

Association between non-melanoma and melanoma skin cancer rates, vitamin D and latitude

MIGUEL RIVAS¹, ELISA ROJAS¹, GLORIA M. CALAF^{2,3}, MARCELA BARBERÁN⁴,
CLAUDIO LIBERMAN⁴ and MARCELO DE PAULA CORREA⁵

¹Department of Physics, Faculty of Science; ²Institute for Advanced Research, Tarapaca University, Arica 8097877, Chile; ³Center for Radiological Research, Columbia University Medical Center, New York, NY 10032, USA; ⁴Endocrinology and Diabetes Section, Clinical Hospital of University of Chile, Santiago 8320000, Chile; ⁵Natural Resources Institute, Federal University of Itajubá, Itajubá, MG 37500-000, Brazil

Received April 11, 2016; Accepted November 17, 2016

DOI: 10.3892/ol.2017.5898

Abstract. Vitamin D synthesis takes place in the skin due to solar ultraviolet-B (UVB) radiation. Several studies have shown the association between low sun exposure, non-melanoma skin cancer (NMSC) and a lack of vitamin D synthesis. Since such synthesis in the body depends on the exposure of the skin to solar UVB radiation (290-320 nm), experimental measurements of this type of solar radiation are important. Tarapaca University in Arica, Chile, established a solar UV radiation laboratory in 2006 and since then this laboratory has performed systematic experimental solar UVB measurements using a calibrated biometer instrument. The results, which are presented in the current study, showed the association between NMSC and MSC rates, and the time required to produce 1,000 IU vitamin D with latitudinal variation. Solar UV index (UVI) levels reported in 6 cities from the north to the south of Chile indicated that the UVI ratio of monthly mean values was 1.8 times higher in Arica than in Punta Arenas in January (summer in Chile), whereas it was 14 times higher in June (winter). This factor is an important consideration, since vitamin D synthesis is directly associated with the exposure of individuals to solar UVB radiation. A similar trend was observed in Antofagasta, Santiago, Concepcion, Valdivia and Punta Arenas. It can be concluded from these data that there is a direct association between NMSC rates and mortality, and UVB radiation, meaning that this type of cancer would not depend on vitamin D synthesis and therefore on calcium uptake. By contrast, MSC rates increased with decreased levels of vitamin D, and thus calcium uptake, in all cities, with the only exception being Punta Arenas.

Introduction

The major role of vitamin D in vertebrate animals and humans is to increase calcium and phosphate absorption for the mineralization of the skeleton. The most important source of this vitamin for individuals living at mid and low latitudes is vitamin D synthesis induced by solar ultraviolet-B (UVB) radiation (1). The recommended daily allowance (RDA) for vitamin D in the United States is 200 IU (5.0 μg), which is reasonable for adults who receive some sun exposure; however, in the absence of sun exposure, this RDA may be 2 to 3 times lower than that actually required to satisfy what the body requires (2). Vitamin D₃ is efficiently produced via pre-vitamin D₃ from the precursor 7-dehydrocholesterol when human skin is exposed to solar UVB (3,4).

The total volume of atmospheric ozone and cloudiness are also important factors that control UVB radiation, and the area of exposed skin and skin type is relevant to the amount of vitamin D synthesis (5). At subtropical latitudes, there is no alteration of vitamin D production during winter. At low latitudes, vitamin D synthesis continues throughout the winter at reduced capacity, and at high latitudes, there is no production for 4-6 months of the year (6). Vitamin D synthesis originates from two sources, firstly from solar or artificial UVB exposure, and secondly from dietary products and supplements in individuals who live at higher latitudes where solar UVB radiation is weak in winter (3,4).

Vitamin D deficiency is commonly found in risk groups such as postmenopausal women and individuals suffering from rickets, osteomalacia and osteoporosis, since vitamin D is vital for normal calcium metabolism and the maintenance of bone density (7). Vitamin D deficiency is also associated with an increased cardiovascular risk and arterial stiffness (8). Furthermore, it is associated with epidemic influenza, as solar radiation produces a seasonal variation that profoundly affects the pathogenesis of the disease (9,10).

