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Title: Association between outdoor light-at-night exposure and colorectal cancer in Spain (MCC-Spain study)

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Short title

Artificial light-at-night and colorectal cancer risk

Conflict of interest

The authors declare that they have no conflict of interest.

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Data and computing code

Due to data confidentiality, the MCC-Spain health data is not available as an open access. In order to obtain data and computing code please contact the corresponding author. However, light exposure dataset of Madrid and Barcelona can be downloaded from Zenodo open-access repository:

Alejandro Sánchez de Miguel. (2019). Madrid light impact impact maps using ISS images [Data set]. Zenodo. http://doi.org/10.5281/zenodo.2656774

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Abstract

Background. Night shift work, exposure to artificial light-at-night and particularly blue light spectrum, and the consequent circadian disruption may increase the risk of breast and prostate cancer. Colorectal cancer risk may also be increased among night-shift workers. We investigated the association between exposure to artificial light at night according to light spectrum and colorectal cancer among subjects who had never worked at night in a general population case–control study in Spain.

Methods. We examined information on 661 incident histologically verified colorectal cancer cases and 1322 controls from Barcelona and Madrid, 2007-2013. Outdoor artificial light at night exposure was based on images from the International Space Station (ISS) including data on remotely sensed upward light intensity. We derived adjusted odds ratio (OR) estimates and confidence intervals (CI) for visual light, blue light, and spectral sensitivities of the five human photopigments assigned to participant's geocoded longest residence.

Results. Exposure to blue light spectrum was positively associated with colorectal cancer (OR=1.6; 95%CI: 1.2-2.2; highest vs. lowest tertile). ORs were similar (OR=1.7; 95%CI: 1.3-2.3) when further adjusting for area socioeconomic status, diet patterns, smoking, sleep and family history. We observed no association for outdoor visual light (full spectrum) (OR = 1.0, 95%CI 0.7-1.2; highest vs. lowest tertile). Analysis of the five photopigments gave similar results with increased risks for shorter wavelengths overlapping with the blue spectrum and no association for longer wavelengths.

Conclusions. Outdoor blue light spectrum exposure that is increasingly prevalent in recent years may be associated with colorectal cancer risk.

Keywords

Light pollution, cancer, light-at-night, colorectal, sleep, blue-light

Introduction

Colorectal cancer is the third most common cancer worldwide following tumors of the lung and breast and the second most common cause of cancer death in 2018 (1). Modifiable risk factors of colorectal cancer include obesity, diet, low physical activity, and consumption of alcohol and tobacco (2). In 2007 the World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) formulated a series of recommendations for cancer prevention based on diet, physical activity and body fatness (3), and adherence to these recommendations has been shown to be associated with a lower risk of developing colorectal cancer (4).

Circadian disruption may be associated with an increased risk of colorectal cancer. In 2007, the International Agency for Research on Cancer (IARC) classified 'shiftwork that involves circadian disruption' as being probably carcinogenic to humans (5). This evaluation was recently confirmed (6) and the IARC working group concluded that there was also "limited evidence" that night shift work causes colorectal cancer. Existing studies have reported mostly positive associations but results are not entirely consistent (2, 7–10). Experimental animal studies have shown an increase in multiple tumors including colon adenocarcinomas following exposure to light at night or protocols simulating shift work or jet lag (5, 6). Molecular and genetic data have shown an association between clock genes and clock-controlled cell cycle genes in murine colorectal tumors and correlations between clock genes expression with pathogenesis, progression, aggressiveness and prognosis of colorectal cancer. These studies indicate overall that dysregulated expression of clock genes may be important in human colorectal tumorigenesis (11–12).

Exposure to artificial light-at-night, depending on its intensity, duration, and wavelength, may decrease and delay production and secretion of melatonin from the pineal gland (5). Melatonin is a hormone normally produced in the dark phase of the 24h cycle and is linked to different impacts on human health (13–15). Melatonin has been associated with tumor initiation and progression through different pathways (16). Of the three types of photoreceptors in the eye (rods, cones and intrinsically photosensitive retinal ganglion cells (ipRGCs)), ipRGCs are the

most relevant for circadian rhythm and melatonin regulation and have a peak of spectral sensitivity at short wavelengths (i.e., blue light) (17). The roles of ipRGCs in melatonin regulation is mediated by the photopigment melanopsin. Therefore, light exposure assessment that provides a comprehensive characterization of photoreceptor inputs is needed to shed light on relevant biological mechanisms of effect on the circadian, neuroendocrine and neurobehavioral systems.

Increasing artificial light at night in cities is altering the natural light levels in the nocturnal environment and is associated with human activities (18). For several decades, high pressure sodium (HPS), low pressure sodium (LPS), metalhalide (MH), and fluorescent lamps were used for outdoor lighting. However, there is now a widespread shift to 'white' light-emitting diode (LED) lamps, due to their lower maintenance costs, but whose light emissions have repeatedly been found to have more severe environmental impacts than previous lamps (19). Different studies have established positive associations between prolonged exposure to artificial light at night and several adverse health effects, including sleep disturbance (20), obesity (21) and elevated risks of hormone-dependent cancers, in general populations i.e. non night-shift workers (22–25). Many of the existing studies were ecologic. Nearly all studies used data from the United States Department of Defense Meteorological Satellite Program (DMSP) to determine the outdoor artificial light at night level and mapping sky brightness and built surfaces and more recently, the Visible Infrared Imaging Radiometer Suite (VIIRS) with its Day-Night Band camera on board the Suomi National Polar-Orbiting Partnership (Suomi NPP) satellite (26,27). However, data obtained from satellite images only detect light intensity but not the spectrum of night time light emissions, therefore neither DMSP or VIIRS specifically measure the more physiologically relevant blue content of light.

In the present study we applied new methodology for evaluating residential artificial light at night (28,29) that made it feasible to derive simple three-band spectral information (e.g. red (R), green (G), blue (B), RGB) from ISS images. We previously used this new methodology (24) to evaluate the association of artificial light at night exposure and breast and prostate cancer in

Spain showing an increased risk in participants with higher exposures to blue light spectrum, modeled using a melatonin suppression index (30) assigned to each participants' geocoded residence. In the present study, we extend this exposure assessment approach to include the spectral sensitivity of the five human photopigments for each pixel of the ISS images. Our objective was to quantify the relationship between colorectal cancer and artificial light at night characterized by levels of visual light, blue light estimated using MeSI, and spectral sensitivity of five human photopigments.

Materials and Methods

Study population

MCC-Spain is a population-based, multicentric case–control study (http://www.mccspain.org) on frequent tumors occurring between 2007 to 2013 in Spain. MCC includes cases and population controls from the catchment areas of 23 hospitals in 12 regions and assesses five types of cancer (breast, colorectal, prostate, and stomach cancers and chronic lymphocytic leukemia). Detailed information on the study is provided elsewhere (31). All cases diagnosed in the participating hospitals who were residents for at least 6 months of the catchment areas of the hospitals were approached. Population controls (used for all cases) were randomly selected from the primary health centers located in the same catchment area as cases, without previous history of cancer and matched by sex and age. Response rates varied by center with an average 72% response rate among cases and 52% among controls with valid telephone numbers in the primary health centers' rosters.

