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Colorectal cancer, sun exposure and dietary vitamin D and calcium intake in the MCC-Spain study

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ABSTRACT

Objectives: To explore the association of colorectal cancer with environmental solar radiation and sun exposure behavior, considering phenotypic variables (eye color, hair color and skin phenotype), dietary intake of vitamin D and calcium, and socio-demographic factors.

Study design: Multicenter population-based frequency matched case-control study in Spain (MCC-Spain), with 2140 CRC cases and 3950 controls.

Methods: Data were obtained through personal interviews using a structured epidemiological questionnaire that included socio-demographic data, residential history, environmental exposures, behavior, phenotypic and dietary information. An environmental-lifetime sun exposure score was constructed combining residential history and average daily solar radiation, direct and diffuse. Logistic regression was used to explore the association between different variables. A structural equation model was used to verify the associations of the conceptual model.

Results: We found a lower risk of CRC in subjects frequently exposed to sunlight during the previous summer and skin burning due to sun exposure. No association was observed in relation to the residential solar radiation scores. Subjects with light eye or light hair colors had a lower risk of CRC that those with darker colors. Dietary calcium and vitamin D were also protective factors, but not in the multivariate model. The structural equation model analysis suggested that higher sun exposure was associated with a decreased risk of CRC, as well as

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dietary intake of calcium and vitamin D, and these factors are correlated among themselves and with environmental solar radiation and skin phenotypes.
Conclusion: The results agree with previous observations that sun exposure, dietary vitamin D and calcium intake, and serum 25(OH)D concentration reduce the risk of CRC and indicate that these factors may be relevant for cancer prevention.

1. Introduction

Colorectal cancer (CRC) is the most frequent intestinal cancer worldwide, accounting for 447,000 incident cases in 2012 and 215,000 deaths in Europe (Arnold et al., 2013; Ferlay et al., 2013; Forman, 2010). Risk factors for CRC include advanced age, medical history of benign adenomatous polyps, inflammatory bowel diseases, diabetes, family history of CRC, low intake of vegetables and fruits, and high intake of dietary fat and processed meat (Potter, 2008; van Duijnhoven et al., 2009; Weitz et al., 2005). There is growing evidence of the association between sun exposure and CRC (van der Rhee et al., 2013). The association of sun exposure and cancer was initially proposed > 80 years ago by Peller, who had observed that occupations with a high incidence of skin cancer, like US Navy personnel, had a lower rate of other cancers (Peller, 1936; Peller and Stephenson, 1937). Following this hypothesis, Apprely described a reduced cancer mortality in North America in relation to solar radiation (Apprely, 1941). Since exposure to ultraviolet-B radiation from the sun produces vitamin D, and this vitamin is involved in calcium absorption, it has been hypothesized that this effect could be mediated through calcium and vitamin-D metabolism (Garland and Garland, 1980), an approach that has been supported by subsequent research (Di Rosa et al., 2013; Hart et al., 2011; Moukayed and Grant, 2017). All these factors, including behavioral, life-style and genetic background, may be interrelated and cross-influenced.

Here we have analyzed the association of CRC with the sun exposure and life-style, considering skin, hair and eye color phenotypes, dietary vitamin D and calcium intake, and other socio-demographic factors in a large multicenter case-control study conducted in Spain.

2. Methods

2.1. Study design and data collection

MCC-Spain is a population-based multicenter case-control study carried out between September 2008 and November 2014 in 12 Spanish provinces (Castano-Vinyals et al., 2015). The study included 6090 participants: 2140 CRC cases and 3950 controls (see Table 1). Cases

Table 1
Baseline characteristics of cases and controls.

