

# Environmental Health Perspectives

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

--Manuscript Draft--

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<b>Abstract:</b>	<p>Background. Night shift work, exposure to light-at-night and the consequent circadian disruption may increase the risk of hormone-dependent cancers.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>Conclusion. Both indoor and outdoor ALAN and particularly blue enriched light spectrum were associated with an increased risk of breast and prostate cancer.</p>													
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1 **Evaluating the association between artificial light-at-night exposure and breast**  
2 **and prostate cancer risk in Spain (MCC-Spain study)**

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#### 89 **Conflict of interest**

90 The authors declare that they have no conflict of interest.

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95

96 **ABSTRACT**

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

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

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

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

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



## 119 INTRODUCTION

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

126 Depending on light intensity and wavelength, exposure to ALAN may affect human  
127 health by decreasing the production and secretion of pineal melatonin (N-acetyl-5-  
128 methoxytryptamine), which is a hormone normally produced in the dark phase of the  
129 24h cycle (Brainard et al. 2001; Chang et al. 2014; Escofet and Bará 2015; Thapan et al.  
130 2013). Melatonin may be involved in epigenetic regulation of limiting cancer initiation  
131 and progression by reducing severe DNA damage that is a consequence of unstable  
132 oxygen and nitrogen-based reactants (Korkmaz and Reiter 2011).

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

138 Moreover, the genetic background of each individual can affect the ability to have a  
139 preferential day or night profile (chronotype), the adaptation to night work and changes  
140 in sleep and wake schedules, and can define groups more or less susceptible to effects of  
141 circadian cycle disruption. For instance, Papanтониου 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 (ER $\alpha$ )  
147 mRNA expression and estrogen induced transcriptional activity of the ER $\alpha$  in (ER $\alpha$ +)   
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,

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

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

## 180 **MATERIALS AND METHODS**

### 181 **Study population**

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

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

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

#### 201 *Data collection*

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

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

221

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

### 229 *Tumour subphenotypes*

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

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

239

## 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

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

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

277 We also calculated an index of outdoor blue light spectrum using an approach described  
278 in Aubé et al. (2013) to calculate the melatonin suppression index (MSI) at each pixel of  
279 the image. The MSI is related to exposure to blue light and is a metric designed to scale  
280 the spectral interaction between a given light spectrum and the published measurements  
281 of the melatonin suppression action spectrum (MSAS) (Brainard et al. 2001; Thapan et  
282 al. 2001). The MSI has been designed to separate the effect of the shape of a spectrum  
283 from its averaged luminous intensity by making use of the MSAS. The MSI  
284 determinations were done for the house location of each participant involved in the  
285 study and derived as a number generally ranging from 0 to 1. The MSI represents to  
286 what extent the spectrum shape of different lights are efficient to suppress the melatonin  
287 production compared to the spectrum shape of the CIE's illuminant D65 that has been  
288 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 ( $\geq 30$ ); urban vulnerability to measure socioeconomic



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

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

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

## 321 **RESULTS**

### 322 *Study population*

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

329 From the initially selected population, around 30% of female population and 50% of  
330 male population had a BMI of 25-30. Female cases were slightly younger than controls  
331 (55.8; SD 11.8 vs 58.8; SD 12.6 years), less often postmenopausal (63.8 vs 71.7 %),  
332 reported more frequently family history of breast cancer (14.8 vs 9.3 %) compared to  
333 controls, and consumed more alcohol (6.2 vs 5.2 gr/day). Male cases also reported more  
334 frequently family history of prostate cancer than controls (16.5 vs 6.5%) and consumed  
335 a higher amount of alcohol compared to controls (31.9 vs 28.7 gr/day). A total of 2578

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

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

#### 346 *Indoor and outdoor ALAN models*

347 The associations between indoor-ALAN exposure models, evaluated in the whole  
348 Spanish study population, for breast and prostate cancer are shown in Table 3. Results  
349 were very similar for basic and further adjustments. We observed an OR of 2.56 (CI  
350 95%: 1.57, 4.17) for prostate cancer cases exposed to the highest level of indoor  
351 illumination during bedtime, reported as “quite illuminated” compared to those  
352 reporting sleeping “in total darkness”. No association was found for breast cancer  
353 (OR=0.95, CI 95%: 0.64, 1.42).

