

# UC San Diego

## UC San Diego Previously Published Works

### Title

Are low ultraviolet B and vitamin D associated with higher incidence of multiple myeloma?

### Permalink

<https://escholarship.org/uc/item/8160m35n>

### Authors

Mohr, Sharif B  
Gorham, Edward D  
Garland, Cedric F  
[et al.](#)

### Publication Date

2015-04-01

### DOI

10.1016/j.jsbmb.2014.12.005

### Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed



## Review

# Are low ultraviolet B and vitamin D associated with higher incidence of multiple myeloma?



Sharif B. Mohr<sup>a,b</sup>, Edward D. Gorham<sup>a,b</sup>, Cedric F. Garland<sup>a</sup>, William B. Grant<sup>c</sup>,  
Frank C. Garland<sup>a,b</sup>, Raphael E. Cuomo<sup>a,d,\*</sup>

<sup>a</sup> Department of Family and Preventive Medicine, University of California, San Diego, La Jolla, CA, United States

<sup>b</sup> Naval Health Research Center, San Diego, CA, United States

<sup>c</sup> Sunlight, Nutrition, and Health Research Center, San Francisco, CA, United States

<sup>d</sup> Graduate School of Public Health, San Diego State University, San Diego, CA, United States

## ARTICLE INFO

## Article history:

Received 28 August 2014

Received in revised form 2 December 2014

Accepted 3 December 2014

Available online 10 December 2014

## Keywords:

Myeloma

Ultraviolet rays

Incidence

Vitamin D

Alcohol

Cigarettes

Multiple regression

International comparisons

## ABSTRACT

**Background:** The purpose of this study was to determine whether an inverse association exists between latitude, solar ultraviolet B (UVB) irradiance, and incidence rates of multiple myeloma. **Methods:** Associations of latitude and UVB irradiance with age-standardized incidence rates of multiple myeloma were analyzed for 175 countries while controlling for sex-specific obesity prevalence, cigarette consumption, and alcohol consumption using multiple linear regression. **Results:** Incidence rates of multiple myeloma were greater at higher latitudes ( $R^2$  for latitude for males = 0.31,  $p < 0.0001$ ; females  $R^2 = 0.27$ ,  $p < 0.0001$ ). In regression models for males ( $R^2 = 0.62$ ,  $p < 0.0001$ ) and females ( $R^2 = 0.51$ ,  $p < 0.0001$ ), UVB irradiance was independently inversely associated with incidence rates. **Conclusions:** Age-adjusted incidence rates of multiple myeloma were higher in countries with lower solar UVB irradiance. Further investigation is warranted in individuals of the association of prediagnostic serum 25 (OH)D with risk.

© 2014 Elsevier Ltd. All rights reserved.

## Contents

1. Introduction	245
2. Materials and methods	246
2.1. Data sources	246
2.2. Statistical analysis	247
3. Results	247
4. Discussion	247
4.1. Strengths	248
4.2. Limitations	249
5. Conclusion	249
Acknowledgements	249
References	251

## 1. Introduction

Worldwide there are an estimated 85,704 cases and 62,534 deaths from multiple myeloma each year [1]. In the United States, multiple myeloma is the second most common cancer of the blood after Non-Hodgkin's lymphoma [2]. In 2008 there were

\* Corresponding author at: University of California, San Diego, Department of Family and Preventive Medicine, 9500 Gilman Dr., La Jolla, CA 92093, United States.  
E-mail address: [raphael.e.cuomo@gmail.com](mailto:raphael.e.cuomo@gmail.com) (R.E. Cuomo).



## 2.2. Statistical analysis

Age-standardized incidence rates for 175 countries were obtained from GLOBOCAN [1] and plotted by latitude of the population centroid. The rates were standardized to the 2000 world population. The best fit to the data points was obtained using a polynomial trend line. Multiple linear regression was employed to examine the associations of UVB irradiance adjusted for cloudiness, while controlling for obesity prevalence, cigarette consumption, and alcohol consumption in 107 countries. All analyses were performed using SAS Version 9.1 and JMP Version 5.1.2 (Cary NC: SAS Institute).

