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Report

Skin cancer mortality in Spain: adjusted mortality rates by province and related risk factors

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Abstract

Background Ultraviolet radiation is the main environmental risk factor responsible for the development of skin cancer. Other occupational, socioeconomic, and environmental factors appear to be related to the risk of skin cancer. Furthermore, the factors appear to differ for melanoma and non-melanoma skin cancer (NMSC). The purpose of this study is to analyze mortality rates of skin cancer in the different provinces of Spain and to determine the influence of socioeconomic conditions and other environmental and demographic factors in rates.

Methods Deaths from melanoma and NMSC in the period 2000–2019 were obtained as well as socioeconomic and environmental variables. Annual standardized mortality rates (SMR) were calculated for all Spanish provinces. The Pearson correlation coefficient was calculated.

Results The SMR of melanoma was 2.10/100,000 inhabitants, while that of NMSC was 1.28/100,000. At the provincial level, a great variability is confirmed. Gross domestic product showed a positive correlation with melanoma mortality but a negative correlation with NMSC. Other environmental and socioeconomic variables also showed correlation, as a positive correlation between tobacco sales and melanoma and between agricultural development and the NMSC.

Conclusions There are still important differences between each province that must be taken into account when planning health care and resource distribution. This ecological and province-wise study helps to elucidate the relationship between social and ambient exposure determinants and skin cancer mortality in Spain.

Introduction

Skin cancer and its three main subtypes, basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and malignant melanoma (MM), represent the most common form of cancer among Caucasians worldwide.[1] Ultraviolet radiation is the main environmental risk factor responsible for the development of skin cancer, with the most common subtype of MM, superficial spreading melanoma, being related to intermittent excessive sun exposure and sunburn in childhood, while SCC has been associated with chronic exposure to ultraviolet radiation.[2–5] However, increased sun exposure does not always imply a greater risk of developing skin cancer, as numerous studies and meta-analyses show how chronic occupational sun exposure seems to be inversely associated with the development of MM, playing a protective role.[6,7]

Melanoma and non-melanoma skin cancer (NMSC), corresponding mostly to SCC and BCC, and to a lesser extent other types such as Merkel or cutaneous sarcomas, have maintained a growing incidence since the end of the last century, reaching an alarming annual increase of up to 7% in the case of melanoma, although mortality rates have remained stable or even decreasing, this decrease in mortality being possible because of the introduction of targeted immunotherapy.[8,9] The increased incidence is probably related to factors that directly influence sun exposure such as the increase in outdoor recreational activities, changes in lifestyle and behavior toward the sun, increase in coastal tourism, or the persistence of the tanning culture, although other unrelated factors may come into play directly with sun exposure such as genetics, population aging, and the increase in the immunosuppressed population.[10,11]

Due to the cultural influence on sun exposure, numerous studies have been conducted globally on the influence of socioeconomic factors on the incidence and mortality of skin cancer, especially in MM, and most of them reaffirm how there is greater incidence but lower mortality in populations with greater economic wealth, possibly because of the greater culture they have for recreational sun exposure habits and earlier dermatological care.[12] However, no similar study has been carried out at the national level in Spain.

The purpose of this study is to analyze how mortality rates behave in the different types of skin cancer in the different provinces of Spain in the period 2000 to 2019, and, parting from the same database, to determine the influence of socioeconomic conditions and other environmental and demographic factors in the mortality rate of MM and NMSC at the national level.