Non-melanoma skin cancer (NMSC) is the most commonly occurring cancer type in the Caucasian population. The non-melanoma tumors may originate from squamous or basal cells. These cells in the skin occasionally change and do not behave normally, resulting in precancerous conditions. As a

Correspondence to: Dr Gloria M. Calaf, Institute for Advanced Research, Tarapaca University, 1520 Calle Antofagasta, Arica 8097877, Chile
E-mail: gmc24@columbia.edu

Key words: vitamin D, skin cancer, ultraviolet light

consequence, there is a high chance that these abnormal cells will become cancerous (11). MSC is a result of the transformation of skin melanocytes. At present, MSC is the most common tumor diagnosed in the United States and numerous other countries, and NMSC and MSC cases have each markedly increased in number over the last few decades. Melanomas represent <10% of all skin cancers, but they are responsible for the majority of skin cancer-related mortalities due to a high metastatic potential and therapeutic resistance (9,12,13). Previous studies demonstrated that risk factors for cutaneous melanoma depended upon the anatomical site and the clinicopathological variant (14), and that there was an inverse association between vitamin D blood levels and cutaneous thickness melanoma at diagnosis (15).

The associations among skin type IV, the time to induce solar erythema (T_{Ery}) and the time required to produce 1,000 IU vitamin D (T_{vitD}) have previously been studied in Arica, a city located in the northern region of Chile, close to the equator and surrounded by desert and ocean (16,17). The association between skin cancer rates per 100,000 inhabitants and the solar UV index (UVI) was previously studied between 2001 and 2006 in this city (18), and between 2007 and 2011 with latitude variation (19). The most common skin types in Chile have been found to be type III for women and type IV for men (20). The skin type is expressed as the number of standard erythema doses (SED) according to the Fitzpatrick skin type classification; skin type III for women (3-5 SED) induced erythema type III in Caucasian skin, whereas skin type IV for men (4.5-6 SED) induced type IV in Mediterranean skin (21). Vitamin D is formed mainly in the skin upon exposure to UVB and it is taken orally with food or through supplements (14,22-24). Since sun exposure is a known factor for skin cancer development, the aim of the present study was to analyze the association between NMSC and MSC rates, and solar UVI data obtained from 6 different cities in Chile ranging from latitude 18 to 53°S.

Materials and methods

Measurements. Solar UVI measurements were obtained using a YES-UVB-1 UV biometer (Yankee Environmental Systems, Inc., Turners Falls, MA, USA), according to the manufacturer's instructions (25), in the Solar Ultraviolet Laboratory of Tarapaca University in Arica, Chile. The data provided by this instrument included the latitude, longitude and altitude, as well as the ozone layer and cloudiness for each location. This laboratory is run in agreement with and as part of the Chilean Meteorological Organization network. This instrument is calibrated in accordance with their recommendations. It is accepted that solar UVI fluctuates from 1 to 11 according to the World Meteorological Organization. An algorithm developed by McKenzie *et al.* (26) was used to calculate the T_{vitD} from experimental measurements of solar UVI in different cities. The minimal erythema dose (MED) is the minimum amount of UV that produces redness 24 h after exposure, where one MED is equal to 240 J/m² of UV doses required to induce erythema (27), according to the Fitzpatrick skin type classification (21). The T_{ery} in unprotected skin (only hands and face, i.e., 10% of the body) was calculated using the following equation:

$$T_{\text{ery}} = \frac{\text{MED}(\text{skin}_{\text{type}})}{UV_{\text{ery}}}$$

The amount of UV solar radiation to induce erythema (UV_{ery}) was directly obtained from the following equation [where the unit for UV_{ery} is milliwatt (mW) divided by square meters (m²)]:

$$UV_{\text{ery}} = \frac{\text{UVI} \left(\frac{\text{mW}}{\text{m}^2} \right)}{40}$$

Population data. The NMSC ratio was calculated in males and females for each city in comparison to Punta Arenas. NMSC and MSC rates were considered for each location and the data for skin cancer rate normalized by patient age was obtained between 2005 and 2007 from the Ministerio de Salud (Ministry of Health) of Chile, where open access to cancer population data has been established by Resolution number 23.01.2002, therefore Ethics/guidelines must be considered in each hospital of Chile.