	Controls	Cases	OR[a] (95% CI)	P value
Age				
Mean (SD)	63.3 (11.8)	67.0 (10.8)	1.03 (1.02–1.03)	< 0.001
Sex. N (%)				
Male	2018 (51.1)	1365 (63.8)	1	< 0.001
Female	1932 (48.9)	775 (36.2)	0.59 (0.53–0.66)	
Education. N (%)				
Basic	739 (18.9)	689 (32.2)	1	< 0.001
Primary	1273 (32.6)	811 (37.9)	0.68 (0.60–0.78)	
Secondary/Professional	1108 (28.3)	427 (20.0)	0.41 (0.35–0.48)	
University	789 (20.2)	212 (9.9)	0.28 (0.24–0.35)	
History of CRC in first-degree relatives. N (%)				
No	3483 (88.2)	1663 (77.7)	1	< 0.001
Yes	467 (11.8)	477 (22.3)	2.36 (2.04–2.74)	
Diabetes. N (%)				
No	3352 (85.2)	1739 (81.8)	1	0.91
Yes	582 (14.89)	386 (18.2)	0.99 (0.85–1.15)	
Acetylsalicylic acid (ASA). N (%)				
Non-use/sporadically use	3068 (77.7)	1698 (79.4)	1	0.01
Regular use in the last year	880 (22.3)	440 (20.6)	0.82 (0.71–0.94)	
Nonsteroidal anti-inflammatory drugs (NSAID). N (%)				
Non-use/sporadically use	2718 (68.8)	1715 (80.2)	1	< 0.001
Regular use in the last year	1230 (31.2)	423 (19.8)	0.62 (0.54–0.79)	
Physical activity in leisure time (MET). N (%)				
No	1633 (41.8)	1100 (51.4)	1	< 0.001
Yes	2274 (58.2)	1039 (48.6)	0.70 (0.63–0.79)	
Body Mass Index at age 45				
Mean (SD)	25.3 (4.1)	26.1 (5.0)	1.03 (1.02–1.04)	< 0.001
Alcohol				
Low consumption	2809 (83.2)	1386 (75.3)	1	< 0.001
High consumption	569 (16.8)	455 (24.7)	1.48 (1.27–1.71)	
Intake of vegetables (g/day)				
Mean (SD)	189.0 (123.4)	174.6 (113.5)	0.86 (0.81–0.90)[b]	< 0.001
Intake of red meat (g/day)				
Mean (SD)	62.2 (39.4)	73.8 (49.7)	1.84 (1.59–2.14)[b]	< 0.001
Intake of cured meat (g/day)				
Mean (SD)	17.4 (16.1)	21.4 (22.2)	2.42 (1.73–3.42)[b]	< 0.001
Energy (kcal/day)				
Mean (SD)	1893.4 (637.6)	2007.9 (710.0)	1.25 (1.14–1.37)[b]	< 0.001

[a] The OR are adjusted for design variables (age, sex and recruiting center).
[b] The summary OR per 100 g/day and 1000 kcal/day.

were identified in the 23 collaborating hospitals through active search and invited to participate as soon as possible after the diagnosis was made. Population-based controls were randomly selected from the administrative records of selected primary care health centers located within the hospitals' catchment areas and were telephonically invited to participate. Inclusion criteria were age 20–85, residence in the catchment area for at least 6 months prior to the recruitment and being capable of answering the epidemiological questionnaire. We included histological confirmed incident cases of cancer of the colon or rectum (C18, C19, C20, D01.0, D01.1, D01.2), with no prior history of the disease. Controls were frequency-matched to cases, by age, sex and region, ensuring that in each region there was at least one control of the same sex and 5-year interval for each case, and we excluded those controls reporting previous personal history of CRC.

2.2. Ethical issues

The protocol of MCC-Spain was approved by the Ethics committees of the participating institutions. All participants were informed about the study objectives and signed an informed consent. Confidentiality of data was secured removing personal identifiers in the datasets.

2.3. Questionnaire

A structured computerized epidemiological questionnaire was administered by trained personnel in a face-to-face interview (http://www.mccspain.org). Information was collected on socio-demographic factors, residential history, lifelong retrospective environmental exposures, including sunbathing, phenotype and personal/family medical history. Participants also filled in a semi-quantitative food frequency questionnaire (FFQ) that was a modified version from a previously validated instrument in Spain (Garcia-Closas et al., 2007) to include regional products. The FFQ was self-administered and returned by mail of filled out face to face (global response rate 88%). The FFQ included 140 food items with portion sizes and photos to assess usual dietary intake during the previous year. Cross-check questions on aggregated food group consumption were used to adjust the frequency of food consumption and reduce misreporting of food groups with large numbers of items. Nutrient intakes, specifically calcium, vitamin D and total energy intake, were estimated using food composition tables published for Spain, and other sources (Farran et al., 2003). These tables included vitamin D from meat and fish products. After the interview, biological samples and anthropometric data were obtained following the study protocol. Height, weight, hip and waist circumference were measured during the interview. Height and weight at different ages prior to interview were self-reported.

2.4. Lifetime solar radiation exposure estimation

The average daily-solar radiation by square meter (kWh/m^2) during the period 1983–2005 was obtained through the network of the National Agency of Meteorology in Spain (www.aemet.es). These measurements were used to estimate a lifetime sun exposure score (S) as the total sum of average daily-solar radiation exposures in the place of residence in life-time (R), weighted by the time living in each place in years (t), divided by age (a) at the time of study inclusion: $S = \sum_{i=1}^{n} R_i t_i / a$. S was estimated separately for direct radiation (those directly received from the sun), and diffuse radiation (those received indirectly through diffusion or reflection of sunlight). Also, total lifetime solar ration exposure was estimated as the sum of direct and diffuse radiation.

2.5. Statistical methods and data management

Unconditional logistic regression was used to assess the association between the different variables and CRC risk. Two types of models were

Table 2
Association of sun exposure variables with colorectal cancer.

