls	192 (33.8)	-	203 (35.7)	-	-	173 (30.5)	-	-
Prostate cancer								
Gleason score <7	69 (32.9)	1.0	65 (31.0)	1.06	(0.7, 1.6)	76 (36.2)	1.57	(1.1, 2.3)
Gleason score >7	67(30.0)	1.0	72(32.3)	1.16	(0.8, 1.7)	84 (37.7)	1.7	(1.1, 2.5)
Controls	231(35.0)	-	233 (35.3)	-	-	196 (29.7)	-	-

a. Basic adjustment: age, centre, educational level and menopausal status (in breast cancer).
b. Breast ALAN-MSI tertiles of exposure: 1st tertile=0.041-0.129; 2nd tertile= 0.130-0.164; 3rd tertile=0.164-0.407. Prostate ALAN-MSI tertiles of exposure: 1st tertile=0.017-0.128; 2nd tertile= 0.129-0.162; 3rd tertile=0.163-0.413
c. Hormone receptors: Estrogen or Progestagen positive receptors and Erb2 negative.

FIGURE LEGENDS

Figure 1. International Space Station night image (https://eol.jsc.nasa.gov) of Madrid 2012 (ISS030-E-82053).

Figure 2. International Space Station night image (https://eol.jsc.nasa.gov) of Barcelona 2013 (ISS045-E-120336).

Figure 3. Classification of the ground level spectral type of the lamps[a] using the green to the red bands (G/R) ratio, to estimate the ground based spectrum of the melatonin suppression index (MSI).

a. Different types of lamps used in the analysis:

CFL=Compact Fluorescent

MV= Mercury Vapour

HAL= Halogen

MH= Metallic Halogen

CMH= Ceramic Metallic Halogen

FL=Fluorescent

LED = LED

INC = Incandescent

HPS = High Pressure Sodium

LPS = Low Pressure Sodium

Figure 4. Relationship between the ratio of the photopic visual light over the green band fluxes detected from the ISS (V(λ)/G) to the ratio of the green to the red bands (G/R) also detected from the ISS image to classify the lamp type.

Figure 5. Generalized Additive Models for breast and prostate cancer and exposure to visual light and blue light (MSI). The models were adjusted by: age, centre, educational level and menopausal status (only breast cancer).

Figure

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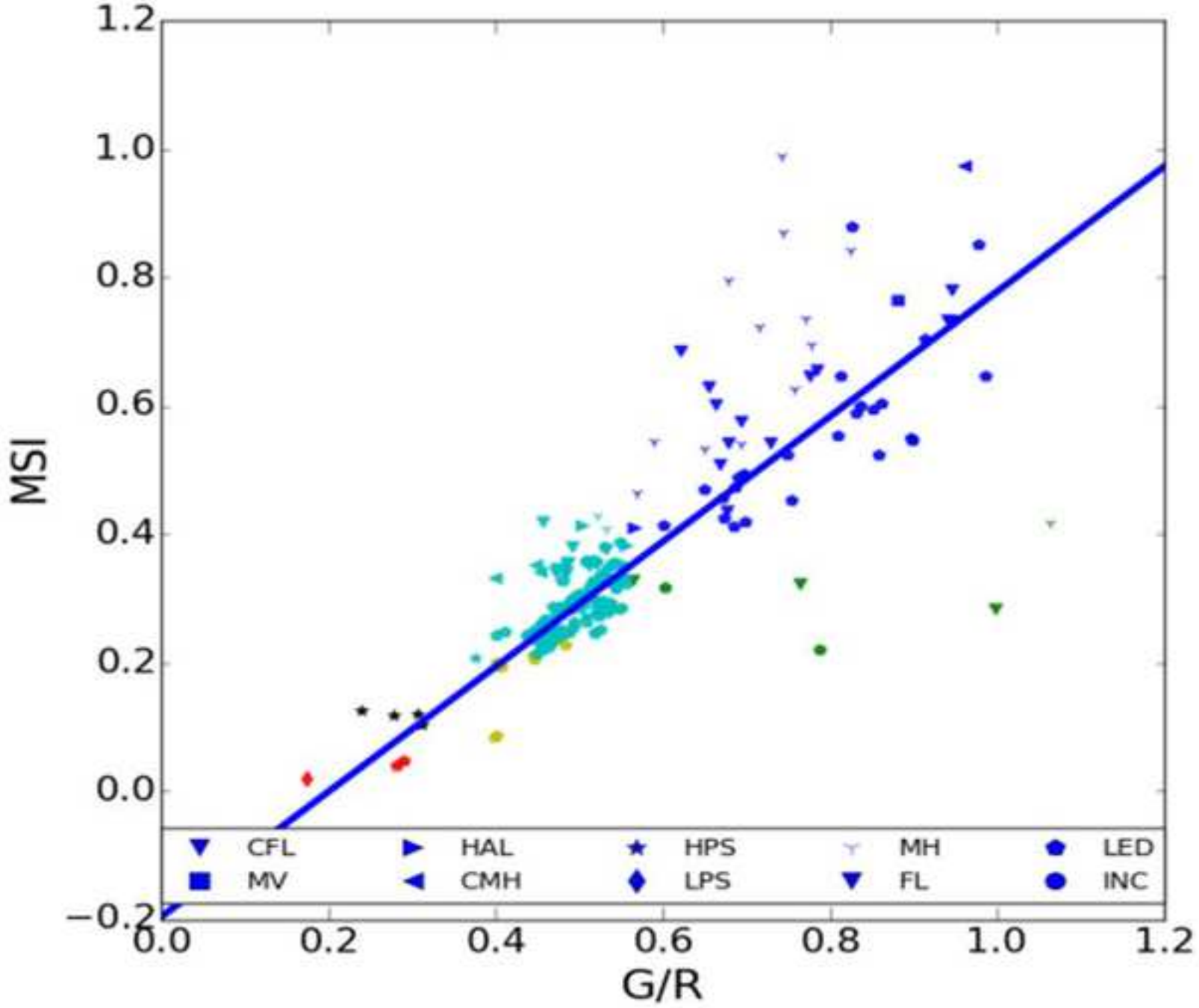
Figure