In the present analysis we limited the study population to colorectal cancer cases and population controls in the two largest areas of the study (Barcelona and Madrid) because images from the International Space Station (ISS) used to evaluate outdoor artificial light at night exposures, were only available for those two regions. Overall, we recruited 926 subjects aged 28 to 85 years with histologically confirmed, newly diagnosed colorectal cancer who lived in the catchment area of each selected hospital for at least 6 months; we selected 1755 controls

selected randomly from the rosters of general practitioners at the primary health centers involved in the study. Nearly all cancers (95%) were adenocarcinomas and 35% were located in the rectum

For the main analysis, we excluded participants who had ever worked in night-shift (i.e., working schedule that involved working partly or entirely between 00:00 and 06:00 hours, at least three times per month). The final study population included 661 cases and 1322 controls in the Barcelona and Madrid regions. A flow chart showing exclusions is shown in eFigure 1. We also present additional analyses without the excluded subjects.

Trained personnel collected data through face-to-face interviews, including lifetime residential and occupational history, current and past (at 30-40 years of age). They collected information on other risk factors such as age, educational level, family socioeconomic level, body mass index (BMI), family history of cancer, smoking status, alcohol consumption, leisure time physical activity information, sleep duration, and diet habits.

We used the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) score which was constructed to evaluate the adherence to cancer prevention recommendations, incorporating six of the WCRF/AICR recommendations regarding body fatness, physical activity, foods and drinks that promote weight gain, plant foods, animal foods, and alcoholic drinks (4). Height and weight at different ages were self-reported and waist and hip circumference were measured with a tape. We calculated the body mass index (BMI, kg/m^2) from self-reported weight 1 year before the interview. Leisure time physical activity information was available for all activities held over lifetime. The cumulative volume of physical activity in terms of Metabolic Equivalent of Task (MET) of 3 h/wk, was calculated for the last 10 years of life, excluding the last 2 years previous to the interview. Subjects completed a semi-quantitative Food Frequency Questionnaire (FFQ), which included food items with portion sizes specified for each item, and assessed usual dietary intake during the previous years. Briefly, when the recommendation was met for each component, 1 point was assigned, 0.5 point when it was partially met and 0 point otherwise. Then the score was divided into tertiles depending on the

participant's gender i.e. (Tertile 1: Men (0.25–3) / women (0.5–3.5); Tertile 2: Men (3.25–4) / women (3.75–4.25); Tertile 3: Men (4.25–6) / women (4.5–6)).

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 Orgánica 15/1999 de 13 Diciembre de Protección de Datos de carácter personal; LOPD). All participants who 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 centers and hospitals reviewed and approved the protocol of the study.

Exposure assessment

Estimates for outdoor light were based on ISS images in 2012–2013, from Madrid: ISS030-E-82052 (Figure 1) and Barcelona: ISS035-E-23385 (Figure 2), respectively. The images were downloaded from the Earth Science and Remote Sensing Unit, NASA Johnson Space Centre (url: https://eol.jsc.nasa.gov). ISS images for early periods of the study were not available or had poor quality, therefore the images selected were evaluated as the most representative of the period examined.

Images were taken with commercial Digital Single-Lens Reflex (DSLR) cameras providing image information in three spectral bands, in the visual range (i.e. RGB) and with the European Space Agency NightPod system (installed in 2012) with 30m of spatial resolution; for more details about the methodology used to calibrate and inferring the observed lighting type from the RGB signature, see the procedure described in (32).

For each pixel of the image we obtained different outdoor-artifical light at night exposures. First, we estimated visual light in units proportional to luminance (Cd/m^2) 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 measure has been referred to as the Normalized Ratio Light Index (NRLI) (32). Secondly, we used synthetic photometry to predict the colors of different spectra typical on street lighting (33). We used a statistical

relationship to infer the percentage of outdoor blue light spectrum, modeled as the Melatonin Suppression Index described in (30). This blue light index was calculated using the melatonin suppression action in the spectral range from 425 nm to 560 nm, compared to the spectrum shape of the International Commission on Illumination's (CIE) illuminant D65 that has been arbitrarily set to the highest value (one). The CIE's Standard Illuminant D65 corresponds approximately to the average midday sunlight in Western and Northern Europe.

Finally, we obtained information on potential physiological light responses and phototransduction processes of the photoreceptors cells in the human retina (rods and cones) and in the intrinsically photosensitive retinal ganglion cells (ipRGC); the spectral sensitivity to irradiance of the five human photopigments (melanopic, cyanopic, rhodopic, chloropic, and erythropic) was calculated for each pixel of the ISS images, following the methodology described by Lucas (17,34,35).

A geographic information system (GIS) (36) was used to assign outdoor-artificial light at night levels of visual light, blue light, and spectral sensitivities based on the geocoded residence with the longest duration for each participant. For 88.1% of the subjects the residence at 10 years prior to the interview (approximate time for the light exposure estimates) was their longest residence. This distribution was very similar in cases and controls. Light exposure dataset of Madrid and Barcelona can be downloaded from the Zenodo open-access repository (37,38)

Statistical analysis

We used generalized additive models (GAMs) with a logit link function to examine the shape of the exposure-response relationship between outdoor artificial light at night and log odds of colorectal cancer for both visual and blue light exposures. The Akaike Information Criterion was used to select the best fit model with the minimum AIC value. We used unconditional logistic regression to estimate adjusted ORs and 95% CIs for all outdoor ALAN exposures transformed as categorical variables using tertiles of exposure among controls. Tertiles were

defined on the basis of the total eligible population of controls with light exposure information (eTable 1).

We adjusted all models including the GAMs (basic adjustment) for age, gender, area (Madrid and Barcelona), and educational level (less than primary school; primary school; secondary school; and university). There is little prior knowledge on potential correlates of light exposure in urban areas so we further adjusted for major lifestyle, sleep, and contextual factors: WCRF/AICR score, urban vulnerability index that measures socioeconomic status at area level coded from 0 to 1 (39), reported family history of colorectal cancer, sleep duration, and sleeping problems (which mainly consisted in difficulties to fall asleep and night awakenings) and smoking habits (ever, never). Adjustment for finer categories of smoking gave practically the same results as for the dichotomous variable (not shown). We conducted a multinomial logistic model to analyze differences between tumor location. To explore whether exclusion of night shift workers may have biased our results we conducted a sensitivity analysis including them. We evaluated effect modification by educational level (Primary school or lower; secondary school or higher) and by smoking status (never; ever) using likelihood ratio test (LRT). To increase efficiency and minimize selection bias, we performed multiple imputation of missing values of the potential confounders using chained equations (40) assuming the missing at random (MAR) hypothesis. Multiple imputations were done separately for cases and controls and we generated 30 complete data sets. We analyzed each data set individually and used Rubin's rule to obtain the overall estimate. We performed all statistical analyses using Stata S.E. (version 12.1; StataCorporation) and the R software environment (41).