## 3. Results

Incidence rates of multiple myeloma were greater at higher latitudes ( $R^2$  for latitude for males=0.31,  $p < 0.0001$ ; females  $R^2 = 0.27$ ,  $p < 0.0001$ ) (Figs. 1–2). In males, UVB irradiance ( $p = 0.01$ ) was independently inversely associated with incidence. Per capita cigarette consumption ( $p = 0.009$ ) and per capita alcohol consumption ( $p < 0.0001$ ) were positively associated with incidence rates ( $R^2$  for overall model=0.62,  $p < 0.0001$ ) (Table 1). In females, UVB irradiance ( $p = 0.05$ ) was independently inversely associated with incidence, and per capita alcohol consumption ( $p < 0.0001$ ) was positively associated with incidence ( $R^2$  for overall model=0.51,  $p < 0.0001$ ) (Table 2).

## 4. Discussion

The etiology of multiple myeloma is still poorly understood. This is the first report of the inverse association between multiple myeloma incidence and UVB irradiance, to our knowledge. Multiple myeloma incidence rates were higher in countries

located at latitudes distant from the equator, where UVB irradiance is low, than in countries closer to the equator, where UVB irradiance is high. In the multiple linear regression model, UVB irradiance was significantly inversely associated with multiple myeloma incidence rates in both sexes even after controlling for other factors. UVB irradiance varies inversely with latitude [17], and it is the source of approximately 95% of circulating vitamin D and its metabolites [18].

This study showed that cloud cover-adjusted UVB is significantly inversely associated with incidence of multiple myeloma, even after controlling for confounders. These findings are consistent with other ecological studies analyzing the relationship between UVB and several other cancers, including those of the colon and rectum [19], ovary [20], endometrium [14], pancreas [21], bladder [22], and brain [23]. This consistency suggests that vitamin D may exhibit general anticarcinogenic effects.

A positive association between BMI and multiple myeloma risk has been reported in the literature [24]. Nevertheless, the mechanism underlying this association is poorly understood. This association also points to vitamin D being a protective factor for this cancer. Numerous studies have reported that obese subjects have lower levels of serum 25(OH)D compared to non-obese, a relationship that is independent of UVB exposure. For example, Wortsman et al. found that obese subjects had a 57% lower incremental increase in 25(OH)D after full body irradiation than non-obese [25]. It is possible that the association observed between high BMI and increased incidence of multiple myeloma may be due to vitamin D deficiency in the overweight and obese.

Results of clinical and laboratory studies on multiple myeloma have also been supportive of the vitamin D hypothesis. Rossi et al. reported decreased proliferation of a myeloma cell line after in vitro application of 1,25(OH)<sub>2</sub>D [26]. In one study, multiple myeloma patients who were given calcitriol over several months

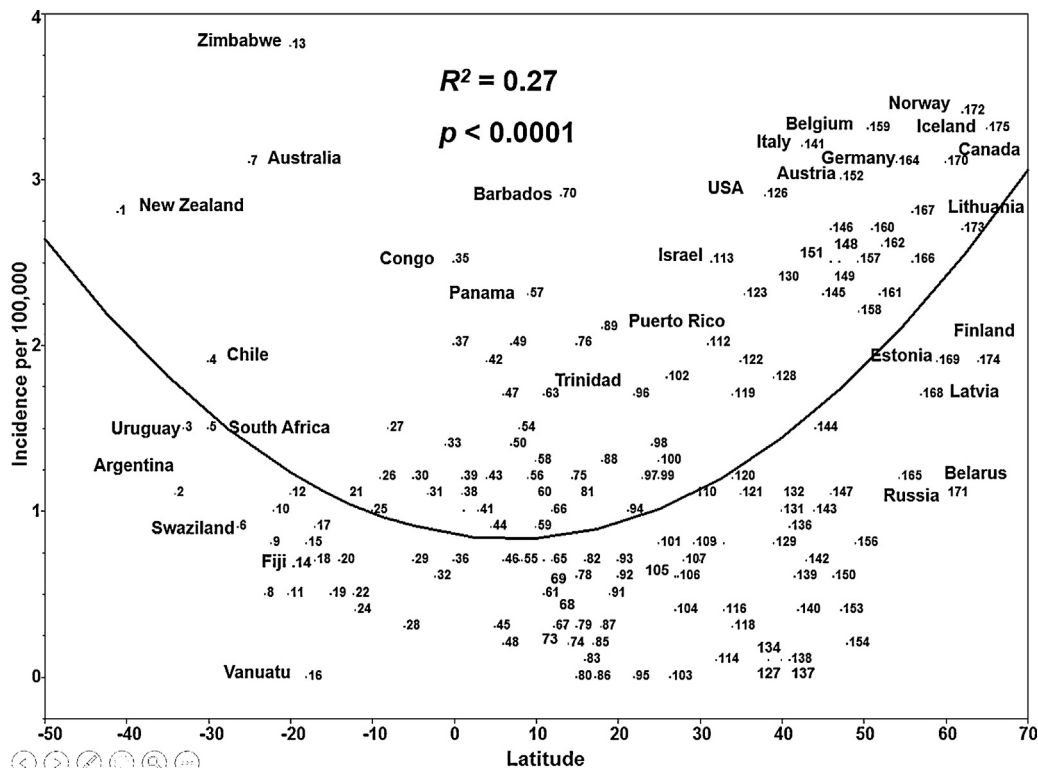


Fig. 2. Age-adjusted incidence rates of multiple myeloma per 100,000 population, females. Source: Data from GLOBOCAN [1]. Labels are the same as in Fig. 1.