Statistical analysis. Statistical analysis was performed using standard statistical criteria, and correlations were assessed by evaluating the quotient between covariance and standard deviation for each variable. Pearson's linear correlation was used for statistical purposes. Statistical analysis performed using StatDisk software (version 12.0.2; Pearson plc., London, UK). $P < 0.05$ was considered to indicate a statistically significant difference.

Results

The present study considered solar UVI measurements, NMSC and MSC rates, mortality rates per 100,000 inhabitants and the association with the time required to synthesize adequate levels of vitamin D in different geographical locations of Chile. T_{vitD} was calculated to explain the association between NMSC and MSC rates in 6 cities in Chile between latitude 18 and 53°S. The monthly averages of the T_{vitD} were calculated from the maximum UVI daily values obtained from Arica, Antofagasta, Santiago, Concepción, Valdivia and Punta Arenas, with latitudes of 18, 23, 33, 36, 39 and 53°S, respectively. Fig. 1 shows the mean solar UVI per month considering the maximum value for each day (at noon) and the latitude of these cities between January and December. Solar UVI values fluctuated from a minimum in winter (June) to a maximum in summer (January), recorded as 5.6-12.3 in Arica, 3.7-11.7 in Antofagasta, 2.0-11.8 in Santiago, 1.7-10.7 in Concepción, 1.1-10.9 in Valdivia and 0.4-6.9 in Punta Arenas.

Tables I-III show solar UVI data, and NMSC and MSC rates from different geographical locations in Chile. Table I presents latitude, longitude and altitude, and solar UVI data per year, from the following geographical locations in Chile: Arica, Antofagasta, Santiago, Concepción, Valdivia and Punta Arenas. Table II presents NMSC and MSC mortality rates per 100,000 inhabitants in the same locations as aforementioned between 1990 and 2005, while Table III presents NMSC and MSC rates in males and females in these cities between 2003 and 2007 (28). Data from Table III is also shown in Fig. 2A and B. The results indicated that the NMSC rates in males and females were greater in the northern cities of Chile, such as Arica and

Table I. Latitude, longitude, altitude and solar UVI data per year in different geographical locations of Chile.

City	Latitude	Longitude	Altitude, m	Solar UVI data, years
Arica	18°18'S	70°18'W	25	2006-2013
Antofagasta	23°38'S	70°24'W	40	1997-2005
Santiago	33°23'S	70°47'W	475	2004-2009
Concepción	36°46'S	73°03'W	8	2003-2007
Valdivia	39°48'S	73°14'W	9	2001-2004
Punta Arenas	53°00'S	70°51'W	37	2001-2005

UVI, ultraviolet index.

Table II. NMSC and MSC mortality rates per 100,000 individuals between 1990 and 2005 (28).

City	NMSC	MSC
Arica	1.07	0.54
Antofagasta	1.89	0.75
Santiago	0.75	1.00
Concepción	0.84	1.07
Valdivia	0.57	0.82
Punta Arenas	0.89	1.21

MSC, melanoma skin cancer; NMSC, non-MSC.

Table III. NMSC and MSC rates per 100,000 individuals in males and females between 2003 and 2007 (28).

City	NMSC rate		MSC rate	
	M	F	M	F
Arica	69.7	52.4	3.7	1.2
Antofagasta	55.5	46.7	2.1	2.1
Santiago	24.7	16.5	2.9	2.5
Concepción	20.9	19.5	3.4	2.5
Valdivia	19.7	21.4	3.6	2.5
Punta Arenas	22.8	29.4	0.8	0.9

MSC, melanoma skin cancer; NMSC, non-MSC; M, male; F, female.