Materials and methods

We have carried out an ecological study that included deaths from melanoma and non-melanoma skin cancer in the different Spanish provinces in the period 2000–2019, obtained from microdata files provided by the National Institute of Statistics[13] (CIE10 codes C43 [MM] and C44 [NMSC]). Population data for each province at mid-year for the same period of years.[13] Annual standardized mortality rates (SMR) were calculated using the direct method for all Spanish provinces, using the 2013 European standard population as a reference and using the Epidat 4.2 program. The results obtained were expressed as deaths per 100,000 and with a 95% CI. Subsequently, the different provincial variables with which the SMR are compared were obtained through the National Institute of Statistics,[13] the State Meteorological Agency,[14] the National Catalog of Hospitals,[15] the Tax Agency,[16] and public data from the Tobacco Market.[17] The Pearson correlation coefficient was calculated with the SPSS V25 program between the SMR of each province and the variables collected annually at the provincial level (number of hospital beds; level of agricultural development [defined as the percentage of workers employed in the agriculture sector by province]; gross domestic product; total tobacco sold by each province; geographical and meteorological variables such as altitude, longitude, and latitude; annual mean irradiation and insolation; annual mean, maximum, and minimum temperature; annual absolute minimum and maximum temperature; annual highest normal minimum normal temperature; annual lowest maximum normal temperature; and number of rainy and foggy days in the year). A significant correlation was considered if it reached an absolute *r* greater than 0.3. To create the map with the color gradient by province, for melanoma, and for NMSC, Microsoft Excel 2016 program was used.

Results

At the national level, the SMR of MM was 2.10/100,000 inhabitants, while that of NMSC was 1.28/100,000. At the provincial level, a great variability is confirmed, with the highest SMR of MM in Albacete (2.57) and Álava (2.48) and of NMSC in Ceuta (2.34) and Soria (2.15). The SMR of each province is shown in Figures 1 and 2 (Tables 1 and 2).