**Table 1**  
Solar ultraviolet B irradiance and other covariates, in association with multiple myeloma incidence rates, multiple regression, 107 countries, males 2002.

Covariate	Regression coefficient	Standard error	t	p
Solar UVB irradiance <sup>a</sup>	−0.0901	0.0342	−2.64	0.01
Alcohol intake (kcal/capita/year) <sup>b</sup>	0.0063	0.0014	4.44	<0.0001
Cigarette consumption, (cigarettes/capita/year) <sup>c</sup>	0.0071	0.0066	2.67	0.009
Male obesity (%) <sup>d</sup>	0.0071	0.0066	1.06	0.29
Intercept	1.4030	0.4829	2.91	0.005

$R^2 = 0.62$ ;  $p < 0.0001$ .

<sup>a</sup> Watts/m<sup>2</sup>, adjusted for cloud cover.

<sup>b</sup> Source: United Nations, Food and Agriculture Organization.

<sup>c</sup> Source: United Nations, Tobacco Atlas.

<sup>d</sup> Source: United Nations, WHO Global.

in addition to the standard treatment showed marked improvement, leading the authors to conclude that calcitriol may have contributed to the arrest of multiple myeloma in the patients [27].

Vitamin D status was also found to be a good predictor of prognosis and staging in multiple myeloma patients. In the study performed by Ng et al., serum 25(OH)D levels were inversely associated with stage at diagnosis [28]. This may result from differential levels of solar and nutritional sources of vitamin D during the period where these patients lived with multiple myeloma, thereby allowing more rapid progression in patients with low levels of serum 25(OH)D. The investigators controlled for BMI in their analysis, and the effect of vitamin D on stage was independent of BMI. This is important for two reasons. First, BMI can effectively serve as a proxy for physical activity. Therefore, the inclusion of BMI may provide some adjustment for differences physical activity among the patients. Second, high BMI is an independent risk factor for multiple myeloma. Controlling for BMI is therefore important to more directly assess the effect of serum vitamin D levels on the development of multiple myeloma.

The racial disparity found in multiple myeloma risk is also consistent with a possible preventative role of vitamin D. In the United States, incidence of multiple myeloma is twice as high in African-Americans compared to whites [29]. Due to increased levels of skin pigmentation, African-Americans synthesize 25(OH)D at one-third the rate as Caucasians [30], and this may account for some of the disparity in multiple myeloma risk. Another explanation is that the difference in risk might be due to higher prevalence of obesity in African-Americans since obesity is a risk factor for vitamin D deficiency that is independent of sun exposure [25]. If adequate vitamin D status does confer protection against multiple myeloma, then the African-American population would be especially vulnerable due to increased skin pigmentation and higher prevalence of obesity.

The various antiproliferative effects of vitamin D metabolites are well-known and have been discussed elsewhere [31].

In this analysis, per capita cigarette consumption and per capita alcohol consumption were significantly positively associated with incidence rates in men. Per capita alcohol consumption was also significantly positively associated with incidence rates in women.

This is in contrast to a recent study which found a protective, albeit non-significant effect of alcohol consumption on risk of multiple myeloma [32]. Although BMI is a risk factor for multiple myeloma, the regression analyses in this study did not show a significant association between obesity prevalence and multiple myeloma in either sex. This may be due to the high degree of collinearity between obesity prevalence and other latitude-dependent factors, including UVB irradiance.

One outlier that deserves mention is the island nation of Barbados. In Barbados, the age-adjusted incidence rate in 2002 was 4.9 and 2.9 per 100,000 for males and females respectively. Considering that Barbados' latitude is the highest in its region, these incidence rates are higher than what would be expected based on the vitamin D hypothesis. However, the notable presence of certain industries, including electronic component manufacture, chemical production, and leather tanning, helps to explain the high incidence of multiple myeloma in Barbados. Workers in these industries have been found to be at higher risk for several cancers [33–35].