Results

Study Population

We included 661 colorectal cancer cases and 1322 population controls. Table 1 shows sociodemographic and lifestyle characteristics of the study population by case–control status

among non-shift workers. Among participants overall, there was approximately the same proportion of males and females; however, a higher proportion of males (59%) presented with colorectal cancer. Cases were slightly older (mean 67 versus 64 years) and had more frequently reported first degree of colorectal cancer family history (14% versus 10%). Regarding the WCRF score, we found that a lower percentage of cases than controls (14% versus 24%) were classified in the higher tertile, which corresponded to the healthiest life-style score (meaning lower body fatness, lower consumption of foods and drinks that promote weight gain and higher physical activity).

Average exposure was 0.010 (standard deviation [SD]: 0.005; min: 0.000; max: 0.042) for visual light ((nW/(cm^2·sr·s·Å)) and 0.166 (adimensional) (SD: 0.053; min: 0.047; max: 0.649) for blue light. There was no correlation between exposure to visual light and blue light (Spearman correlation coefficient of -0.27) (eTable1).

ALAN Models

In GAM models evaluating exposure-response of ALAN and cancer risk (Figure 3) we observed higher risks for higher exposures for blue light while no clear dose-response was found for visual light. There was no clear departure from linearity ($p>0.05$ for both curves). We conducted subsequent analyses based on tertiles of exposure defined for the total population of controls (eTable 1).

Associations of outdoor artificial light at night (visual light and blue light) and colorectal cancer are shown in Table 2. Patterns of ORs were similar for the basic and fully adjusted models; exposure to higher versus lower tertile of blue light spectrum (Melatonin Suppression index-MESI) was positively associated with colorectal cancer (OR_{basic}=1.6; 95%CI: 1.2-2.2) and ($OR_{further}$= 1.7; 95%CI: 1.3,2.3). Visual light (full spectrum) was not associated with colorectal cancer (OR_{basic} = 1.0; 95%CI: 0.7, 1.2) and ($OR_{further}$= 0.9; 95%CI: 0.7, 1.1). Additional adjustment for air pollutants (NO_2 and $PM_{2.5}$) did not modify results (eTable 2).

Patterns of ORs values obtained for the spectral sensitivities of the five human photo pigments (melanopic, cyanopic, rhodopic, chloropic, and erythropic) are shown in Table 3. We found practically identical results to blue light spectrum results evaluated through the melatonin suppression index for human photo pigments with sensitivity to wavelengths overlapping with the blue spectrum (eFigure 2). For melanopsin (ipRGCs, maximum sensitivity at 480 nm) the OR (further adjusted) was 1.7 (95%CI 1.2, 2.3, highest vs lowest tertile) and a similar OR was observed for the cyanopic opsin (S cones, maximum sensitivity at 420 nm and Rods, maximum sensitivity at 500 nm). The ORs for the rhodopic and erythropic opsins were lower and in the case of chloropic (M cones, peak sensitivity at 535) the OR was negative (OR=0.6, 95%CI 0.5, 0.8).

Exposure distributions between the photopigments among controls were strongly correlated (eTable 3). Specifically, the correlation between melanopic and cyanopic was 1, that of melanopic/cyanopic with chloropic -1, melanopic and rhodopic 0.34, and melanopic and erythropic 0.15. Rhodopic and erythropic were also highly negatively correlated (-0.85). Given the high correlations we carried out an analysis mutually adjusting for melanopic/erythropic and melanopic/rhodopic rather than adjusting in one model for all photopigments (eTable 4) Results from these analyses were similar to those shown in Table 3.

Subgroup and sensitivity analyses

About 95% of tumor cases (n=626) were histologically identified as adenocarcinomas, 64% of tumors were located in the colon, and 35% in the rectum; for 1% location was not specified. The associations of outdoor artificial light at night and colorectal cancer cases sub-classified by tumor location are shown in Table 4. ORs for blue light spectrum exposure were higher for colon cancer (OR_{basic}=1.8, 95%CI: 1.3, 2.5; highest vs lowest tertile), compared to ORs for cancer in the rectum (OR_{basic}= 1.4; 95%CI: 0.9, 2.1). We found no association with visual light for either location (Table 4).

We examined in a sensitivity analysis the population including participants who reported ever having worked night shift. Estimated associations were similar (eTable 5) when including night workers than the main analyses that excluded them (Table 2). There was a positive association for blue light spectrum exposure (models as previously but additionally adjusting for night shift work as a covariate) both for basic adjustment (OR_{basic} = 1.7; 95%CI: 1.3, 2.2) and further adjusted models ($OR_{further}$= 1.8; 95%CI: 1.4, 2.4). No association was observed for visual light (eTable 5).

We evaluated effect modification by educational level (eTable 6) and by smoking status (eTable 7). The association with blue light was observed in both socioeconomic strata but was more pronounced in the high education stratum (OR_{basic} = 2.1; 95%CI: 1.3, 3.5) compared to those with primary or less education (OR_{basic} = 1.4; 95%CI: 1.0, 2.0). There were pronounced differences by smoking status with the association with blue light observed only among ever smokers (OR_{basic} = 1.8; 95%CI: 1.2, 2.5) while no association was observed for never smokers (OR_{basic} = 1.0; 95%CI: 0.7, 1.5). There were no differences between strata for visual light.

Discussion

We evaluated the association between light-at-night exposures during sleeping time and risk of colorectal cancer among a non-night shift worker population within a case–control study in Spain (MCC-Spain). We found evidence of a positive association of the blue content of outdoor artificial light at night and colorectal cancer risk but not with overall visual light. The association with blue light spectrum was observed only among ever smokers. Results for the photopigments indicated a similar pattern with an increased risk observed for exposure to pigments in the blue light spectrum and no or negative association for pigments in longer wavelengths. Comparison of our findings with previous studies, many of which are ecologic, is difficult since this is the first study evaluating the blue content of outdoor artificial light at night and colorectal cancer.

Most previous studies investigating the association between night-shift work and colorectal cancer risk found that long-term rotating shift work was associated with an increased risk for colorectal cancer (7-9) but results are not entirely consistent (6). Only one ecologic study has attempted to estimate the effect of exposure to artificial light at night and colorectal cancer risk (42) comparing the incidence rates of the most common cancers in men (prostate, lung, and colon) from 164 different countries with the population-weighted light-at-night exposure using data from satellite images (DMSP) of light intensity i.e. with no information on light spectrum, and found no association with colon or lung cancer which is, in part, consistent with the absence of a positive association regarding visual light in our results.