Click here to download Figure Figure2.JPG

Figure

Click here to download Figure Figure3.jpg



Figure

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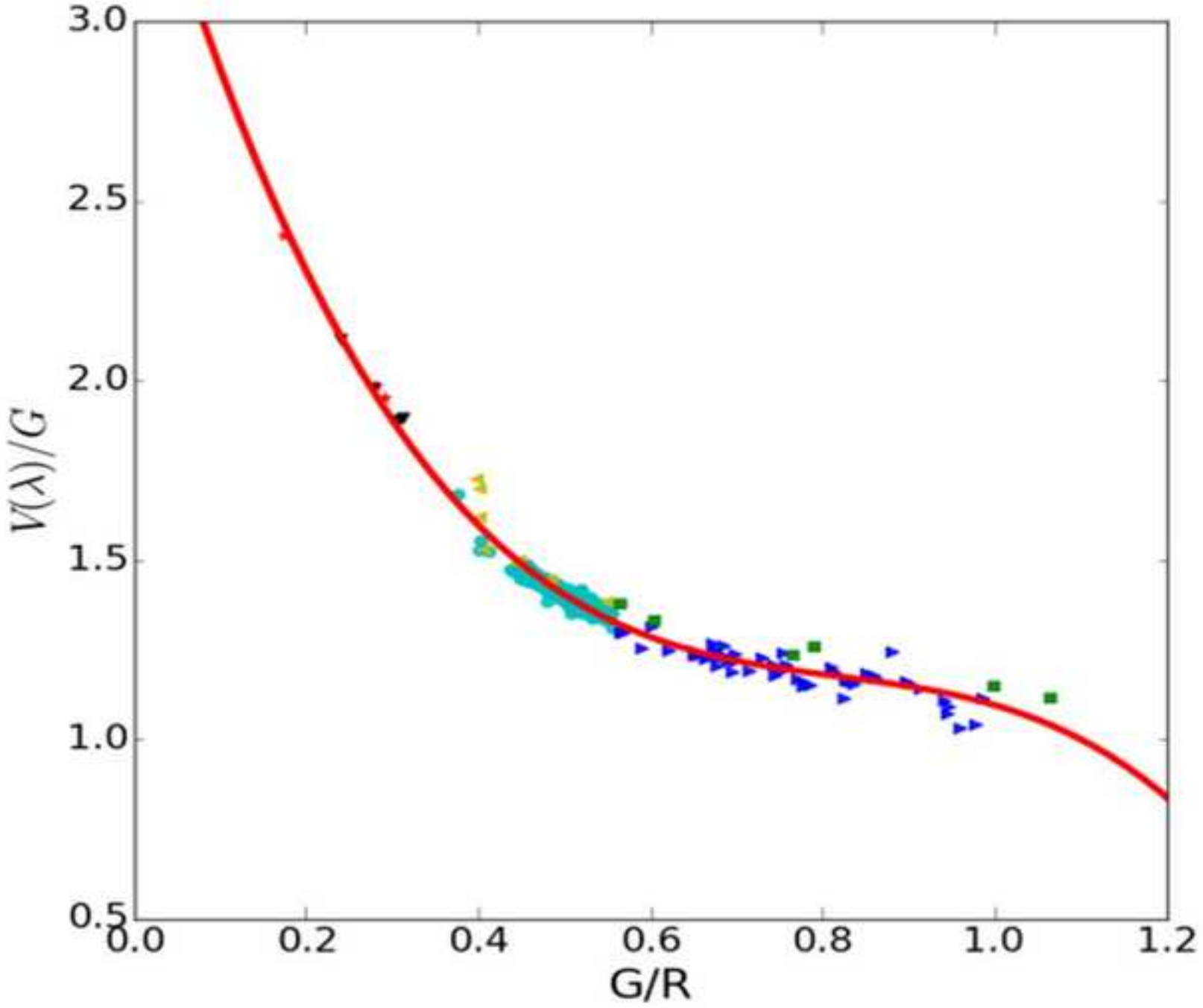