Several additional countries exhibit incidence rates for multiple myeloma that are higher than what would be expected based on latitude alone. Much of this deviation is explained by three covariates: obesity prevalence, alcohol consumption, and cigarette smoking. Prevalence of these was considerably higher for Australia and the USA than the world averages. The associations between cloud cover-adjusted UVB and age-standardized multiple myeloma incidence were adjusted for these three important potential contributors to multiple myeloma etiology, and the association persisted.

#### 4.1. Strengths

This study had several strengths. To our knowledge, no other studies have analyzed incidence rates of multiple myeloma by latitude and UVB irradiance in a large number of countries located at widely different latitudes. It accounts for several known risk factors using multiple linear regression. The regression model accounted for 62% of the variation in age-standardized incidence rates of multiple myeloma in men and 51% in women. There was an

**Table 2**  
Solar ultraviolet B irradiance and other covariates, in association with multiple myeloma incidence rates, multiple regression, 107 countries, females, 2002.

Covariate	Regression coefficient	Standard error	t	p
Solar UVB irradiance <sup>a</sup>	−0.0530	0.0266	−1.99	0.05
Alcohol intake, (kcal/capita/year) <sup>b</sup>	0.0047	0.0011	4.22	<0.0001
Cigarette consumption, (cigarettes/capita/year) <sup>c</sup>	0.0002	0.0001	1.85	0.07
Female obesity, (%) <sup>d</sup>	0.0023	0.0052	0.45	0.65
Intercept	1.0940	0.3751	2.92	0.004

$R^2 = 0.51$ ;  $p < 0.0001$ .

<sup>a</sup> Watts/m<sup>2</sup>, adjusted for cloud cover.

<sup>b</sup> Source: United Nations, Food and Agriculture Organization.

<sup>c</sup> Source: United Nations, Tobacco Atlas.

<sup>d</sup> Source: United Nations, WHO Global InfoBase.

independent inverse association of UVB irradiance with incidence rates of multiple myeloma, while controlling for several other factors.

The percentage of variation among countries explained for multiple myeloma was similar to cancers for which a role of vitamin D has been established in observational studies of individuals, including those of breast ( $R^2=0.55$ ,  $p < 0.0001$ ) [36], colon ( $R^2=0.68$ ,  $p < 0.0001$ ) [36], and ovary ( $R^2=0.60$ ,  $p < 0.0001$ ) [20]. However, studies of this type should be considered as hypothesis-generating, rather than definitive.

#### 4.2. Limitations

This was a study of aggregates rather than individual subjects. Findings that apply to aggregates may not apply to individuals [37]. For example, all individuals living in areas of high UVB irradiance may not have high exposure to UVB. This can result from urbanization and industrialization. On the other hand, regional solar UVB irradiance may affect a broad range of individuals, and the association was present despite the possible misclassification of exposure. Nondifferential misclassification of exposure generally obscures associations, though, rather than creating them [38].

Ecological studies are a potential source of variables to be investigated using other methods. On the other hand, the diverse geographic distribution of populations in areas with different levels of UVB irradiance provides a natural experiment on a large scale. Natural experiments can be valuable in identifying

potentially relevant etiological factors. For example, ecological comparisons of areas with different levels of fluoride in drinking water showed that higher fluorine content was associated with lower incidence of dental caries [39].

#### 5. Conclusion

Further investigation is warranted to confirm the associations observed in this study with observational studies of individuals. New research on the association of the prediagnostic serum 25 (OH)D levels of individuals with their risk of multiple myeloma might be particularly informative.

#### Acknowledgements

This research was supported by a Congressional allocation to the Hollings Cancer Center of the Medical University of South Carolina, Charleston SC, through the Department of the Navy, Bureau of Medicine and Surgery, under Work Unit No. 60126. The views expressed in this report are those of the authors and do not represent an official position of the Department of the Navy, Department of Defense, or the U. S. Government.

#### Appendix A.

**Table A1**

Countries included in this study, country name, latitude, age-standardized male multiple myeloma incidence (cases per 100,000), age-standardized female multiple myeloma incidence (cases per 100,000).