The role of night-shift work and exposure to artificial light at night in colorectal carcinogenesis is still unclear because this type of tumor does not fully share carcinogenic mechanisms with hormone dependent cancers, like breast and prostate that have been previously associated with artificial light at night exposures among night-shift workers and in the general population. Colon adenocarcinomas are, however, among the cancers identified in animal experimentation to be associated with circadian disruption. The circadian system is closely related to the endocrine system and exposure to light at night can alter the normal production of melatonin and steroid hormones (43,44). Moreover, genetic studies have shown that disruption of circadian genes could be one of the endogenous factors that contribute to colorectal tumor initiation and progression, as among the transcriptional targets of clock genes are some cell cycle mediators, tumor suppressor genes and oncogenes regulating cell cycle, cellular metabolism, and DNA repair (11).

We applied new methods to convert ISS images into maps of artificial light at night using the spectral information of each pixel at high spatial resolution (30m), to assess for the first time exposure to artificial light at night according to spectra and colorectal cancer. More widely available data from satellite sensors (VIIRS/DNB and DMSP/OLS) do not provide information about the spectra of the emissions of outdoor artificial light sources. Currently, only nighttime images taken with DSLR (digital single lens reflex) cameras from the International Space

Station (ISS) provide spectral information; however, these are available only for specific cities around the globe. We limited the light analysis to the study population in Madrid and Barcelona because of the availability of high resolution ISS images for those cities. Both cities are highly illuminated. There is limited background information on light exposure distribution between and within cities particularly for light spectra and it is therefore difficult to extrapolate our findings to other areas.

Our approach assumes that the emitted or ground reflected light measured by the camera sensor is a good proxy for the light intensity at ground level. This approach, however, may not capture the total amount of light at street level or that penetrates indoors via windows due to the influence of atmospheric-induced optical distortion as well as spectral and geometrical transformations from the underlying ground surfaces and obstacles(45). These interferences are likely to affect less the light spectrum than the total amount of light (24) and this may be, in part, an explanation for the unexpected large difference in association of blue light and visual light with colorectal cancer. Assessing exposure to light intensity using ISS images does not take into account individual behaviors, for example the use of blinds, which is common in Spain and throughout other Mediterranean countries. Our estimate of exposure to blue light (MeSI) can be interpreted as the amount of light people are exposed to when outside (a common pattern in Spain) and also light that gets through the windows when not completely blocking the light during sleep or, even more, through exposure in hours before bed (before blinds are closed). Interpretation of results from the analysis on blue light spectrum (compared to other spectra) is complex since models essentially evaluate proportions and a high proportion of blue light spectrum corresponds to low proportions of other spectra. In addition, there are only limited biologic explanations for the difference in effect estimates for visual as compared to blue light. The circadian melatonin rhythm has higher sensitivity to short wavelengths (blue light) even at low levels of light intensity (14, 46), so a stronger effect for blue light could be expected. However, all light spectra have the potential to suppress the circadian system at different rates so we could have expected some effects observed also for visual light.

Through the ISS images it was also possible to obtain spectral information corresponding to sensitivity of human retinal photoreceptors (rods and cones) and melanopsin, an opsin photopigment found in the intrinsically photosensitive retinal ganglion cells (ipRGCs) which has the function to synchronize endogenous circadian clocks to the external light:dark cycle (17). This analysis allowed us to compare the association of colorectal cancer and blue light exposure using different approaches. We calculated the Melatonin Suppression Index (MeSI) using a spectral range from 425 nm to 560 nm, corresponding to blue light. We calculated the sensitivity curves of five human retinal photopigments (erythropic, chloropic, rhodopic, cyanopic and melanopic) including the dominant wavelength of each one. Practically identical results to the blue light estimates from the melatonin suppression index were found for the cyanopic and rhodopic photopigments, and melanopsin, the photopigment of ipRGCs, these results provide additional support that short wavelengths (i.e. blue light) are most biologically relevant for health effects related to artificial light at night. The use of photopigments in health and exposure assessment studies has been promoted by international committees on artificial light at night but there is still little knowledge on their population distribution and this complicates interpretation.

Potential confounding and misclassification of light exposure are among the main limitations of the study. The factors that could be associated with light exposure in urban centers are not well examined. A recent study in The Netherlands identified an association between light exposure and air pollution (47). In our study, air pollutants did not confound the association with light exposure. We adjusted for socioeconomic status both at individual and at area level to take into account, at least in part, a potential bias due to an association of socioeconomic factors with urban structure and light. Additionally, we evaluated diet patterns, life style including sleep, smoking, and family history, which have been described as risk factors for colorectal cancer and effect estimates did not change substantially. The association with blue light spectrum exposure was only observed among smokers and the interpretation of this finding is not obvious. Smoking is a recognized colorectal cancer carcinogen (2) but is not a major risk factor for these

cancers although has been strongly related to precancerous lesions (adenomas). Other studies on light should evaluate this difference in risk by smoking status and, if replicated, should identify potential biologic mechanisms.

The selection of the time period for exposure assessment was conditioned by the availability of ISS digital photos prior to recent changes in the use of LEDs in Spain. Mobility is fairly low in Spain and for 88.1% of the subjects the residence at 10 years prior to the interview was their longest residence. The exposure window covered by the light estimates may, therefore, be fairly long. According to statistics of the energy consumption of the town halls (48) during the period of study, there were no major changes on the street lightning of Madrid and Barcelona, although at present many cities across Europe are experiencing marked increases in night time brightness (49) due to the massive use and exponential growth of LEDs that replace the incandescent and high-pressure sodium lamps (50).

In this research we could not estimate the potential exposure reaching the retinae of each participant because this would require an experimental design with more accurate measures of indoor light through light sensors and this was beyond the scope of our study. We could not evaluate either the cumulative exposure to artificial light in the hours before bed which could also affect the circadian rhythm.

Conclusions

Overall this is the first study that has analyzed exposures to artificial light at night at the individual level according to spectrum and colorectal cancer risk in a non-night-shift worker population. We found evidence of positive associations for colorectal cancer with exposure to outdoor light in the blue spectrum that suppresses most effectively melatonin, whereas exposure to outdoor light in the visible spectrum was not associated with colorectal cancer. There is increasing concern of the effects of light on the ecosystems and on human health. Research on potential effects on humans is in an early phase and most recommendations are based on experimental rather than on population-based evidence. Research in different populations across

the world should provide a more substantial set of evidence to evaluate the effects of light and light spectrum on different health effects across different ages and provide recommendations for prevention.

Table 1. Distribution of potential colorectal cancer risk factors among non-shift workers from Barcelona and Madrid (MCC-Spain) included in the artificial light-at-night model.

Table 2. Association of outdoor artificial light at night, visual, and blue light spectrum with colorectal cancer in Barcelona and Madrid (MCC-Spain).

Table 3. Associations of spectral sensitivities of the five human photopigments to outdoor artificial light at night with colorectal cancer in Barcelona and Madrid (MCC-Spain).