	Controls	Cases	Adjusted by design variables			Adjusted by factors associated with CRC		
			OR (95% CI)	P value	P value for trend	OR (95% CI)	P value	P value for trend
Reported time spent on sun during the last summer								
1–2 h/day	2380 (61.7)	1364 (67.2)	1		0.0036	1		0.002
2–4 h/day	798 (20.7)	339 (16.7)	0.77 (0.67–0.90)	0.001		0.81 (0.70–0.95)	0.008	
> 4 h per day	678 (17.6)	328 (16.1)	0.83 (0.71–0.97)	0.022		0.81 (0.69–0.95)	0.010	
Reported time spent on sun during the summer 10 years ago								
1–2 h/day	1995 (53.0)	1023 (55.1)	1		0.84	1		0.32
2–4 h/day	862 (22.9)	405 (21.8)	1.00 (0.86–1.16)	0.87		1.02 (0.87–1.18)	0.83	
> 4 h per day	904 (24.1)	430 (23.1)	0.97 (0.84–1.13)	0.70		0.92 (0.79–1.06)	0.26	
Reported frequency of skin burning episodes yearly during the last 30 years								
Rarely	1984 (52.7)	1095 (58.9)	1		0.080	1		0.080
Less than five	1222 (32.5)	532 (28.6)	0.91 (0.80–1.04)	0.16		0.91 (0.80–1.05)	0.20	
More than five	559 (14.8)	233 (12.5)	0.87 (0.72–1.04)	0.12		0.87 (072–1.04)	0.13	
Outdoor professional activity								
No	3002 (83.3)	1396 (83.1)	1			1		
Yes	475 (13.7)	284 (16.9)	0.86 (0.72–1.02)	0.09		0.85 (0.71–1.01)	0.060	
Score of lifestyle sun exposure								
Score (mean, SD)	1.93 (1.73)	1.65 (1.65)	0.92 (0.89–0.95)	< 0.0001		0.93 (0.90–0.96)	< 0.0001	
Lifetime sun exposure score (kWh/m^2. SD)								
Direct	2.88 (0.55)	2.93 (0.52)	0.90 (0.52–1.57)	0.71		0.98 (0.88–1.10)	0.76	
Diffuse	1.55 (0.04)	1.55 (0.04)	1.06 (0.02–56.61)	0.98		0.68 (0.14–3.21)	0.62	
Total	4.43 (0.53)	4.48 (0.5)	0.89 (0.50–1.59)	0.70		0.98 (0.97–1.10)	0.73	

used. First, one that include design variables and major CRC risk factors that should be considered to avoid confounding: age, gender, site of recruitment, education level and Body Mass Index (BMI) estimated at 45 years old or 10 years-previous to cancer diagnosis. The second model, called multiple adjusted, also included all other variables related to sun exposure and diet assessed in this study. Multivariate-adjusted odds ratios (OR) and their corresponding 95% confidence intervals (CI) were calculated for each exposure. To adjust the effect of total energy intake, estimates of calcium and vitamin D dietary intake were expressed as nutrient density values: the ratio of the amount of a nutrient intake to the total energy in kcal (Drewnowski and Fulgoni, 2014).

We also fitted structural equation models (SEM) in an attempt to verify the conceptual model and assess the direct effect of sun exposure on CRC, and also its indirect effect mediated through dietary intake and lifestyle-related factors. SEM consider simultaneously the covariance structure among latent variables that have been quantified by diverse directly measured variables, and the regression of these variables with the outcome, CRC. SEM allows to test the conceptual model, distinguishing between direct and indirect effects and provides information on the degree of fit for the entire model. The maximum likelihood estimate method yields estimates of the regression coefficients in the model, standard errors and an overall goodness-of-fit test. Since SEM require complete data, missing values for dietary intake, BMI and sun exposure were imputed using a k-nearest neighbors approach. Also, to adjust for multiple known risk factors for CRC, a quantitative adjustment score was calculated from the linear predictor of a logistic regression model that included age, sex, recruiting site, education, family history of CRC, regular aspirin or NSAID use, BMI at age 45, physical activity, alcohol, vegetable intake, red and cured meat intake. These analyses were performed with the R package Lavaan (Rosseel, 2012).

3. Results

Table 1 summarizes the characteristics of the study participants, disaggregated by cases and controls. Although we used a frequency matched controls, some imbalances were observed. Controls were younger, more often women and had attained a higher level of education than cases. For this reason, all analyses were adjusted for these design factors. Usual risk factors for CRC were confirmed in this study: family history of CRC, diabetes, alcohol, energy intake, red and processed meat intake, and BMI. Physical activity, regular aspirin and NSAID use and intake of vegetables were protective factors.