Country/region	Latitude	Male multiple myeloma incidence	Female multiple myeloma incidence
Afghanistan	34.0	0.4	0.3
Albania	41.0	1.6	0.9
Algeria	28.0	0.8	0.7
Angola	-12.3	0.8	0.5
Argentina	-34.0	1.6	1.1
Armenia	40.0	1.0	1.0
Australia	-25.0	4.7	3.1
Austria	47.2	3.8	3.0
Azerbaijan	40.3	1.0	1.1
Bahamas	24.2	2.1	1.4
Bahrain	26.0	2.9	1.8
Bangladesh	26.4	0.1	0.0
Barbados	13.1	4.9	2.9
Belarus	54.3	1.3	1.2
Belgium	50.5	4.8	3.3
Belize	17.3	0.0	0.0
Benin	6.0	0.3	0.7
Bhutan	27.3	0.9	0.6
Bolivia	-17.0	2.0	0.9
Bosnia Herzegovina	44.2	2.0	1.5
Botswana	-22.0	1.2	1.0
Brazil	-9.0	1.4	1.2
Brunei	4.6	1.2	0.9
Bulgaria	43.0	1.0	0.7
Burkina Faso	12.2	0.3	0.3
Burundi	-3.2	1.1	1.1
Cambodia	13.0	0.3	0.3
Cameroon	6.0	2.0	1.7
Canada	60.0	4.5	3.1
Cape Verde	16.0	0.3	0.7
Central African Republic	7.0	1.6	2.0
Chad	15.0	1.6	2.0
Chile	-30.0	2.4	1.9
China	33.0	0.6	0.4
Colombia	4.0	2.3	1.9
Comoros	-12.1	1.1	1.1
Congo	0.0	1.8	2.5
Congo Brazzaville	-1.0	1.2	1.4
Costa Rica	10.0	1.6	1.3
Cote d'Ivoire	8.0	1.0	0.7

**Table A1** (Continued)

Country/region	Latitude	Male multiple myeloma incidence	Female multiple myeloma incidence
Croatia	45.1	2.8	2.3
Cuba	21.3	1.3	1.0
Cyprus	35.0	2.3	1.1
Czech Republic	49.3	3.6	2.5
Denmark	56.0	4.1	2.5
Djibouti	11.4	1.1	1.1
Dominican Republic	19.0	1.8	1.3
Ecuador	0.0	0.8	0.7
Egypt	27.0	0.5	0.4
El Salvador	13.5	0.3	0.3
Equatorial Guinea	0.0	1.6	2.0
Eritrea	15.2	1.1	1.1
Estonia	59.0	2.6	1.9
Ethiopia	9.0	1.2	1.2
Fiji	−18.0	0.0	0.0
Finland	64.0	2.7	1.9
France	46.0	4.0	2.7
Gabon	−1.0	0.3	1.1
Gambia	13.3	0.3	0.6
Georgia	42.0	0.6	0.4
Germany	51.0	3.9	2.7
Ghana	8.0	0.3	0.7
Greece	39.0	2.7	1.8
Guam	13.3	2.1	0.7
Guatemala	14.4	1.6	1.2
Guinea	11.0	0.2	0.5
Guinea-Bissau	12.0	0.3	0.7
Guyana	5.0	0.7	0.3
Haiti	19.0	0.7	0.5
Honduras	15.0	1.6	1.2
Hungary	47.0	3.4	2.5
Iceland	65.0	4.1	3.3
India	20.0	1.0	0.6
Indonesia	−5.0	1.3	0.7
Iran, Islamic Republic of	32.0	0.2	0.1
Iraq	33.0	1.8	0.8
Ireland	53.0	4.0	2.7
Israel	31.4	3.4	2.5
Italy	42.5	4.5	3.2
Jamaica	18.2	1.8	1.3
Japan	36.0	1.6	1.1
Jordan	31.0	2.0	2.0
Kazakhstan	48.0	0.5	0.2
Kenya	1.0	2.4	1.1
Korea, Democratic Republic of	36.3	2.0	1.1
Korea, Republic of	40.0	2.0	1.1
Kuwait	29.3	1.8	0.8
Kyrgyzstan	41.0	0.3	0.1
Lao People Democratic Republic	18.0	0.5	0.3
Latvia	57.0	2.2	1.7
Lebanon	34.0	2.7	1.7
Lesotho	29.3	0.4	1.1
Liberia	6.0	0.9	0.2
Libya	27.0	0.7	0.6
Lithuania	56.0	2.1	2.8
Luxembourg	49.4	2.8	2.2
Macedonia	41.6	1.1	0.6
Madagascar	−20.0	1.1	1.1
Malawi	−12.0	0.4	0.4
Malaysia	3.0	1.1	1.0
Mali	17.0	0.1	0.7
Malta	35.5	1.6	2.3
Mauritania	20.0	0.3	0.7
Mauritius	−20.2	0.5	0.5
Melanesia	−13.0	0.5	1.1
Mexico	23.0	1.6	1.2
Micronesia	11.0	2.1	0.7
Moldava	46.3	0.6	0.6
Mongolia	47.3	0.9	0.4
Morocco	32.0	1.0	0.8
Mozambique	−18.0	0.4	0.8
Myanmar	22.0	0.1	0.0
Namibia	−22.3	0.8	0.8
Nepal	28.0	0.9	0.6
Netherlands	52.2	4.3	2.6
New Zealand	−41.0	5.1	2.8
Nicaragua	13.0	0.9	0.6