Table 4. Associations of outdoor-artificial light at night (visual and blue light spectrum) with colorectal cancer in Barcelona and Madrid (MCC-Spain), by tumor location

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: Generalized Additive Models for colorectal cancer and exposure to visual light and blue light (MESI, melatonin suppression index). The models were adjusted by: age, sex, area, educational level and WCRF score.

eTable 1. Outdoor-artifical light at night exposures levels. Mean (SD) median (IQR)

eTable 2. Associations of outdoor-artificial light at night (visual and blue light spectrum) and colorectal cancer adjusting for air pollutants.

eTable 3. Spearman correlation coefficients between spectral photopigments in controls (N=1322)

eTable 4. Association of spectral sensitivities of the melanopic with rhodopic photopigments mutually adjusted, and melanopic with erythorpic photopigments mutually adjusted with colorectal cancer in Barcelona and Madrid (MCC-Spain).

eTable 5. Associations of outdoor-ALAN (visual and MeSI) with colorectal cancer from Barcelona and Madrid (MCC-Spain), including night-shift workers.

eTable 6. Associations of outdoor-ALAN (visual and blue light spectrum) and colorectal cancer stratified by education.

eTable 7. Associations of outdoor-ALAN (visual and blue light spectrum) and colorectal cancer stratified by smoking.

eFigure 1. Flow chart showing initial population, exclusions and final population in analysis

eFigure 2. Sensitive curves of the 5 photopigments of the eye plus the action spectrum of the melatonin.

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Table

Table 1. Distribution of potential colorectal cancer (CRC) risk factors among non–shift workers from Barcelona and Madrid (MCC-Spain) included in the artificial light-at-night (ALAN)models.

Characteristic	Controls N=1322	Cases N=661
Age (years); mean(SD)	64 (11.1)	67.3 (10.4)
Sex, n (%)		
Male	716 (54)	392 (59)
Female	606 (46)	269 (41)
Educational level, n (%)l		
Less than primary school	244 (19)	226 (34)
Primary school	398 (30)	260 (39)
Secondary school	378 (29)	129 (20)
University	302 (23)	46 (7)
Area, n (%)		
Madrid	565 (43)	151 (23)
Barcelona	757 (57)	510 (77)
WCRF score, n (%)		
Low adherence	513 (43)	293 (49)
Medium adherence	387 (33)	218 (37)
High adherence	287 (24)	81 (14)
Family history of CRC, n(%)		
No family history	1039 (78)	439 (66)
First degree family history	130 (10)	92 (14)
Other degree family history	153 (12)	130 (20)
Urban vulnerability index; mean (SD)	.5 (.2)	.5 (.1)
Smoking status[a] , n (%)		
Never	576 (44)	302 (46)
Former		
Current	746 (56)	359 (54)
Sleeping problems, n(%)		
No	698 (65)	398 (68)
Yes	380 (35)	185 (32)
Sleep duration, (hours) mean (SD)	6.9 (1.4)	7.3 (1.6)

[a] 1 year before the interview

Table 2. Association of outdoor artificial light at night (ALAN), visual and blue light spectrum with colorectal cancer in Barcelona and Madrid (MCC-Spain).

	Controls N=1322 N (%)	Cases N=661 N (%)	OR (95%CI)[a]	OR (95%CI)[b]
Blue Light [c]				
1st tertile (lowest)	441 (33)	147 (22)	1 (ref)	1 (ref)
2nd tertile	441 (33)	198 (30)	1.0 (0.8, 1.4)	1.1 (0.8, 1.5)
3rd tertile	440 (33)	316 (48)	1.6 (1.2, 2.2)	1.7 (1.3, 2.3)
P for trend			*<0.0001*	*<0.0001*
Visual light				
1st tertile (lowest)	441 (33)	241 (36)	1 (ref)	1 (ref)
2nd tertile	441 (33)	203 (31)	0.8 (0.7, 1.1)	0.8 (0.6, 1.0)
3rd tertile	440 (33)	217 (33)	1.0 (0.7, 1.2)	0.9 (0.7, 1.1)
P for trend			*0.69*	*0.27*

[a]Basic adjustment: area, age, sex, educational level.

[b]Further adjustment: area, age, sex, educational level, WCRF score, Urban Vulnerability Index, family history, smoking habits, sleeping problems, sleep duration. Models using imputed data.

Table 3. Association of spectral sensitivities of the five human photopigments to outdoor artificial light at night with colorectal cancer in Barcelona and Madrid (MCC-Spain).

	Controls N=1322 N (%)	Cases N=661 N (%)	OR (95%CI)[a]	OR (95%CI)[b]
Melanopic				
1st tertile (lowest)	441 (33)	147 (22)	1 (ref)	1 (ref)
2nd tertile	441 (33)	200 (30)	1.0 (0.8, 1.4)	1.1 (0.8, 1.5)
3rd tertile	440 (33)	314 (48)	1.6 (1.2, 2.1)	1.7 (1.2, 2.3)
P for trend			*<0.0001*	*<0.0001*
Cyanopic				
1st tertile (lowest)	441 (33)	147 (22)	1 (ref)	1 (ref)
2nd tertile	441 (33)	198 (30)	1.0 (0.8, 1.4)	1.1 (0.8, 1.5)
3rd tertile	440 (33)	316 (48)	1.6 (1.2, 2.2)	1.7 (1.3, 2.3)
P for trend			*<0.0001*	*<0.0001*
Rhodopic				
1st tertile (lowest)	442 (33)	192 (29)	1 (ref)	1 (ref)
2nd tertile	440 (33)	200 (30)	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)
3rd tertile	440 (33)	269 (41)	1.1 (0.9, 1.5)	1.1 (0.9, 1.5)
P for trend			*0.31*	*0.32*
Chloropic				
1st tertile (lowest)	443 (34)	317 (48)	1 (ref)	1 (ref)
2nd tertile	439 (33)	198 (30)	0.6 (0.5, 0.8)	0.6 (0.5, 0.8)
3rd tertile	440 (33)	146 (22)	0.6 (0.5, 0.8)	0.6 (0.4, 0.8)
P for trend			*<0.0001*	*<0.0001*
Erytropic				
1st tertile (lowest)	448 (34)	220 (33)	1 (ref)	1 (ref)
2nd tertile	436 (33)	201 (30)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)
3rd tertile	438 (33)	240 (36)	1.2 (1.0, 1.6)	1.3 (1.0, 1.6)
P for trend			*0.07*	*0.05*

[a]Basic adjustment: area, age, sex, educational level.

[b]Further adjustment: area, age, sex, educational level, WCRF score, Urban Vulnerability Index, family history, smoking habits, sleeping problems, sleep duration. Models using imputed data.