3.1. Sun exposure behavior

We found a decreased risk of CRC for participants that reported frequent or very frequent (OR = 0.81, 95% CI = 0.69–0.95) exposure to the sun during the last summer (P value for trend 0.002, Table 2). The association was not observed for the reported exposure during the summer 10 years before. A marginally non-significant association was found for the reported high frequency of episodes of skin burning during the last 30 years (OR = 0.87, 95% CI = 0.72–1.04). Outdoor professional activity (farmer or mason) also showed a marginally non-significant association with CRC in the multivariate adjusted model (OR = 0.85, 95% CI = 0.71–1.01). A lifestyle score was calculated for each individual, as the sum of previous variables coded as 0,1,2. This score, which summarized the diverse questionnaire variables in an unweighted additive form, confirmed the negative association of sun exposure to CRC (OR per score point = 0.96, 95% CI = 0.93–0.99).

3.2. Lifetime residential solar radiation exposure

We calculated individual scores of life-time residential exposure to direct and diffuse solar radiation. Overall, cases had received similar solar radiation than controls, with a mean total radiation of 4.48 kWh/m^2 for cases and 4.43 kWh/m^2 for controls (Table 2).

3.3. Phenotypic variables

We did not find any association between skin darkness phenotype and CRC (Table 3). Regarding hair and eye color, the analysis showed higher risk for individuals with dark hair (OR = 1.16, 95% CI = 1.00–1.35) or dark eyes (OR = 1.40, 95% CI = 1.25–1.57), compared to individuals with light color.

3.4. Dietary factors

We found for both calcium (OR = 0.89, 95% CI = 0.85–0.94) and vitamin D intake (OR = 0.93, 95% CI = 0.86–1.01) showed a protective effect, though these associations were not significant in the multivariate adjusted model (Table 4).

3.5. Analysis of subgroups

The analyses were consistent between women and men, though the associations were weaker among women (Supplementary Table 1). The analysis stratified by cancer site also showed similar associations for tumors in the colon and in the rectum. Though the effect estimates were similar, associations often did not reach statistical significance for rectal cancer, due to the smaller sample size of this group (Supplementary Table 2).

3.6. Structural equation model analysis of the conceptual model

We built a conceptual model from the observed associations in the multivariate analyses previously described and tried to fit structural equation models to identify the associations resistant to adjustment for

Table 3
Association of phenotype variables (hair, skin and eyes color) with colorectal cancer.

	Controls	Cases	Adjusted by design variables			Adjusted by factors associated with CRC		
			OR (95% CI)	P value	P value for Trend	OR (95% CI)	P value	P value for Trend
Skin color								
Very white/white	1696 (45.0)	803 (43.2)	1		0.86	1		0.91
Middle	1396 (37.1)	691 (37.2)	0.97 (0.85–1.10)	0.63		0.98 (0.86–1.12)	0.39	
Dark brown/black	672 (17.8)	365 (19.6)	1.00 (0.85–1.17)	0.96		1.02 (0.86–1.20)	0.83	
Hair color								
Light brown/redhead/blond	838 (21.2)	392 (18.3)	1		0.012	1		0.02
Brown	1291 (32.7)	616 (28.8)	0.99 (0.85–1.17)	0.94		0.99 (0.84–1.17)	0.90	
Black/intense brown	1821 (46.1)	1132 (52.9)	1.18 (1.02–1.37)	0.03		1.16 (1.00–1.35)	0.05	
Eyes color								
Blue/grey/green/light brown	1901 (49.0)	881 (43.1)	1			1		
Black/intense brown	1977 (51.0)	1165 (56.9)	1.40 (1.25–1.57)	< 0.001		1.40 (1.25–1.57)	< 0.001	

Table 4
Association of dietary intake of vitamin D and calcium with colorectal cancer.

	Controls	Cases	Adjusted by design variables			Adjusted by factors associated with CRC		
			OR	95% CI	P value	OR	95% CI	P value
Dietary intake[a] (mean, SD)								
Dietary calcium	495.9 (148.1)	468.6 (137.2)	0.89	(0.85–0.93)	< 0.001	0.97	(0.93–1.02)	0.22
Dietary vitamin D	1.52 (0.93)	1.43 (0.84)	0.92	(0.86–0.98)	0.02	0.96	(0.89–1.03)	0.23

[a] Expressed as the amount of the nutrient per 1000 kcal of energy intake (nutrient density).

indirect effects. From a fully related model, a backward elimination stepwise procedure ended with the model shown in Fig. 1. Arrows represent those associations that remain significant in the model, and the corresponding number is an estimate of the standardized effect size. Circles represent the latent variables and squares the measured variables. The results confirmed the direct protective effect of sun exposure on CRC and a stronger effect of dietary calcium and vitamin D, that correlated negatively with sun exposure. Environmental residence radiation had no direct effect on CRC, but it was significantly correlated with sun exposure and phenotypes. Similarly, phenotypes did not show a direct effect on CRC, but were correlated with dietary intake and sun exposure.