Table A1 (Continued)

Country/region	Latitude	Male multiple myeloma incidence	Female multiple myeloma incidence
Niger	16.0	0.2	0.1
Nigeria	10.0	0.2	0.9
Norway	62.0	4.9	3.4
Oman	22.0	2.0	1.7
Pakistan	30.0	0.9	0.7
Panama	9.0	2.6	2.3
Papua New Guinea	−5.0	0.6	1.2
Paraguay	−23.0	0.6	0.5
Peru	−10.0	2.2	1.0
Philippines	12.0	0.8	1.0
Poland	52.0	3.1	2.3
Polynesia	−17.0	0.6	0.7
Portugal	39.3	3.0	2.4
Puerto Rico	18.2	3.4	2.1
Qatar	25.0	0.9	1.2
Romania	46.0	1.5	1.1
Russian Federation	60.0	1.2	1.1
Rwanda	−2.3	1.3	0.6
Samoa	−14.0	0.6	0.7
Saudi Arabia	25.0	2.1	1.3
Senegal	14.0	0.3	0.2
Serbia and Montenegro	44.0	1.7	1.0
Sierra Leone	8.3	0.3	0.7
Singapore	1.2	1.8	1.0
Slovakia	48.5	3.0	2.4
Slovenia	46.2	2.3	2.4
Solomon Islands	−8.0	0.6	1.5
Somalia	10.0	1.1	1.1
South African Republic	−30.0	2.3	1.5
Spain	40.0	3.2	2.4
Sri Lanka	7.0	1.6	1.4
Sudan	15.0	0.8	0.6
Suriname	4.0	1.3	1.2
Swaziland	−26.3	0.4	0.9
Sweden	62.0	3.7	2.7
Switzerland	46.0	3.6	2.5
Syrian Arab Republic	35.0	2.7	1.9
Tajikistan	38.4	0.3	0.1
Tanzania	−6.0	0.7	0.3
Thailand	15.0	0.5	0.3
Togo	8.0	0.3	0.7
Trinidad and Tobago	11.0	2.9	1.7
Tunisia	34.0	1.4	1.2
Turkey	39.0	0.8	0.8
Turkmenistan	40.0	0.3	0.1
Uganda	1.0	0.1	1.2
Ukraine	49.0	0.9	0.8
United Arab Emirates	25.0	2.2	0.8
United Kingdom	54.0	4.3	3.1
United States of America	38.0	4.8	2.9
Uruguay	−33.0	1.9	1.5
Uzbekistan	41.0	0.3	0.1
Vanuatu	−18.0	0.0	0.0
Venezuela	8.0	1.8	1.5
Viet Nam	17.0	0.2	0.2
Yemen	15.0	0.3	0.0
Zambia	−15.0	0.7	0.5
Zimbabwe	−20.0	2.8	3.8