Table 4. Association of artificial light at night (visual and blue light spectrum) with colorectal cancer in Barcelona and Madrid (MCC-Spain) by tumor location

	Controls N=1322 N (%)	Colon cases N=424 N (%)	Rectum cases N=228 N (%)	OR (95%CI)[a] colon vs controls	OR (95%CI)[a] rectum vs controls
Blue Light					
1st tertile (lowest)	441 (33)	89 (21)	56 (25)	1 (ref)	1 (ref)
2nd tertile	441 (33)	123 (29)	73 (32)	1.1 (0.8, 1.5)	1.0 (0.7, 1.5)
3rd tertile	440 (33)	212 (50)	99 (43)	1.8 (1.3, 2.5)	1.4 (0.9, 2.1)
P for trend				*<0.0001*	*0.10*
Visual light					
1st tertile (lowest)	441 (33)	160 (38)	77 (34)	1 (ref)	1 (ref)
2nd tertile	441 (33)	123 (29)	78 (34)	0.8 (0.6, 1.0)	1.0 (0.7, 1.4)
3rd tertile	440 (33)	141 (33)	73 (32)	0.9 (0.7, 1.2)	1.0 (0.7, 1.4)
P for trend				*0.65*	*0.88*

[a]Basic adjustment: area, age, sex, educational level.

Figure

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Figure

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Figure 3

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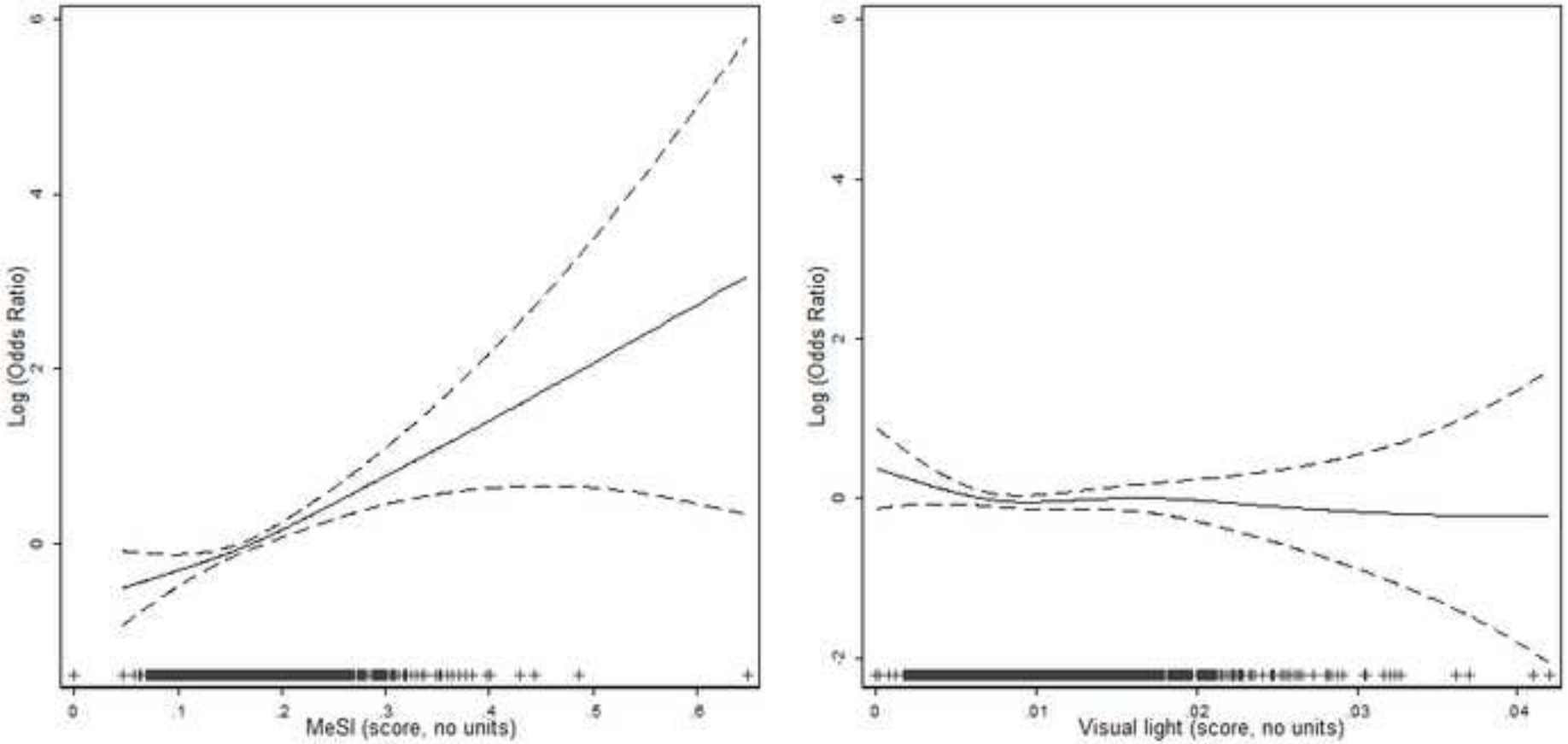


eTables

eTable 1. Outdoor-ALAN exposures levels [a]. Mean (SD) median (IQR)

	Controls (N=1322)		Cases (N=661)		All (N=1983)	
	Mean (SD)	Median (p25-p75)	Mean (SD)	Median (p25-p75)	Mean (SD)	Median (p25-p75)
Blue light	0.16 (0.05)	0.16 (0.12-0.19)	0.18 (0.06)	0.17 (0.14-0.21)	0.17 (0.05)	0.16 (0.13-0.19)
Visual light	0.01 (0.01)	0.01 (0.01-0.01)	0.01 (0.00)	0.01 (0.01-0.01)	0.01 (0.00)	0.01 (0.01-0.01)
Melanopic	0.39 (0.08)	0.39 (0.33-0.45)	0.42 (0.08)	0.42 (0.36-0.48)	0.40 (0.08)	0.40 (0.34-0.46)
Cyanopic	0.19 (0.10)	0.18 (0.11-0.25)	0.23 (0.11)	0.22 (0.15-0.29)	0.20 (0.10)	0.20 (0.13-0.26)
Rhodopic	0.39 (0.10)	0.37 (0.31-0.45)	0.41 (0.11)	0.39 (0.33-0.47)	0.40 (0.11)	0.38 (0.32-0.46)
Chloropic	1.10 (0.06)	1.10 (1.06-1.15)	1.08 (0.06)	1.08 (1.04-1.12)	1.09 (0.06)	1.09 (1.05-1.14)
Erythropic	2.36 (0.39)	2.41 (2.18-2.59)	2.36 (0.44)	2.41 (2.15-2.63)	2.36 (0.41)	2.41 (2.16-2.61)

[a] Units: blue light: adimensional; visual light: ((nW/(cm2·sr·s·Å))

eTable 2. Associations of outdoor-ALAN (visual and blue light spectrum) and colorectal cancer adjusting for air pollutants.