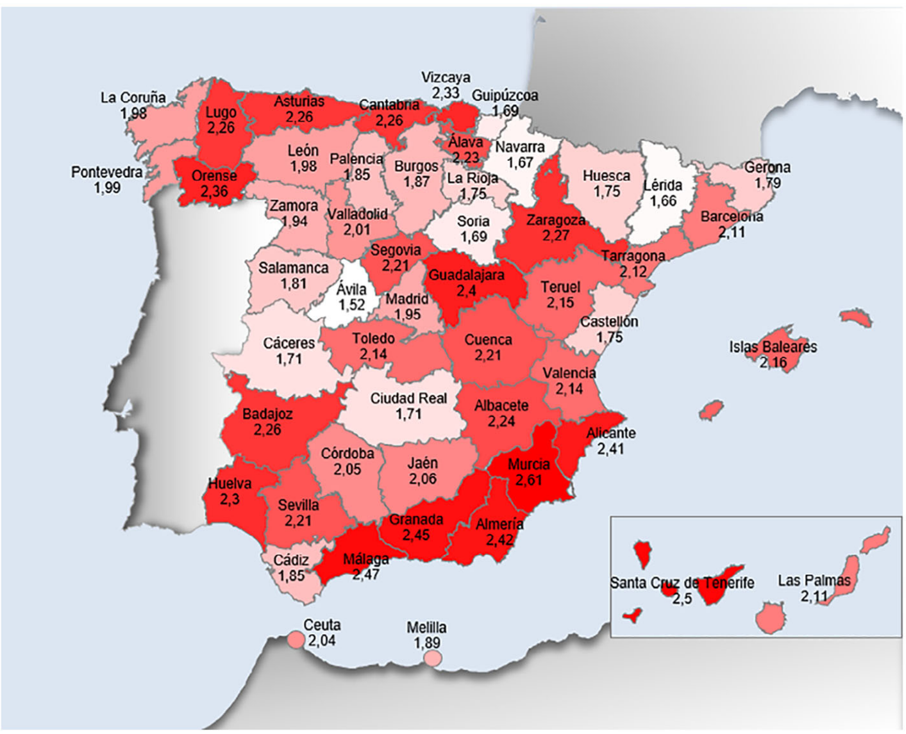

Figure 1 Standardized annual melanoma mortality rates by province, 2000–2019

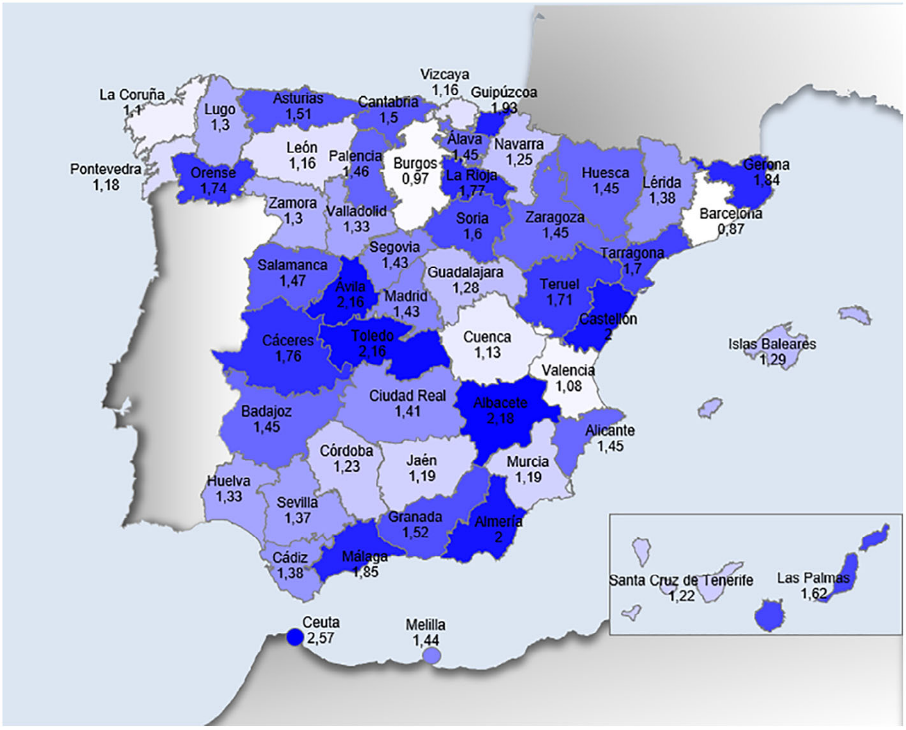

Figure 2 Standardized annual SCC mortality rates by province, 2000–2019

Table 1 Age-specific and standardized melanoma mortality rate per 100,000 inhabitants (European standard population) in Spain

	Both genders				Males				Females			
Age (years)	**2000–2004**	**2005–2009**	**2010–2014**	**2015–2019**	**2000–2004**	**2005–2009**	**2010–2014**	**2015–2019**	**2000–2004**	**2005–2009**	**2010–2014**	**2015–2019**
0–4	0	0	0.02	0	0	0	0.02	0	0	0	0.02	0
5–9	0.01	0	0	0.01	0	0	0	0.02	0.02	0	0	0
10–14	0.02	0.01	0.03	0	0.02	0.02	0.02	0	0.02	0	0.04	0
15–19	0.04	0.03	0.03	0.01	0.02	0.03	0.05	0	0.07	0.04	0	0.02
20–24	0.17	0.11	0.06	0.07	0.2	0.1	0.05	0	0.14	0.13	0.08	0.14
25–29	0.26	0.21	0.16	0.32	0.28	0.23	0.23	0.31	0.23	0.19	0.09	0.33
30–34	0.58	0.42	0.42	0.39	0.63	0.48	0.46	0.43	0.53	0.36	0.37	0.35
35–39	0.84	0.69	0.66	0.68	0.85	0.77	0.68	0.74	0.84	0.61	0.63	0.63
40–44	1.02	1.11	0.87	0.86	1.15	1.21	0.93	0.95	0.89	0.99	0.81	0.77
45–49	1.56	1.37	1.39	1.24	1.7	1.45	1.53	1.48	1.43	1.28	1.25	0.99
50–54	1.97	1.87	1.74	1.71	2.52	2.15	2.06	1.88	1.44	1.6	1.41	1.54
55–59	2.42	2.48	2.4	2.16	3.07	2.98	3.03	2.53	1.81	2	1.8	1.79
60–64	3.14	3.16	3.17	2.89	4.32	4.05	4.06	3.75	2.05	2.32	2.32	2.07
65–69	4.12	4.23	4.32	3.91	4.94	5.41	5.64	5.1	3.4	3.16	3.12	2.82
70–74	5.01	5.55	5.63	5.71	6.61	7.18	8.08	7.66	3.71	4.21	3.56	4.02
75–79	6.04	6.79	7.61	7.22	7.61	9.17	10.32	10.23	4.92	5.03	5.54	4.86
80–84	7.51	8.84	9.18	10.87	10.3	11.64	13.36	14.65	5.89	7.09	6.44	8.31
>85	12.68	12.19	13.29	14.31	14.76	16.12	17.47	18.63	11.78	10.45	11.31	12.13
SMR	2.01	2.06	2.1	2.1	2.5	2.6	2.75	2.7	1.64	1.65	1.6	1.63

SMR, standardized mortality rates.