## References

- [1] J. Ferlay, F. Bray, P. Pisani, D. Parkin, GLOBOCAN (2002): Cancer Incidence, Mortality and Prevalence Worldwide. IARC CancerBase No. 5. version 2.0. <http://www-dep.iarc.fr/> (accessed 10.07.11).
- [2] A. Jemal, R. Siegel, E. Ward, M.J. Thun, Cancer facts and figures, (2008). <http://www.cancer.org/downloads/STT/2008CAFFfinalsecured.pdf>, (accessed 06.07.08).
- [3] D.D. Alexander, P.J. Mink, H.O. Adami, P. Cole, J.S. Mandel, M.M. Oken, D. Trichopoulos, Multiple myeloma: a review of the epidemiologic literature, *Int. J. Cancer* 120 (Suppl. 12) (2007) 40–61.
- [4] M. Holick, Photosynthesis of previtamin D<sub>3</sub> in human skin and the physiological consequences, *Science* 210 (1980) 203–255.
- [5] S. Abbas, J. Linseisen, T. Slinger, S. Kropp, E.J. Mutschelknauss, D. Flesch-Janys, J. Chang-Claude, Serum 25-hydroxyvitamin D and risk of post-menopausal breast cancer – results of a large case–control study, *Carcinogenesis* 29 (1) (2008) 93–99.
- [6] E.R. Bertone-Johnson, W.Y. Chen, M.F. Holick, G.A. Hollis, W.C. Willett, S.E. Hankinson, Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of breast cancer, *Cancer Epidemiol. Biomarkers Prev.* 14 (8) (2005) 1991–1997.
- [7] C.F. Garland, E.D. Gorham, S.B. Mohr, W.B. Grant, E.L. Giovannucci, M. Lipkin, H. Newmark, M.F. Holick, F.C. Garland, D. Vitamin, prevention of breast cancer: pooled analysis, *J. Steroid. Biochem. Mol. Biol.* 103 (3–5) (2007) 708–711.
- [8] L.C. Lowe, M. Guy, J.L. Mansi, C. Peckitt, J. Bliss, R.G. Wilson, K.W. Colston, Plasma 25-hydroxy vitamin D concentrations: vitamin D receptor genotype and breast cancer risk in a UK Caucasian population, *Eur. J. Cancer* 41 (8) (2005) 1164–1169.
- [9] D. Feskanich, J. Ma, C.S. Fuchs, G.J. Kirkner, S.E. Hankinson, B.W. Hollis, E.L. Giovannucci, Plasma vitamin D metabolites and risk of colorectal cancer in women, *Cancer Epidemiol. Biomarkers Prev.* 13 (9) (2004) 1502–1508.