	Controls N=1322 N (%)	Cases N=661 N (%)	OR (95%CI)[a]	OR (95%CI)[b]	OR (95%CI)[c]
Blue Light					
1st tertile (lowest)	441 (33)	147 (22)	1 (ref)	1 (ref)	1 (ref)
2nd tertile	441 (33)	198 (30)	1.0 (0.8, 1.4)	1.1 (0.8, 1.5)	1.1 (0.8, 1.5)
3rd tertile	440 (33)	316 (48)	1.6 (1.2, 2.2)	1.7 (1.3, 2.3)	1.7 (1.3, 2.3)
P for trend			*0.000*	*0.000*	*0.000*
Visual light					
1st tertile (lowest)	441 (33)	241 (36)	1 (ref)	1 (ref)	1 (ref)
2nd tertile	441 (33)	203 (31)	0.8 (0.7, 1.1)	0.8 (0.6, 1.0)	0.8 (0.6, 1.0)
3rd tertile	440 (33)	217 (33)	1.0 (0.7, 1.2)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)
P for trend			*0.685*	*0.269*	*0.258*

aBasic adjustment: area, age, sex, educational level
bFurther adjustment: area, age, sex, educational level, WCRF score, Urban Vulnerability Index, family history, smoking habits, sleeping problems, sleep duration
cFurther adjustment: area, age, sex, educational level, WCRF score, Urban Vulnerability Index, family history, smoking habits, sleeping problems, sleep duration, $PM_{2.5}$, NO_2

eTable 3. Spearman correlation coefficients between spectral photopigments in controls (N=1322)

	Melanopic	Cyanopic	Rhodopic	Chloropic	Erythropic
Melanopic	1				
Cyanopic	1.00	1			
Rhodopic	0.34	0.34	1		
Chloropic	-1.00	-1.00	-0.34	1	
Erythropic	0.15	0.15	-0.84	-0.15	1

eTable 4. Association of spectral sensitivities of the melanopic with rhodopic photopigments mutually adjusted, and melanopic with erythorpic photopigments mutually adjusted with colorectal cancer in Barcelona and Madrid (MCC-Spain).

	Controls N=1322 N(%)	Cases N=661 N(%)	OR (95%CI)[a]	OR (95%CI)[b]
Melanopic				
1st tertile (lowest)	441 (33)	147 (22)	1 (ref)	1 (ref)
2nd tertile	441 (33)	200 (30)	1.0 (0.8, 1.4)	1.1 (0.8, 1.5)
3rd tertile	440 (33)	314 (48)	1.6 (1.2, 2.1)	1.7 (1.2, 2.2)
P for trend			*<0.0001*	*<0.0001*
Rhodopic				
1st tertile (lowest)	442 (33)	192 (29)	1 (ref)	1 (ref)
2nd tertile	440 (33)	200 (30)	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)
3rd tertile	440 (33)	269 (41)	1.1 (0.8, 1.4)	1.1 (0.8, 1.4)
P for trend			*0.52*	*0.55*
Melanopic				
1st tertile (lowest)	441 (33)	147 (22)	1 (ref)	1 (ref)
2nd tertile	441 (33)	200 (30)	1.0 (0.8, 1.4)	1.1 (0.8, 1.4)
3rd tertile	440 (33)	314 (48)	1.5 (1.1, 2.0)	1.6 (1.2, 2.2)
P for trend			*0.001*	*0.001*
Erytropic				
1st tertile (lowest)	448 (34)	220 (33)	1 (ref)	1 (ref)
2nd tertile	436 (33)	201 (30)	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)
3rd tertile	438 (33)	240 (36)	1.2 (0.9, 1.5)	1.2 (0.9, 1.5)
P for trend			*0.29*	*0.24*

[a]Basic adjustment: area, age, sex, educational level.

[b]Further adjustment: area, age, sex, educational level, WCRF score, Urban Vulnerability Index, family history, smoking habits, sleeping problems, sleep duration. Models using imputed data.

eTable 5. Associations of outdoor-ALAN (visual and MSI) with colorectal cancer from Barcelona and Madrid (MCC-Spain), including night-shift workers. (N=2363)

	Controls N=1586 N (%)	Cases N=777 N (%)	OR (95%CI)[a]	OR (95%CI)[b]
Blue Light				
1st tertile (lowest)	528 (33)	175 (23)	1 (ref)	1 (ref)
2nd tertile	541 (34)	241 (31)	1.1 (0.8, 1.4)	1.2 (0.9, 1.5)
3rd tertile	517 (33)	361 (46)	1.7 (1.3, 2.2)	1.8 (1.4, 2.4)
P for trend			*<0.0001*	*<0.0001*
Visual light				
1st tertile (lowest)	523 (33)	290 (37)	1 (ref)	1 (ref)
2nd tertile	543 (34)	237 (31)	0.8 (0.6, 1.0)	0.7 (0.6, 0.9)
3rd tertile	520 (33)	250 (32)	0.9 (0.7, 1.2)	0.8 (0.7, 1.1)
P for trend			*0.44*	*0.12*

[a]Basic adjustment: area, age, sex, educational level.

[b]Further adjustment: area, age, sex, educational level, WCRF score, Urban Vulnerability Index, family history, smoking habits, sleeping problems, sleep duration. Models using imputed data.

eTable 6. Associations of outdoor-ALAN (visual and blue light spectrum) and colorectal cancer stratified by education.

	Primary or lower			Secondary or higher			
	Controls N=642 N (%)	Cases N=486 N (%)	OR (95%CI)[a]	Controls N=680 N (%)	Cases N=175 N (%)	OR (95%CI)[a]	LR Test p-value
Blue Light							
1st tertile (lowest)	221 (34)	121 (25)	1 (ref)	220 (32.4)	26 (14.9)	1 (ref)	0.04
2nd tertile	224 (35)	137 (28)	0.8 (0.6, 1.1)	217 (31.9)	61 (34.9)	1.7 (1.0, 2.9)	
3rd tertile	197 (31)	228 (47)	1.4 (1.0, 2.0)	243 (35.7)	88 (50.3)	2.1 (1.3, 3.5)	
P for trend			*0.01*			*0.002*	
Visual light							
1st tertile (lowest)	182 (28)	171 (35)	1 (ref)	259 (38.1)	70 (40.0)	1 (ref)	0.44
2nd tertile	220 (34)	149 (31)	0.8 (0.6, 1.0)	221 (32.5)	54 (30.9)	1.0 (0.7, 1.5)	
3rd tertile	240 (37)	166 (34)	0.9 (0.7, 1.2)	200 (29.4)	51 (29.1)	1.2 (0.8, 1.8)	
P for trend			*0.40*			*0.48*	