Antofagasta, compared with the rate in cities located farther south, such as Concepción and Valdivia (Fig. 2A). Fig. 2B shows MSC rates in males and females from Arica to Punta Arenas; the data indicated that the rate of MSC was lower in females than males in Arica and in cities located farther south, such as Santiago, Concepción and Valdivia. An inverse association was observed between NMSC and latitude in males and females, as observed at 18°S in Arica and 36°S in Concepción (Fig. 2C); thus rates decreased as latitude increased. Fig. 2D shows that the MSC rates in males and females increased as latitude increased (23 and 40°S), with the exception of Punta Arenas (53°S), in which the MSC rates in males and females decreased.

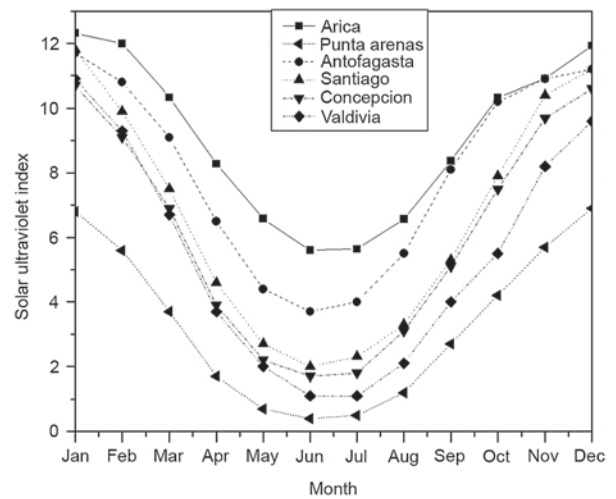


Figure 1. Solar ultraviolet index per month obtained in several cities of Chile between January and December.

In Chile, the most common skin types are type III for women that tan moderately and uniformly, with an MED of 0.30-0.50 kJ/m², and skin type IV for men with corresponding light brown skin that tans minimally, moderately and easily with an MED of 0.40-0.60 kJ/m² (27). Fig. 3 shows the T_{viD} in 6 cities of Chile every month. The maximum values were observed in June (winter) and varied from 18-700 min in Arica and Punta Arenas, respectively.

Fig. 4A-B shows NMSC and MSC mortality rates with regard to latitude and T_{viD} accumulated over 1 year. Fig. 4A shows that there was a negative correlation between NMSC mortality rates and latitude (r=-0.53), and no correlation between NMSC mortality rate and T_{viD} accumulated in 1 year (r=-0.25). A strong correlation was also found between MSC mortality rates and latitude (r=0.88), and between MSC and T_{viD} accumulated over 1 year (r=0.72), as shown in Fig. 4B. The NMSC ratio was calculated in males and females for each city in comparison to Punta Arenas. This was found to be 3.1 and 1.8 in Arica, 2.4 and 1.6 in Antofagasta, 1.1 and 0.6 in Santiago, 0.9 and 0.7 in Concepción, and 0.9 and 0.7 in Valdivia, respectively. This was probably due to the low solar UVB radiation levels in the southern cities of Chile in winter (June 21 to September 20). The MSC ratio was calculated for each city in comparison to Punta Arenas in males and females. This was found to be 4.6 and 1.3 in Arica, 2.6