4. Discussion

The hypothesis that sun exposure may reduce the risk of cancer, and specifically CRC, has been explored before, generally with consistent results (Moukayed and Grant, 2013, 2017; van der Rhee et al., 2013; van der Rhee et al., 2006). Most prior studies are consistent with ours in finding a protective effect of sun exposure towards CRC, but this effect was only significant in some subgroup analysis in studies with individual level data (Freedman et al., 2010; Lin et al., 2012). Our results suggest that this effect is real, possibly mediated by vitamin D metabolism, and cooperates with dietary calcium and vitamin D, since a significant direct effect remains in the joint analysis adjusted for dietary variables.

Regarding sun exposure, we have found a number of questionnaire variables related to behavior and outdoor professional activity that were protective regarding CRC. Our analyses were multivariate adjusted, including education as a measure of socioeconomic status and all established risk factors for CRC to reduce confounding. Previous studies have found outdoor activity (sun exposure) as a protective risk factor against CRC (van der Rhee et al., 2013), but these studies used rather different exposure measurements (based on personal interviews about ambient exposure or outdoor activity), and it is difficult to replicate the same findings elsewhere. The relation between sun exposure and cancer risk was initially assessed by Apprely (1941), who followed the hypothesis proposed by Peller (Peller, 1936; Peller and Stephenson, 1937) and observed CRC mortality among different latitudes in the US. Since then, increasing evidence has cumulated from ulterior ecological and association studies (Grant, 2007, 2012; van der Rhee et al., 2013; van der Rhee et al., 2006). However, we are not aware of studies that use direct measurements of solar radiation to ascertain the causal effect of solar radiation on CRC risk, surely due to the methodological constraints to carry out such measurements. In our study we explored this hypothesis using questionnaire data and a lifetime score of estimated exposure disaggregating between direct and diffuse radiation (as an estimate of individual sunlight exposure). Though these variables were not statistically significant when analyzed in logistic regression models, the combined analysis in the SEM model did show that these variables are significantly correlated to questionnaire measurements of sun exposure and also to skin phenotypes, which supports the hypothesis that solar radiation plays a role in the etiology of CRC. Our data suggest that high frequency of episodes of skin burning during the last 30 years or outdoor professional activity are associated with a reduced risk of CRC. These factors, combined in a personal sun exposure score, show a clear significant association that is more difficult to see in specific questionnaire variables, that show a tendency but not completely clear as previously seen (Yang et al., 2011).

The widespread belief is that the effect of sun exposure was mediated through the promotion of 25(OH)D synthesis in the skin, the active form of vitamin D, as pointed out in the seminal paper of Garland and Garland (Garland and Garland, 1980; Grant, 2018). The main role of 25(OH)D is the regulation of absorption of calcium and other minerals in the gut, though it exerts other actions relevant for cancer prevention (Moukayed and Grant, 2017). In addition to sun exposure, food intake is a relevant source of vitamin D. Animal meat and fish are rich in vitamin D, but nutrient estimates from food frequency questionnaires involve measurement error, and nutrient composition tables may not

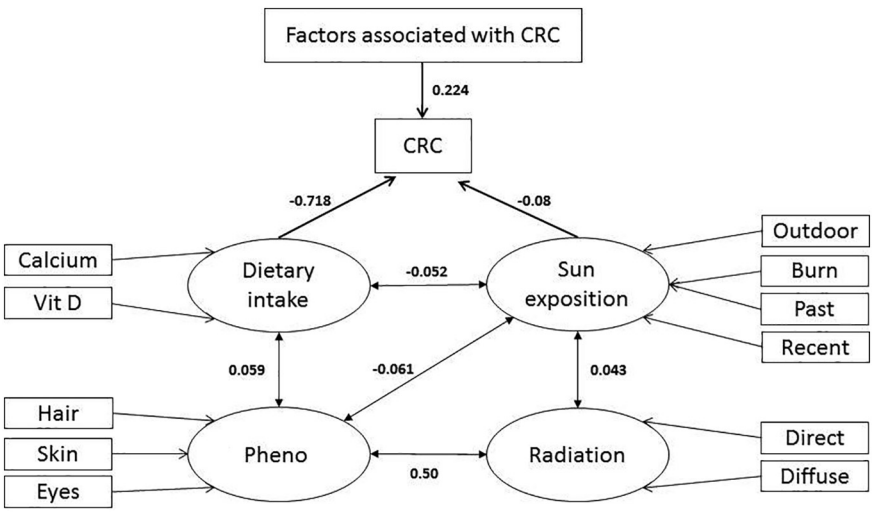

Fig. 1. The structural equation model diagram of the final best-fit model. The ellipses represent latent variables and the squares represent observed variables. The single-headed arrows represent the impact of one variable on another, and bidirectional arrows represent significant correlations. The numerical values are the standardized effect estimates.

accurately reflect the vitamin D content (Crowe et al., 2011). Also, dairy products, mainly milk and butter, are often supplemented with vitamin D and calcium. Unfortunately, we do not have direct measurements of nutrient levels to completely analyze the mediation effect, but in agreement with this hypothesis, we have found lower risk of CRC with higher dietary calcium and vitamin D intake (Garland et al., 1985; Garland and Gorham, 2017; Song et al., 2015) and the SEM model estimates a significant association with CRC. Also, our SEM estimates revealed a significant correlation between the latent variables related to dietary intake of vitamin D and calcium, sun exposure and skin phenotype, which indicate that these variables may play a coordinated role in CRC prevention (Fig. 1).