Table 2 Age-specific and standardized NMSC mortality rate per 100,000 inhabitants (European standard population) in Spain

	Both genders				Males				Females			
Age (years)	2000–2004	2005–2009	2010–2014	2015–2019	2000–2004	2005–2009	2010–2014	2015–2019	2000–2004	2005–2009	2010–2014	2015–2019
0–4	0	0	0	0	0	0	0	0	0	0	0	0
5–9	0	0.01	0	0	0	0	0	0	0	0.02	0	0
10–14	0	0	0	0	0	0	0	0	0	0	0	0
15–19	0.01	0.01	0	0	0.02	0.02	0	0	0	0	0	0
20–24	0.03	0.01	0.01	0.02	0.02	0	0.02	0	0.04	0.01	0	0.04
25–29	0.04	0.02	0.05	0.02	0.07	0.01	0.04	0	0.01	0.02	0.05	0.03
30–34	0.05	0.03	0.04	0.03	0.06	0.05	0.03	0.05	0.04	0.01	0.05	0.01
35–39	0.08	0.06	0.05	0.04	0.11	0.08	0.07	0.03	0.05	0.04	0.03	0.04
40–44	0.1	0.11	0.15	0.05	0.13	0.14	0.18	0.05	0.08	0.08	0.12	0.04
45–49	0.22	0.1	0.2	0.11	0.3	0.13	0.22	0.14	0.15	0.07	0.19	0.09
50–54	0.3	0.25	0.3	0.24	0.49	0.38	0.49	0.33	0.11	0.13	0.11	0.16
55–59	0.49	0.6	0.55	0.37	0.77	0.97	0.78	0.58	0.22	0.25	0.33	0.16
60–64	0.72	0.72	0.81	0.67	1.07	1.1	1.12	1.1	0.4	0.36	0.52	0.28
65–69	1.15	1.37	1.26	1.13	1.96	2.28	1.97	1.82	0.44	0.56	0.62	0.51
70–74	2.01	1.8	2.06	1.88	3.13	2.83	3.4	3.32	1.1	0.96	0.92	0.65
75–79	3.39	3.66	3.91	3.54	5.3	6.06	6.6	6.1	2.02	1.89	1.86	1.54
80–84	7.94	7.52	7.42	7.44	11.66	12.32	12	12.47	5.78	4.53	4.41	4.02
>85	31.87	26.16	26.55	26.87	42.59	34.53	37.94	38.19	27.26	22.45	21.15	21.18
SMR	1.43	1.28	1.32	1.25	2.03	1.87	1.98	1.92	1.06	0.89	0.88	0.81

SMR, standardized mortality rates.

A positive correlation was obtained between the MM SMR and the provincial gross domestic product (GDP) (r = 0.47), and the sale of tobacco in each province (r = 0.33) and negative with geographic longitude (r = −0.47; Table 3).

Regarding NMSC, a positive correlation was obtained between the NMSC SMR and the level of provincial agricultural development (r = 0.35), mean annual temperature (r = 0.41), maximum mean annual temperature (r = 0.41), annual mean minimum temperature (r = 0.36), absolute minimum temperature (r = 0.31), highest minimum temperature of the year (r = 0.40), and lowest maximum temperature of the year (r = 0.38). A negative correlation was obtained between NMSC mortality and the number of provincial hospital beds (r = −0.40), provincial GDP (r = −0.50), and latitude (r = −0.40) (Table 3).