Figure

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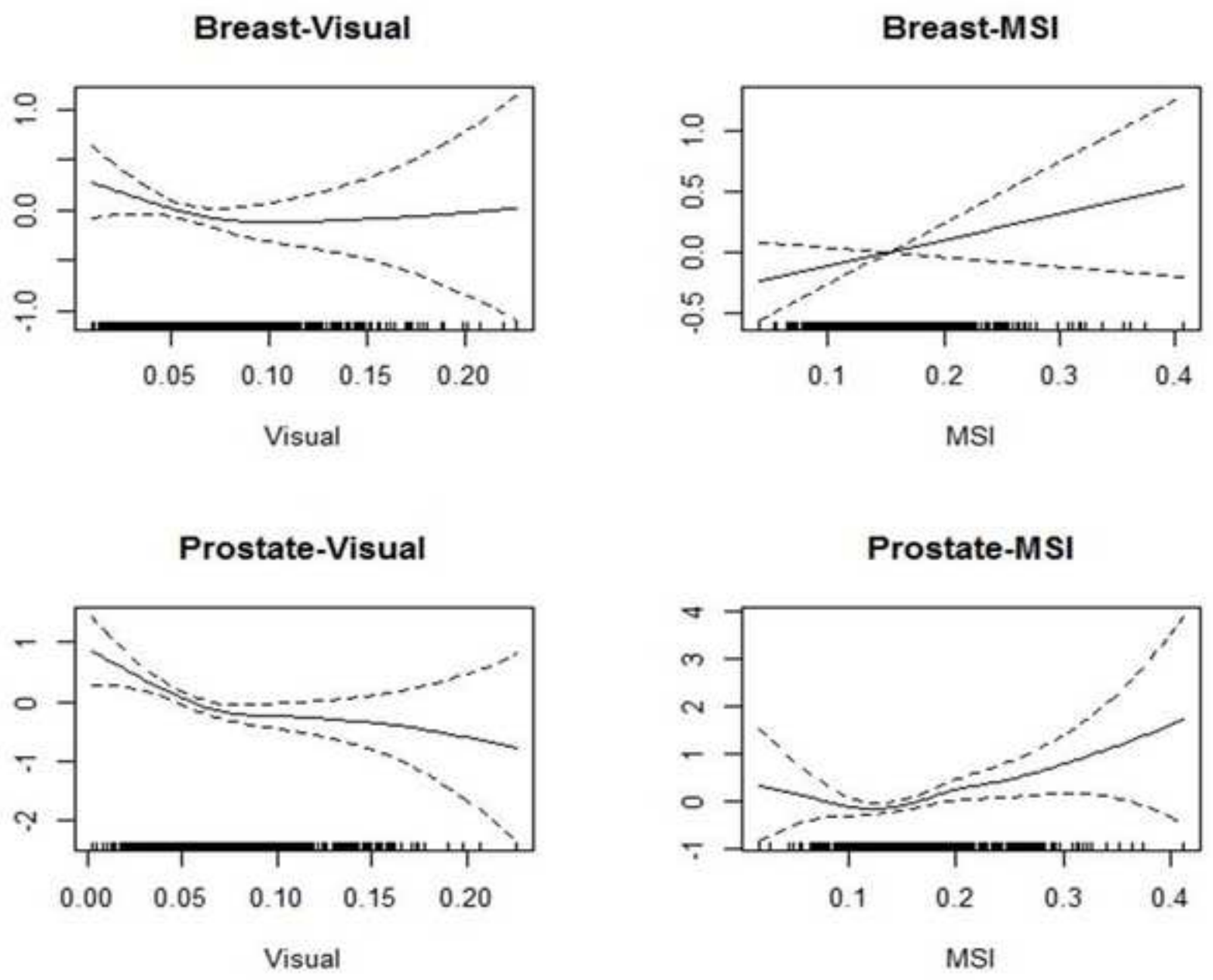

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