The mechanisms underlying the protective effect of vitamin D and dietary calcium intake are still poorly understood. It has been suggested that Ca^{2+} exerts various protective mechanisms in the colon like binding toxic bile acids and ionized fatty acids (vitamin D independent pathway) (Van der Meer and De Vries, 1985) or by regulating cellular proliferation or stimulating apoptosis at intracellular level (probably vitamin D dependent) (Ahearn et al., 2011). Vitamin D regulates calcium absorption, but there is growing evidence suggesting that it may act through multiple biological calcium-independent pathways, promoting or suppressing specific cellular events, including tumor genesis (Ferrer-Mayorga et al., 2018; Hargrove et al., 2014). Vitamin D is involved in mitochondrial metabolism (Ricca et al., 2018; Seyfried, 2015) and may have an anti-inflammatory effect (Meeker et al., 2016; Yin and Agrawal, 2014). Also, vitamin D may interfere with the colon microbiota metabolism (Shang and Sun, 2017). Then, without excluding a synergistic/interaction between vitamin D and calcium, results to date suggest that they may act as independent protective factors against CRC. It is worth noting that we did not find any statistical interaction between vitamin D and calcium intake, supporting this last idea. Finally, regarding mechanisms, it has been suggested that solar exposure may also influence cancer development by pathways independent of vitamin D, and an induced immune-suppression effect has been attributed to ultraviolet radiation (Gibbs and Norval, 2013).

Unfortunately, sunscreen use was not requested in our study's questionnaire. We know, however, that sunscreen use is very frequent in Spain, at least during the summer (> 75% of the population) (Cercato et al., 2015; Galan et al., 2011). Sunscreen is recommended to prevent skin cancer, but guidelines (WHO, 2003) are not universally followed and a history of sunburns is very common (70%).

The intriguing finding that dark eyes or dark hair color, but not dark skin, was associated with a risk was inconsistent with previous results from Sweden (Yang et al., 2011). This finding could be explained either by a subtle selection bias or it might be related to behavior. In our data, people with dark eyes were less exposed to sun, which is consistent with an indirect increased risk of CRC as manifested in the SEM model, where the phenotype latent variable was not directly associated to CRC.

According to our findings and exposed arguments, Fig. 1 presents the idea that the pathogenesis of CRC is a complex process influenced by multiple dietary, genetic (phenotype) and environmental factors, all acting directly or through different mediating pathways.

The results were consistent between women and men, though associations were weaker among women (Supplementary Table 1). This could be related to differential adiposity, which may have an effect in the availability of vitamin D (Lagunova et al., 2009). Similar associations were observed for tumors in the colon and in the rectum (Supplementary Table 2). Statistical power to find significant associations or interaction was limited in these subgroup analyses, but no relevant differences were observed in the effect estimates.

This study has several limitations. Firstly, it is a retrospective study and subject to a number of biases (recall and selection bias), there is no direct measurement of sun exposure and we used self-reported questionnaire data and an ecological imputation of sun exposure based on the place of birth and life-time places of residence, which in turn may be confounded by other environmental factors. Also, we do not have direct measurements of vitamin D levels to analyze the mediation effect of this vitamin as an explanation of the observed protective effect of sun exposure.

In summary, the consistent findings with previous research regarding sun exposure and dietary vitamin D and calcium intake reducing the risk of CRC indicate that these factors may be relevant for cancer prevention.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.09.030.

Competing interest statement

The authors have no competing interests.

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References

Ahearn, T.U., McCullough, M.L., Flanders, W.D., Long, Q., Sidelnikov, E., Fedirko, V., Daniel, C.R., Rutherford, R.E., Shaukat, A., Bostick, R.M., 2011. A randomized clinical trial of the effects of supplemental calcium and vitamin D3 on markers of their metabolism in normal mucosa of colorectal adenoma patients. Cancer Res. 71, 413–423.

Apprely, F., 1941. The relation of solar radiation to cancer mortality in North America. Cancer Res. 5.

Arnold, M., Karim-Kos, H.E., Coebergh, J.W., Byrnes, G., Antilla, A., Ferlay, J., Renehan, A.G., Forman, D., Soerjomataram, I., 2015. Recent trends in incidence of five common cancers in 26 European countries since 1988: analysis of the European Cancer Observatory. Eur. J. Cancer 51, 1164–1187 (PMID: 24120180).