354 We could only evaluate the joint effect of indoor and outdoor ALAN for the population  
355 in Barcelona and Madrid. Outdoor-ALAN variables were included into the models as  
356 categorical variables using tertiles of exposure. Original values were used for the GAM  
357 models. Visual light data (units proportional to the luminance, a quantity generally  
358 expressed in units of  $\text{Cd/m}^2$ ) had an average of 0.065 (SD: 0.034; Min: 0.009; Max:  
359 0.225) for breast cancer and an average of 0.066 (SD: 0.034; Min: 0.002; Max: 0.225)

360 for prostate cancer. Values of MSI had an average of 0.152 (SD: 0.046; Min: 0.041;  
361 Max: 0.407) for breast cancer and an average of 0.151 (SD: 0.047; Min: 0.017; Max:  
362 0.412) for prostate cancer. No correlation was found between indoor-ALAN and  
363 outdoor-ALAN either for MSI or visual, in the subsample population of Barcelona and  
364 Madrid.

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

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

### 378 *Chronotype and tumour subphenotypes*

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

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

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

## 398 **DISCUSSION**

399 We evaluated the association between exposure to indoors and outdoors artificial light-  
400 at-night (ALAN) during sleep time and breast and prostate cancer risk, two cancers that  
401 have been associated with circadian disruption. We found that outdoor light at night and  
402 specifically exposure to blue light that has been shown to reduce melatonin levels was  
403 associated with an increased risk of both prostate and breast cancer. Indoor-ALAN was  
404 associated with an increased risk of prostate cancer. Evening types tended to have  
405 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; Papanтониou 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

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

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

453 The methodology we used provides information on the spatial distribution and on the  
454 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.

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

487 We found a higher risk of prostate cancer, and slightly similar trend for breast cancer,  
488 among participants with a more illuminated bedroom at night (indoor-ALAN). There  
489 was no association between outdoor visual-ALAN and indoor-ALAN. This lack of  
490 correlation could be due to the use of shutters at night among subjects with high outdoor  
491 visual ALAN, or perhaps a lack of relationship between the light reaching the ISS and  
492 the light reaching the house's windows. Similar results were described in a previous  
493 study carried out by Rea et al (2011) concluding that satellite-measured sky brightness  
494 (visual light) was unrelated to personal light exposures. Additionally, most human made  
495 surfaces are less reflective in the blue part of the spectrum and the MSI parameters can  
496 be underestimated even though, the results showed a higher correlation with prostate  
497 cancer. Indoor-ALAN measurements are very important to complement outdoor visual-  
498 ALAN impact on hormone-dependent cancers in countries like Spain, where the use of  
499 closed curtains or shutters is extended. In addition, other sources rather than street light  
500 might be contributing to indoor-ALAN exposures like light coming from neighbours, or  
501 the use of portable electronic devices with self-luminous displays and energy-efficient  
502 lighting (LEDs). The use of such devices is increasing and has a significant effect on  
503 decreasing melatonin production if they are used before bedtime (Bonmati-Carrion et al.  
504 2014; Chang et al. 2014).



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

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

528

529 **CONCLUSIONS**

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

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711 **TABLES**

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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

<b>Factors</b>	<b>Indoor ALAN</b>		<b>Outdoor-Visual</b>	
	<b>Controls N=1385 N (%)</b>	<b>Cases N=1219 N (%)</b>	<b>Controls n=568 n (%)</b>	<b>Cases n=446 n (%)</b>
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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Factors	Prostate	Indoor ALAN		Outdoor-Visual	
		Controls	Cases	Controls	Cases
		N=879 N (%)	N=623 N (%)	n=660 n (%)	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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729 **Table 3.** Association of Indoor artificial light-at-night (ALAN) when sleeping, with  
 730 breast and prostate cancer in the total MCC-Spain population (OR: odds ratio; 95% CI:  
 731 95% confidence interval)

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	<b>Controls/Cases N (%)</b>	<b>ORs (95%CI)</b>	<b>Controls/Cases N(%)</b>	<b>ORs (95%CI)</b>
<b>Basic adjustment<sup>a</sup></b>	<b>Breast Cancer (N=2604)</b>		<b>Prostate Cancer (N=1502)</b>	
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)
<b>Further adjustment<sup>b</sup></b>	<b>Breast Cancer (N=1590)</b>		<b>Prostate Cancer (N=1096)</b>	
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)