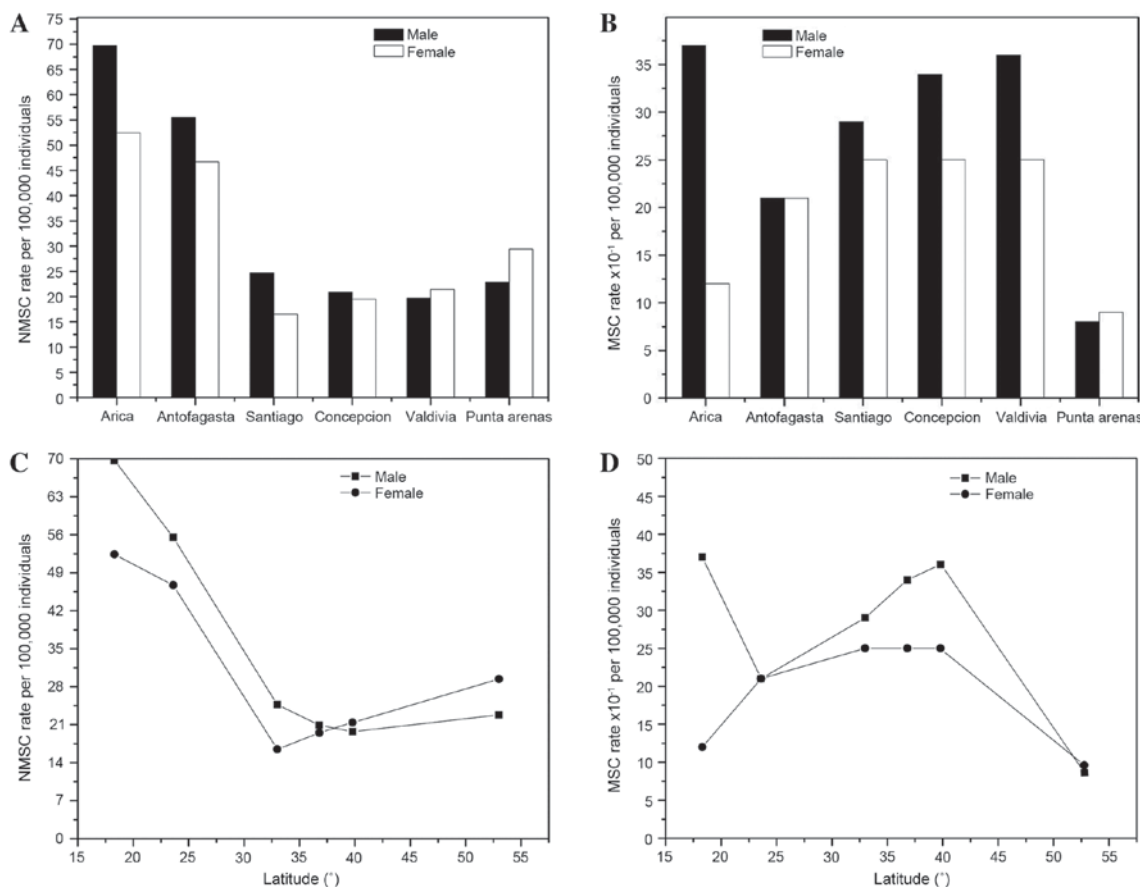


Figure 2. (A) NMSC and (B) MSC rates in 6 cities, and (C) NMSC and (D) MSC rates at different latitudes in males and females in Chile. MSC, melanoma skin cancer; NMSC, non-MSC.

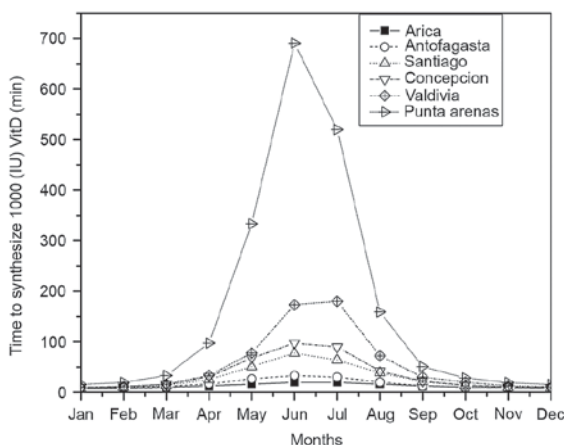


Figure 3. Exposure time to synthesize 1,000 IU vitamin D (min) in 6 cities of Chile per month.

and 2.3 in Antofagasta, 3.6 and 2.8 in Santiago, 4.3 and 2.8 in Concepción, and 4.5 and 2.8 in Valdivia, respectively.