Castano-Vinyals, G., Aragones, N., Perez-Gomez, B., Martin, V., Llorca, J., Moreno, V., Altzibar, J.M., Ardanaz, E., de Sanjose, S., Jimenez-Moleon, J.J., Tardon, A., Alguacil, J., Peiro, R., Marcos-Gragera, R., Navarro, C., Pollan, M., Kogevinas, M., 2015. Population-based multicase-control study in common tumors in Spain (MCC-Spain): rationale and study design. Gac. Sanit. 29, 308–315 (PMID: 25613680).

Cercato, M.C., Ramazzotti, V., Sperduti, I., Asensio-Pascual, A., Ribes, I., Guillen, C., Nagore, E., 2015. Sun protection among Spanish beachgoers: knowledge, attitude and behaviour. J. Cancer Educ. 30, 4–11.

Crowe, F.L., Steur, M., Allen, N.E., Appleby, P.N., Travis, R.C., Key, T.J., 2011. Plasma concentrations of 25-hydroxyvitamin D in meat eaters, fish eaters, vegetarians and vegans: results from the EPIC-Oxford study. Public Health Nutr. 14, 340–346.
Di Rosa, M., Malaguarnera, M., Zanghi, A., Passaniti, A., Malaguarnera, L., 2013. Vitamin D3 insufficiency and colorectal cancer. Crit. Rev. Oncol. Hematol. 88, 594–612.
Drewnowski, A., Fulgoni III, V.L., 2014. Nutrient density: principles and evaluation tools. Am. J. Clin. Nutr. 99, 1223S–1228S.
Farran, A., Zamora, R., Cervera, P., 2003. Cesnid. Tablas de Composicion de Alimentos Del CESNID. McGraw Hill-Interamericana de España S.A.U., Edicions Universitat de Barcelona, Barcelona.
Ferlay, J., Steliarova-Foucher, E., Lortet-Tieulent, J., Rosso, S., Coebergh, J.W., Comber, H., Forman, D., Bray, F., 2013. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur. J. Cancer 49, 1374–1403.
Ferrer-Mayorga, G., Larriba, M.J., Crespo, P., Munoz, A., 2018. Mechanisms of action of vitamin D in colon cancer. J. Steroid Biochem. Mol. Biol (pii: S0960-0760(18) 30295-4).
Forman, D.M., Parkin, C.D., D. GLOBOCAN, 2010. Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10. International Agency for Research on Cancer, Lyon, France.
Freedman, D.M., Rajaraman, P., Fuhrman, B., Hoffbeck, R., Alexander, B.H., 2010. Sunlight, hormone replacement status and colorectal cancer risk in postmenopausal women. Int. J. Cancer 126, 1997–2001.
Galan, I., Rodriguez-Laso, A., Diez-Ganan, L., Camara, E., 2011. Prevalence and correlates of skin cancer risk behaviors in Madrid (Spain). Gac. Sanit. 25, 44–49.
Garcia-Closas, R., Garcia-Closas, M., Kogevinas, M., Malats, N., Silverman, D., Serra, C., Tardon, A., Carrato, A., Castano-Vinyals, G., Dosemeci, M., Moore, L., Rothman, N., Sinha, R., 2007. Food, nutrient and heterocyclic amine intake and the risk of bladder cancer. Eur. J. Cancer 43, 1731–1740.
Garland, C.F., Garland, F.C., 1980. Do sunlight and vitamin D reduce the likelihood of colon cancer? Int. J. Epidemiol. 9, 227–231.
Garland, C.F., Gorham, E.D., 2017. Dose-response of serum 25-hydroxyvitamin D in association with risk of colorectal cancer: a meta-analysis. J. Steroid Biochem. Mol. Biol. 168, 1–8.
Garland, C., Shekelle, R.B., Barrett-Connor, E., Criqui, M.H., Rossof, A.H., Paul, O., 1985. Dietary vitamin D and calcium and risk of colorectal cancer: a 19-year prospective study in men. Lancet 1, 307–309.
Gibbs, N.K., Norval, M., 2013. Photoimmunosuppression: a brief overview. Photodermatol. Photoimmunol. Photomed. 29, 57–64.
Grant, W.B., 2007. An ecologic study of cancer mortality rates in Spain with respect to indices of solar UVB irradiance and smoking. Int. J. Cancer 120, 1123–1128.
Grant, W.B., 2012. Role of solar UVB irradiance and smoking in cancer as inferred from cancer incidence rates by occupation in Nordic countries. Dermato-endocrinology 4, 203–211.
Grant, W.B., 2018. A review of the evidence supporting the vitamin D-cancer prevention hypothesis in 2017. Anticancer Res. 38, 1121–1136.
Hargrove, L., Francis, T., Francis, H., 2014. Vitamin D and GI cancers: shedding some light on dark diseases. Ann. Transl. Med. 2, 9.