- [10] C.F. Garland, G.W. Comstock, F.C. Garland, K.J. Helsing, E.K. Shaw, E.D. Gorham, Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study, *Lancet* 2 (8673) (1989) 1176–1178.
- [11] E.D. Gorham, C.F. Garland, F.C. Garland, W.B. Grant, S.B. Mohr, M. Lipkin, H.L. Newmark, E. Giovannucci, M. Wei, M.F. Holick, Optimal vitamin D status for colorectal cancer prevention: a quantitative meta analysis, *Am. J. Prev. Med.* 32 (3) (2007) 210–216.
- [12] J. Tangrea, K. Helzlsouer, P. Pietinen, P. Taylor, B. Hollis, J. Virtamo, D. Albanes, Serum levels of vitamin D metabolites and the subsequent risk of colon and rectal cancer in Finnish men, *Cancer Causes Control* 8 (4) (1997) 615–625.
- [13] S.S. Tworoger, I.M. Lee, J.E. Buring, B. Rosner, B.W. Hollis, S.E. Hankinson, Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of incident ovarian cancer, *Cancer Epidemiol. Biomarkers Prev.* 16 (4) (2007) 783–788.
- [14] S.B. Mohr, C.F. Garland, E.D. Gorham, W.B. Grant, F.C. Garland, Is ultraviolet B irradiance inversely associated with incidence rates of endometrial cancer: an ecological study of 107 countries, *Prev. Med.* 45 (2007) 327–331.
- [15] United Nations Food and Agriculture Organization, FAOSTAT Food and Agriculture database. Available from: <http://www.fao.org/geonetwork/srv/en/main.search>. (accessed 10.06.11).
- [16] National Aeronautics and Space Administration International Satellite Cloud Climatology Project database. Accessed; Available from: <http://isccp.giss.nasa.gov/products/browsed2.html>.
- [17] J. Frederick, D. Lubin, The budget of biologically active ultraviolet radiation in the earth-atmosphere system, *J. Geophys. Res.* 93 (1988) 3825–3832.
- [18] J.S. Adams, T.L. Clemens, J.A. Parrish, M.F. Holick, Vitamin-D synthesis and metabolism after ultraviolet irradiation of normal and vitamin-D-deficient subjects, *N. Engl. J. Med.* 306 (12) (1982) 722–725.
- [19] R.E. Cuomo, S.B. Mohr, E.D. Gorham, C.F. Garland, What is the relationship between ultraviolet B and global incidence rates of colorectal cancer? *Dermato-Endocrinol.* 5 (1) (2013) 181–185.
- [20] C. Garland, S. Mohr, E. Gorham, W. Grant, F. Garland, Role of ultraviolet B irradiance and vitamin D in prevention of ovarian cancer, *Am. J. Prev. Med.* 31 (6) (2006) 512–514.
- [21] S.B. Mohr, C.F. Garland, E.D. Gorham, W.B. Grant, F.C. Garland, Ultraviolet B irradiance and vitamin D status are inversely associated with incidence rates of pancreatic cancer worldwide, *Pancreas* 39 (5) (2010) 669–674.
- [22] S.B. Mohr, C.F. Garland, E.D. Gorham, W.B. Grant, F.C. Garland, Ultraviolet B irradiance and incidence rates of bladder cancer in 174 countries, *Am. J. Prev. Med.* 38 (3) (2010) 296–302.
- [23] S.B. Mohr, E.D. Gorham, C.F. Garland, S.F. Grant, C.F. Garland, Low ultraviolet B and increased risk of brain cancer: an ecological study of 175 countries, *Neuroepidemiology* 35 (2010) 281–290.
- [24] A. Wallin, S. Larsson, Body mass index and risk of multiple myeloma: a meta-analysis of prospective studies, *Eur. J. Cancer* 47 (11) (2011) 1606–1615.
- [25] J. Wortsman, L.Y. Matsuoka, T.C. Chen, Z. Lu, M.F. Holick, Decreased bioavailability of vitamin D in obesity, *Am. J. Clin. Nutr.* 72 (3) (2000) 690–693.
- [26] J. Rossi, B. Durri, C. Duperray, T. Braich, S. Marion, J. Pike, M. Haussler, C. Janbon, R. Bataille, Phenotypic and functional analysis of 1,25-dihydroxyvitamin D3 receptor mediated modulation of the human myeloma cell line RPMI 8226, *Cancer Res.* 48 (5) (1988) 1213–1216.
- [27] R.E. Imseis, J.M. Palmieri, M.R. Leventhal, J.I. Sebes, Effect of calcitriol and pamidronate in multiple myeloma, *Am. J. Med. Sci.* 318 (1) (1999) 61–66.
- [28] A.C. Ng, S.K. Kumar, S.V. Rajkumar, M.T. Drake, Impact of vitamin D deficiency on the clinical presentation and prognosis of patients with newly diagnosed multiple myeloma, *Am. J. Hematol.* 84 (7) (2009) 397–400.
- [29] M.S. Raab, K. Podar, I. Breitkreutz, P.G. Richardson, K.C. Anderson, Multiple myeloma, *Lancet* 374 (9686) (2009) 324–339.
- [30] T. Clemens, S. Henderson, J. Adams, M. Holick, Increased skin pigment reduces the capacity of skin to synthesise vitamin D3, *Lancet* 1 (8263) (1982) 74–76.
- [31] C. Garland, F. Garland, E. Gorham, Epidemiology of cancer risk and Vitamin D, in: M. Holick (Ed.), *Vitamin D: Molecular Biology, Physiology, and Clinical Applications*, Humana, New Jersey, 1999, pp. 375–409.
- [32] G. Gorini, E. Stagnaro, V. Fontana, L. Miligi, V. Ramazzotti, D. Amadori, S. Rodella, R. Tumino, P. Crosignani, C. Vindigni, A. Fontana, P. Vineis, A. Senori Costantini, Alcohol consumption and risk of Hodgkin's lymphoma and multiple myeloma: a multicentre case-control study, *Ann. Oncol.* 18 (1) (2007) 143–148.
- [33] C. Johnson, M. Spitz, Childhood nervous system tumours: An assessment of risk associated with paternal occupations involving use, repair, or manufacture of electrical or electronic equipment, *Int. J. Epidemiol.* 18 (4) (1989) 756–762.
- [34] H. Gibb, P. Lees, P. Pinsky, B. Rooney, Lung cancer among workers in chromium chemical production, *Am. J. Ind. Med.* 38 (2) (2000) 115–126.
- [35] P. Decouple, Cancer risks associated with employment in the leather and leather products industry, *Arch. Environ. Health: Int. J.* 34 (1) (1979) 33–37.
- [36] S. Mohr, C. Garland, E. Gorham, W. Grant, R. Highfill, F. Garland, Mapping vitamin D deficiency, breast cancer, and colorectal cancer, *Proceedings of the ESRI International User Conference 2005*, ESRI: Redlands, CA, 2005, pp. 1468.
- [37] W.S. Robinson, Ecological correlations and the behavior of individuals, *Am. Sociol. Rev.* 15 (1950) 351–357.
- [38] M. Szklo, J. Nieto, *Epidemiology: Beyond the Basics*, Aspen Publishers, Gaithersburg, MD, 2000, pp. 141–145.
- [39] H.T. Dean, F.A. Arnold Jr., P. Jay, J.W. Knutson, Studies on mass control of dental caries through fluoridation of the public water supply, *Public Health Rep.* 65 (43) (1950) 1403–1408.