Discussion

The dose-response associations between vitamin D and cancer risk reduction have been previously estimated, and data has indicated that it takes 1,500 IU vitamin D3 per day to obtain a 29% cancer risk reduction for male cancer

mortality rates in the United States (29). The present study provides an analysis of solar UVI levels reported in 6 cities from the north to the south of Chile in different months. The results showed that the solar UVI ratio of monthly mean values was 1.8 times higher in Arica than in Punta Arenas in January (summer in Chile), whereas it was 14 times higher in June (winter in Chile). This factor is an important consideration since vitamin D synthesis is directly associated with the exposure of individuals to solar UVB radiation. A similar trend was observed in Antofagasta, Santiago, Concepcion, Valdivia and Punta Arenas.

Therefore, high solar UVB radiation levels imply a great capability to synthesize vitamin D in the northern regions of Chile. A recent analysis determined that the diagnosis of NMSC was associated with a reduced risk of several vitamin D-sensitive cancers (30,31). This was in accordance with low solar UVB radiation levels in the southern cities of Chile in winter. Therefore, high solar UVB radiation levels imply a lower capability to synthesize vitamin D in the southern regions of Chile than in the northern regions. Melanoma is another cancer that has been linked to solar UV irradiance. However, it has been associated with sun burning, limited solar UV irradiance (32), solar UVA irradiance (24,33,34), low dietary vitamin D intake (35) and a lack of chronic solar UVB irradiation at higher latitudes (36,37).

An inverse correlation was found between NMSC rates in males and females, and different latitudes of 18°S in Arica and 36°S in Concepción. NMSC rates decreased as latitude

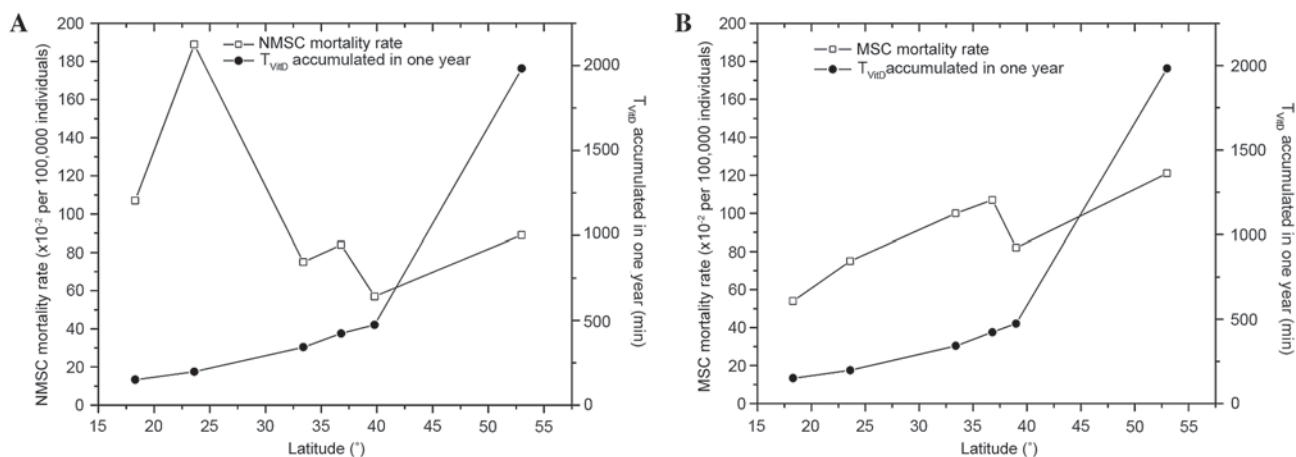


Figure 4. (A) NMSC and (B) MSC mortality rate and mean T_{vitD} accumulated over 1 year with respect to latitude. MSC, melanoma skin cancer; NMSC, non-MSC; T_{vitD} , exposure time to synthesize 1,000 IU vitamin D.