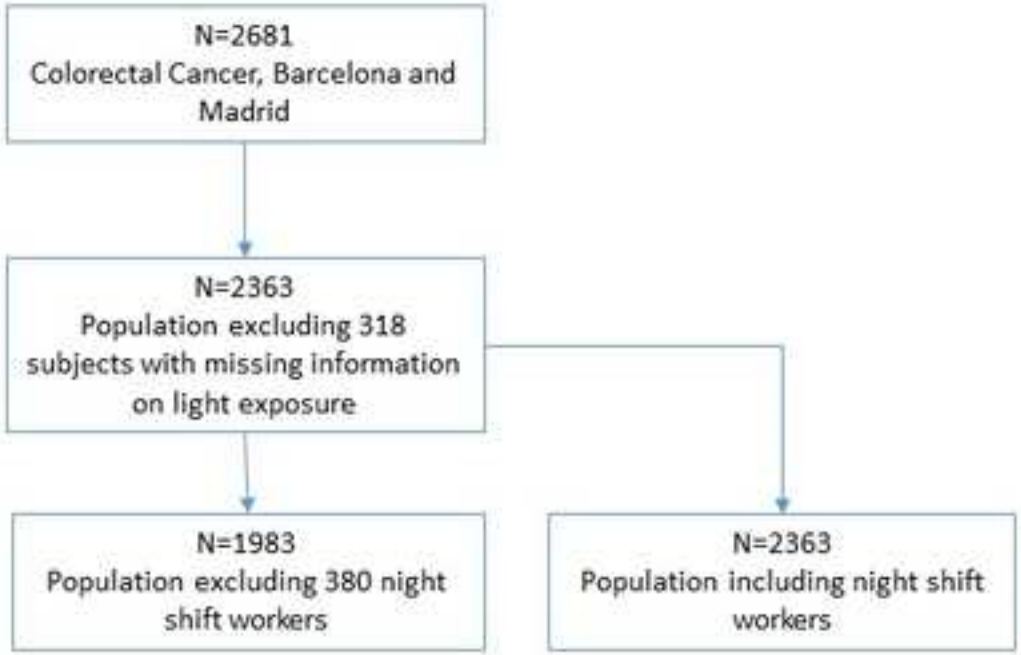
[a]Basic adjustment: area, age, sex, educational level.

eTable 7. Associations of outdoor-ALAN (visual and blue light spectrum) and colorectal cancer stratified by smoking.

	Never			Ever			
	Controls N=576 N (%)	Cases N=302 N (%)	OR (95%CI)[a]	Controls N=746 N (%)	Cases N=359 N (%)	OR (95%CI)[a]	LR Test p-value
Blue Light							
1st tertile (lowest)	178 (31)	79 (26)	1 (ref)	263 (35)	68 (19)	1 (ref)	0.008
2nd tertile	200 (35)	78 (26)	0.6 (0.4, 0.9)	241 (32)	120 (33)	1.3 (0.9, 1.9)	
3rd tertile	198 (34)	145 (48)	1.0 (0.7, 1.5)	242 (32)	171 (48)	1.8 (1.2, 2.5)	
P for trend			*0.561*			*0.001*	
Visual light							
1st tertile (lowest)	202 (35)	110 (36)	1 (ref)	239 (32)	131 (36)	1 (ref)	0.60
2nd tertile	191 (33)	93 (31)	1.0 (0.7, 1.4)	250 (34)	110 (31)	0.9 (0.6, 1.2)	
3rd tertile	183 (32)	99 (33)	1.3 (0.9, 1.8)	257 (35)	118 (33)	1.0 (0.7, 1.4)	
P for trend			*0.212*			*0.928*	

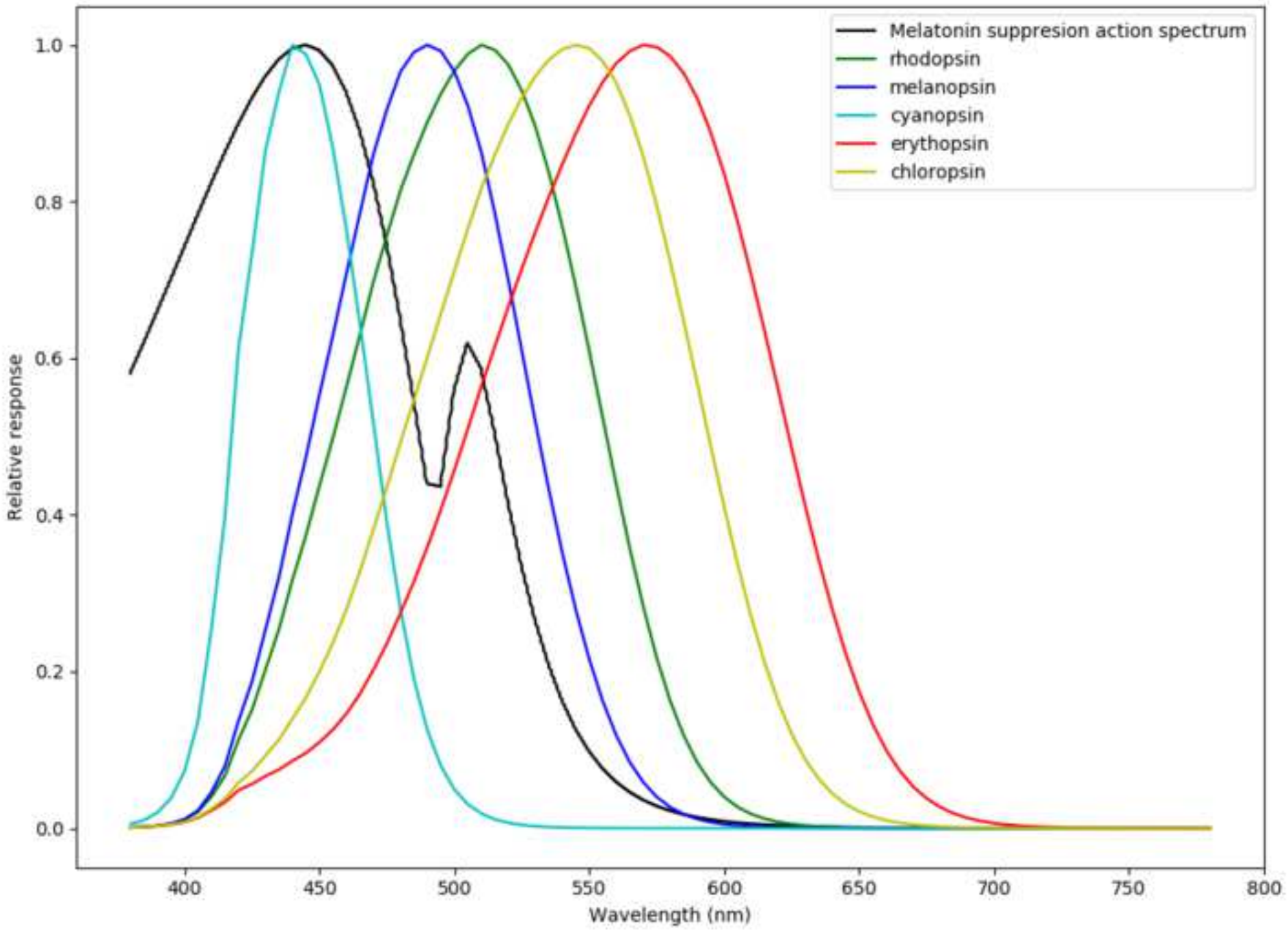
[a]Basic adjustment: area, age, sex, educational level

eFigure 1. Flow chart showing initial population, exclusions and final population in analysis



Figure

Click here to access/download;Figure;eFig2_opsin.png



Dear Emily

I did all the changes requested

Manolis