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

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

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

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	<b>Controls/Cases N (%)</b>	<b>ORs (95%CI)</b>	<b>Controls/Cases N(%)</b>	<b>ORs (95%CI)</b>
<b>Basic adjustment<sup>c</sup></b>	<b>Breast Cancer (N=705)</b>		<b>Prostate Cancer (N=738)</b>	
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=1 <sup>st</sup> tertile (lowest)	122(30.8)/107(34.6)	1.0	130(30.4)/124(40.0)	1.0
2 <sup>nd</sup> 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)
3 <sup>rd</sup> 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=1 <sup>st</sup> tertile	136(27.4)/106(34.3)	1.0	157(36.7)/98(31.6)	1.01.18(0.8,
2 <sup>nd</sup> tertile	236(47.6)/92(29.8)	0.9(0.6, 1.3)	151(35.3)/100(32.3)	1.7)
3 <sup>rd</sup> 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)
<b>Further adjustment<sup>d</sup></b>	<b>Breast Cancer (N=521)</b>		<b>Prostate Cancer (N=659)</b>	
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=1 <sup>st</sup> tertile	107(31.2)/99(37.4)	1.0	123(32.0)/108(39.3)	1.0
2 <sup>nd</sup> 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)
3 <sup>rd</sup> 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=1 <sup>st</sup> tertile	117(34.2)/89(33.6)	1.0	141(36.7)/85(30.9)	1.0
2 <sup>nd</sup> 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)
3 <sup>rd</sup> 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)

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755 a. Breast ALAN-Visual Light tertiles of exposure: 1<sup>st</sup> tertile=0.009-0.046; 2<sup>nd</sup> tertile= 0.047-  
756 0.071; 3<sup>rd</sup> tertile=0.072-0.225. Prostate ALAN- Visual Light tertiles of exposure: 1<sup>st</sup>  
757 tertile=0.002-0.047; 2<sup>nd</sup> tertile= 0.048-0.073; 3<sup>rd</sup> tertile=0.074-0.225.

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

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

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

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768 **Table 5.** Association of Outdoor ALAN-MSI (blue light) with breast and prostate  
769 cancer subphenotypes. Models with basic adjustment<sup>a</sup>. Relative risk ratios (RRR) for  
770 Outdoor ALAN-MSI exposures in tertiles<sup>b</sup>.

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Outdoor- ALAN-MSI	1st tertile		2nd tertile			3rd tertile		
	N (%)	RRR	N (%)	RRR	95%CI	N (%)	RRR	95%CI
<b>Breast cancer</b>								
Hormone receptors <sup>c</sup>	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)	-	-
<b>Prostate cancer</b>								
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)	-	-

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

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808 **FIGURE LEGENDS**

809 **Figure 1.** International Space Station night image (<https://eol.jsc.nasa.gov>) of Madrid  
810 2012 (ISS030-E-82053).

811 **Figure 2.** International Space Station night image (<https://eol.jsc.nasa.gov>) of Barcelona  
812 2013 (ISS045-E-120336).

813 **Figure 3.** Classification of the ground level spectral type of the lamps<sup>a</sup> using the green  
814 to the red bands (G/R) ratio, to estimate the ground based spectrum of the melatonin  
815 suppression index (MSI).

816 a. Different types of lamps used in the analysis:

817 CFL=Compact Fluorescent

818 MV= Mercury Vapour

819 HAL= Halogen

820 MH= Metallic Halogen

821 CMH= Ceramic Metallic Halogen

822 FL=Fluorescent

823 LED = LED

824 INC = Incandescent

825 HPS = High Pressure Sodium

826 LPS = Low Pressure Sodium

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

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

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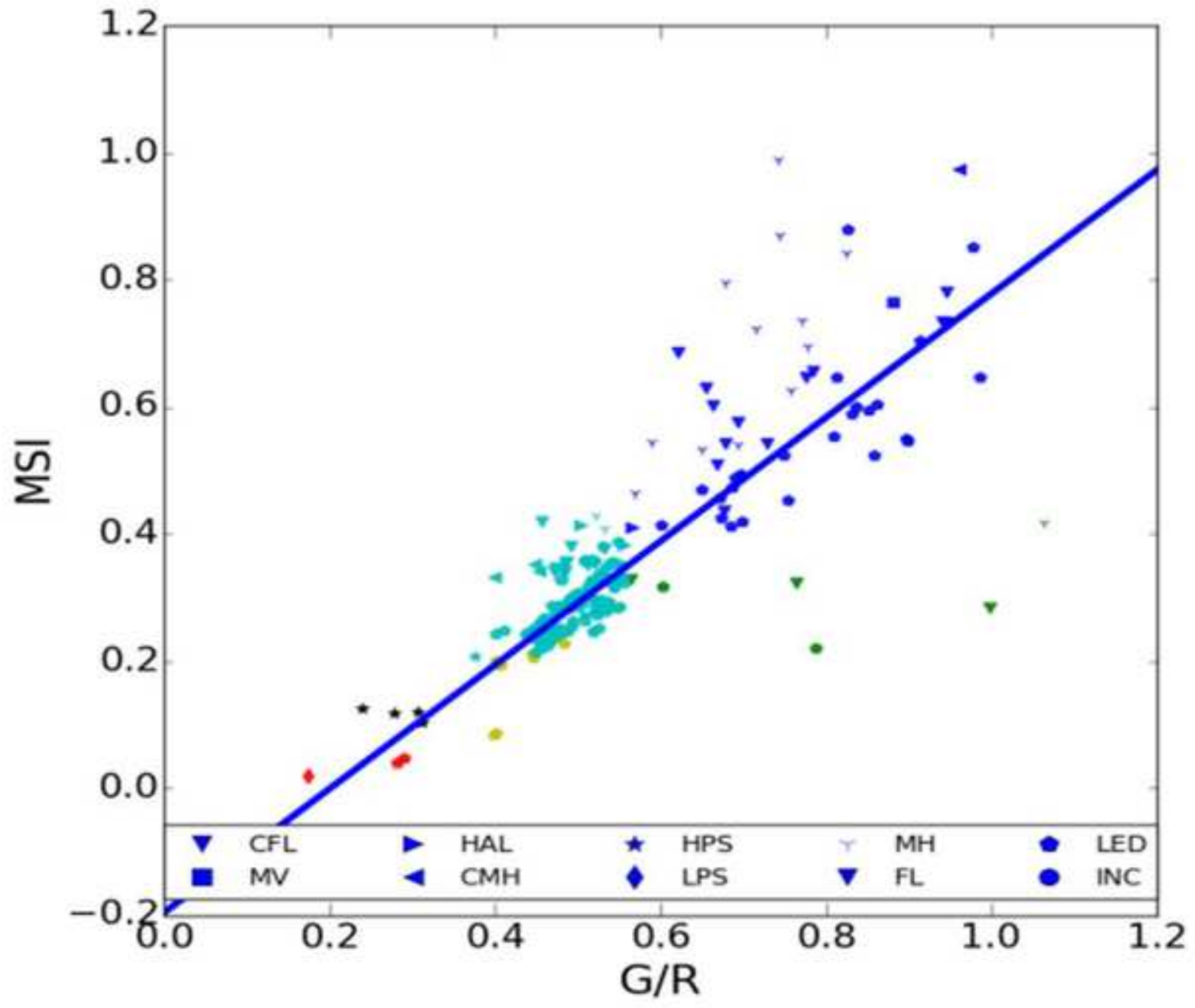
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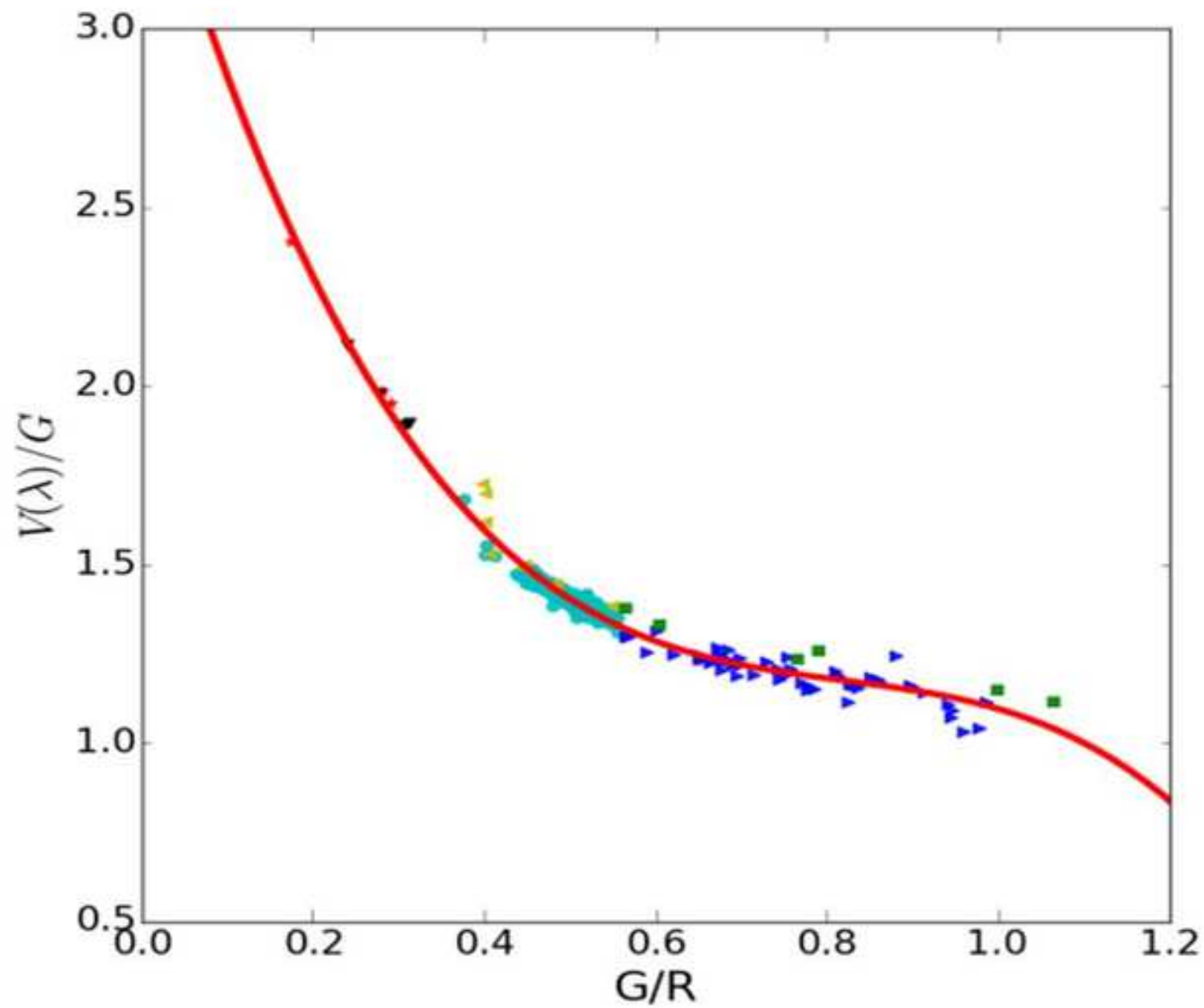