increased, which was in accordance with the low UVI values measured in those cities. There was a strong inverse correlation coefficient between NMSC rate and latitude ($r=-0.84$) among males, whereas there was a weak inverse correlation in females ($r=-0.65$). The NMSC rate in males in Punta Arenas was similar to the rates in Santiago and Concepcion, however, this rate was higher in females. NMSC appears to be directly associated with the Caucasian type of skin, that is, types II and III. It is notable that the population from Punta Arenas has a Croatian origin, with skin types II and III (50% of the population according to the Republic of Croatia State Office for Croats Abroad) (38). NMSC is the most common malignant neoplasm in fair-skinned people, and in a number of sunny countries this frequency exceeds the total number of all other neoplasms. The incidence of basal cell carcinoma is always greater than that of squamous cell carcinoma, varying by latitude from 10:1 to 2.5:1 (39). Studies have also indicated that NMSC has been increasing by 2-3% per year, at least in the United States, which is most likely caused by greater outdoor exposure for leisure and social reasons.

The results of the present study indicated that MSC decreased between latitude 18°S (Arica) and 23°S (Antofagasta) in males. MSC rates increased between latitude 23°S (Antofagasta) and 40°S (Valdivia) in males and females. However, MSC rates decreased at higher latitudes in each gender; this trend is consistent with the reported annual doses of UVA radiation, which decreased with increasing latitude (24).

There was a weak inverse coefficient correlation between MSC rate and latitude ($r=-0.56$) among males, and none ($r=-0.12$) in females. T_{vitD} was similar in Arica, Antofagasta, Santiago and Concepción, with maximum values that varied from 175 to 700 min in Valdivia and Punta Arenas in winter, and where T_{vitD} was 39 times higher in Punta Arenas than in Arica.

There was a weak inverse correlation coefficient between NMSC mortality rates and latitude ($r=-0.53$). However, there was a strong correlation between MSC mortality rates and latitude ($r=0.88$). Mortality rate and T_{vitD} accumulated in 1 year were analyzed. Results showed that there was no correlation between NMSC and T_{vitD} accumulated in 1 year. However, there was a strong correlation between MSC mortality rates

and T_{vitD} accumulated over the same period ($r=0.72$). In Punta Arenas, the MSC mortality rate was higher despite a lower MSC incidence.

When explaining the lack of correlation between different skin cancers and sunny cities, such as Arica, and less sunny cities, such as Punta Arenas, there are several aspects to take into consideration; for example, less body exposure to solar UVB, which thereby reduces the amount of vitamin D production (23,40), and lower UVB doses. The low risk for skin cancers in dark-skinned individuals is partly attributable to the photo-protection provided by the epidermal melanin barrier, which halves the penetration of UVB through the epidermis in black people compared with that in those of individuals of white European ethnicity (Caucasians, corresponding to type I and type II skin classification) (41). One study previously reported a comprehensive bibliographic search of the literature that identified studies on cutaneous malignant melanomas and non-melanomas, vitamin D receptor polymorphisms, vitamin D intake and 25(OH) D serum levels. An association was found for two types of polymorphisms and melanoma (42). It can be concluded from these studies that there is a direct correlation between NMSC rates and mortality with UVB radiation, meaning that this type of cancer would not depend on vitamin D synthesis and therefore on calcium uptake; by contrast, MSC rates increased with decreased levels of vitamin D and thus calcium uptake in all cities, with the only exception being Punta Arenas.

Acknowledgements

This study was supported by grants from Tarapacá University, Arica, Chile (Grant UTA-Mayor-4728-2016) (MR and ER) and Convenio de Desempeño UTA1117 (GMC). The authors would like to thank Mr. Leodán A. Crispin for his suggestions and the Chilean Meteorological Organization (Santiago, Chile).

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