Hart, P.H., Gorman, S., Finlay-Jones, J.J., 2011. Modulation of the immune system by UV radiation: more than just the effects of vitamin D? Nat. Rev. Immunol. 11, 584–596.
Lagunova, Z., Porojnicu, A.C., Lindberg, F., Hexeberg, S., Moan, J., 2009. The dependency of vitamin D status on body mass index, gender, age and season. Anticancer Res. 29, 3713–3720.
Lin, S.W., Wheeler, D.C., Park, Y., Cahoon, E.K., Hollenbeck, A.R., Freedman, D.M., Abnet, C.C., 2012. Prospective study of ultraviolet radiation exposure and risk of cancer in the United States. Int. J. Cancer 131, E1015–E1023.
Meeker, S., Seamons, A., Maggio-Price, L., Paik, J., 2016. Protective links between vitamin D, inflammatory bowel disease and colon cancer. World J. Gastroenterol. 22, 933–948.
Moukayed, M., Grant, W.B., 2013. Molecular link between vitamin D and cancer prevention. Nutrients 5, 3993–4021.
Moukayed, M., Grant, W.B., 2017. The roles of UVB and vitamin D in reducing risk of cancer incidence and mortality: a review of the epidemiology, clinical trials, and mechanisms. Rev. Endocr. Metab. Disord. 18, 167–182.
Peller, S., 1936. Carcinogenesis as a means of reducing cancer mortality. Lancet 2, 552–556.
Peller, S., Stephenson, C.S., 1937. Skin irritation and cancer in the United States Navy. Am J Med Sci 194, 326–333.
Potter, J.H.D., 2008. Colorectal Cancer. Oxford University Press, New York.
Ricca, C., Aillon, A., Bergandi, L., Alotto, D., Castagnoli, C., Silvagno, F., 2018. Vitamin D receptor is necessary for mitochondrial function and cell health. Int. J. Mol. Sci. 19.
Rosseel, Y., 2012. lavaan: an R package for structural equation modeling. J. Stat. Softw. 48, 1–36.
Seyfried, T.N., 2015. Cancer as a mitochondrial metabolic disease. Front. Cell Dev. Biol. 3, 43.
Shang, M., Sun, J., 2017. Vitamin D/VDR, probiotics, and gastrointestinal diseases. Curr. Med. Chem. 24, 876–887.
Song, M., Garrett, W.S., Chan, A.T., 2015. Nutrients, foods, and colorectal cancer prevention. Gastroenterology 148, 1244–1260 (e1216).
Van der Meer, R., De Vries, H.T., 1985. Differential binding of glycine- and taurine-conjugated bile acids to insoluble calcium phosphate. Biochem. J. 229, 265–268.
van der Rhee, H.J., de Vries, E., Coebergh, J.W., 2006. Does sunlight prevent cancer? A systematic review. Eur. J. Cancer 42, 2222–2232.
van der Rhee, H., Coebergh, J.W., de Vries, E., 2013. Is prevention of cancer by sun exposure more than just the effect of vitamin D? A systematic review of epidemiological studies. Eur. J. Cancer 49, 1422–1436.
van Duijnhoven, F.J., Bueno-De-Mesquita, H.B., Ferrari, P., Jenab, M., Boshuizen, H.C., Ros, M.M., Casagrande, C., Tjonneland, A., Olsen, A., Overvad, K., Thorlacius-Ussing, O., Clavel-Chapelon, F., Boutron-Ruault, M.C., Morois, S., Kaaks, R., Linseisen, J., Boeing, H., Nothlings, U., Trichopoulou, A., Trichopoulos, D., Misirli, G., Palli, D., Sieri, S., Panico, S., Tumino, R., Vineis, P., Peeters, P.H., van Gils, C.H., Ocke, M.C., Lund, E., Engeset, D., Skeie, G., Suarez, L.R., Gonzalez, C.A., Sanchez, M.J., Dorronsoro, M., Navarro, C., Barricarte, A., Berglund, G., Manjer, J., Hallmans, G., Palmqvist, R., Bingham, S.A., Khaw, K.T., Key, T.J., Allen, N.E., Boffetta, P., Slimani, N., Rinaldi, S., Gallo, V., Norat, T., Riboli, E., 2009. Fruit, vegetables, and colorectal cancer risk: the European Prospective Investigation into Cancer and Nutrition. Am. J. Clin. Nutr. 89, 1441–1452.
Weitz, J., Koch, M., Debus, J., Hohler, T., Galle, P.R., Buchler, M.W., 2005. Colorectal cancer. Lancet 365, 153–165.
WHO, 2003. INTERSUN - The global UV Project: A Guide and Compendium. Geneva.
Yang, L., Veierod, M.B., Lof, M., Sandin, S., Adami, H.O., Weiderpass, E., 2011. Prospective study of UV exposure and cancer incidence among Swedish women. Cancer Epidemiol. Biomark. Prev. 20, 1358–1367.
Yin, K., Agrawal, D.K., 2014. Vitamin D and inflammatory diseases. J. Inflamm. Res. 7, 69–87.