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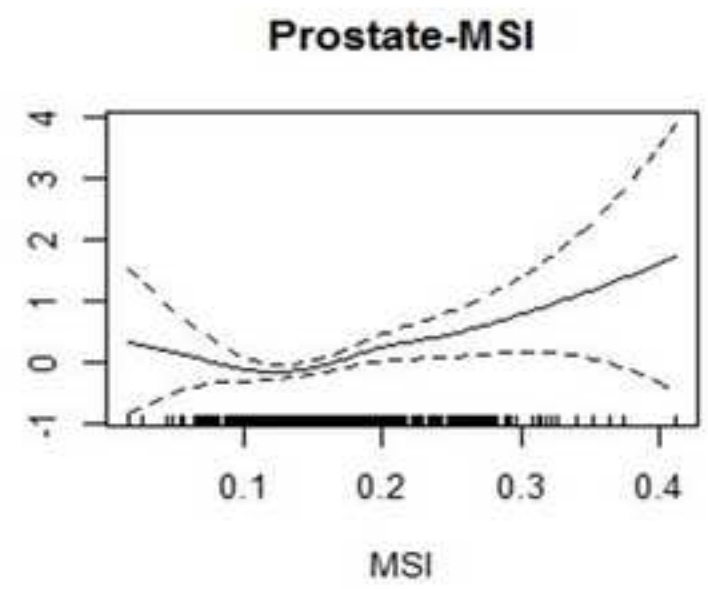
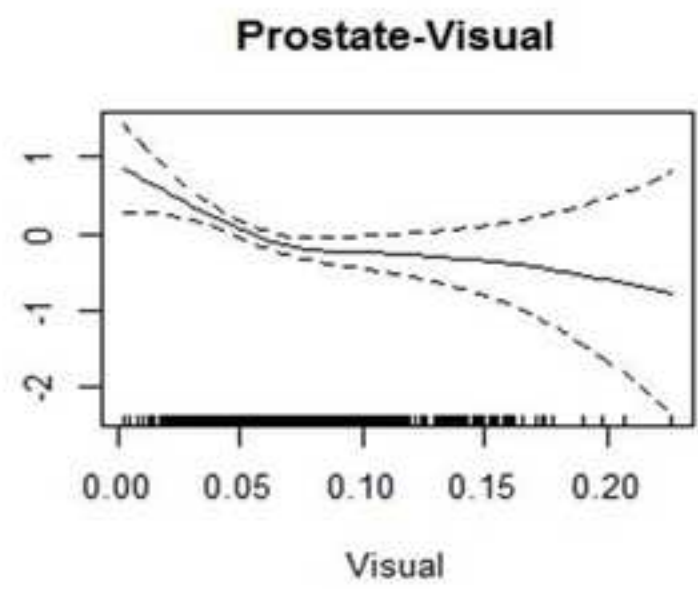
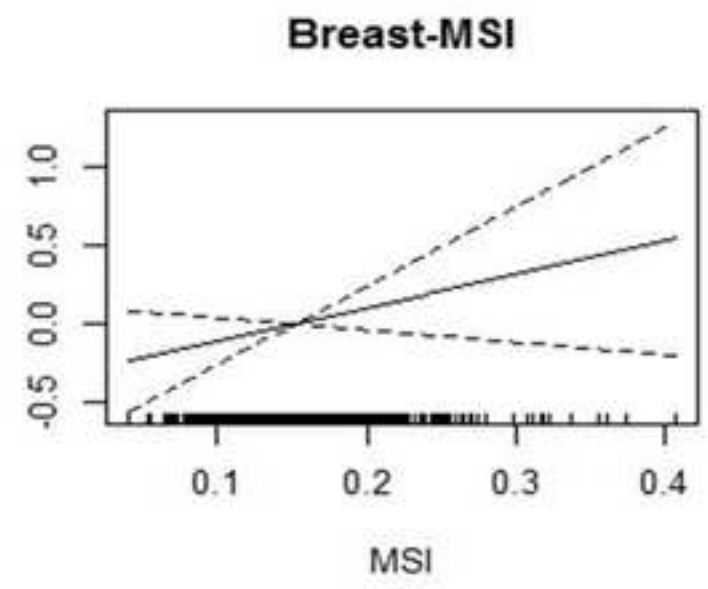
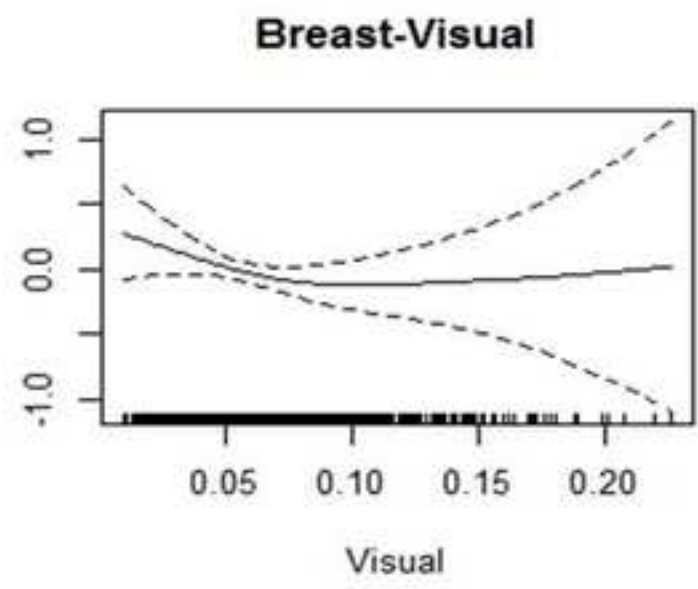
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1st of march 2017

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