Discussion

In Europe, melanoma incidence rates follow a north–south gradient, with the highest rates in northern European countries. This distribution is similar in the rest of the world, with a higher incidence rate as we move away from the equator. In Spain, a crude global incidence of 8.82 cases per 100,000 people/year has been estimated, with a crude global mortality of 2.17 cases per 100,000 people/year and a low standardized incidence rate compared to other countries in Europe, the USA, Australia, and New Zealand.[18]

Regarding SCC, in a recent 2016 meta-analysis,[19] it was estimated that the crude incidence rate in Spain was 38.16 per 100,000 person-years, our country being in the low range of incidence along with countries such as Germany or Slovakia. The mortality of SCC, although low, represents the highest percentage of it for NMSC.

The melanoma mortality at the national level obtained in our analysis (2.10/100,000 inhabitants) is very similar to that obtained in recent studies (2.17/100,000 inhabitants[19] and 2.13/100,000 inhabitants,[9] respectively). Despite the fact that the mortality gradient due to MM in Europe is well-known, with higher mortality in the southern and eastern countries,[20] our results have shown that Spain continues to be an exception, possibly explained by the protective role that plays in chronic sun exposure, the higher skin phototype, and universal and free access to the health system.[21] To our knowledge, this is the first study to analyze mortality at the provincial level. It highlights a higher mortality in the eastern provinces of the country, a fact confirmed by the statistically significant positive correlation between SMR and geographical longitude (r = −0.47, P = 0.001). This phenomenon could be because of multiple factors, such as the greater beach culture of these provinces and, consequently, the greater intermittent sun exposure that predisposes to the development of MM, as well as the greater number of foreigners with a lower skin phototype. Paradoxically, contrary to what might be expected, no correlation was observed with the number of hospital beds and the mean irradiation, and the mean insolation.

However, the standardized NMSC mortality rate obtained (1.28 per 100,000 inhabitants) is practically identical to that

Table 3 Pearson correlation coefficient (bilateral significance) between adjusted mortality rates for melanoma and non-melanoma skin cancer and multiple socioeconomic and environmental variables by province during the period 2000–2019

	NMSC 2000–2019	Melanoma 2000–2019
Hospital beds	−0.40**	0.16
Agricultural development	0.35*	−0.26
GDP	−0.50**	0.47**
Tobacco	−0.26	0.33*
Altitude	−0.14	0.06
Longitude	0.04	−0.47**
Latitude	−0.40**	0.22
Irradiation	0.40	0.16
Insolation	0.266	−0.113
TM_MAX	0.41**	−0.23
TM_MES	0.41**	−0.20
TM_MIN	0.36*	−0.14
TA_MAX	0.24	−0.28*
TA_MIN	0.31*	−0.17
TS_MIN	0.40**	−0.12
TI_MAX	0.38**	−0.22
N_LLU	−0.29*	0.04
N_FOG	−0.28*	−0.05

NMSC, non-melanoma skin cancer; GDP, gross domestic product; TM_MAX, average annual maximum temperature (°C); TM_MES, average annual temperature (°C); TM_MIN, average annual minimum temperature (°C); TA_MAX, annual absolute maximum temperature (°C); TA_MIN, annual absolute minimum temperature (°C); TS_MIN, annual highest normal minimum normal temperature (°C); TI_MAX, annual lowest maximum normal temperature (°C); N_LLU, number of rainy days in the year; N_FOG, number of foggy days in the year.
*< 0.05.
**< 0.01.

described by Sendin et al.[22] which was 1.27 per 100,000 inhabitants in 2018 and slightly higher than the one reported in a 2016 meta-analysis[19] (1.10 per 100,000 person-years). The mortality rate of NMSC is low; it is to a greater extent caused by the high-risk variant of SCC and is similar to that of other European countries.[23–25] At the provincial level, higher mortality from NMSC is found in provinces with greater agricultural development ($r = 0.35$, $P = 0.024$), with higher average temperature, and in those with lower latitude ($r = 0.4$, $P = 0.004$). Provincial agricultural development and average temperature can be seen as indirect markers of chronic exposure to the sun, which is well-known to be an important risk factor for the development of SCC.[4] The statistically significant negative correlation obtained with the meteorological variables that are inversely related to chronic solar radiation, such as the number of days of fog or rain, reinforces the theory of association between chronic sun exposure and SCC.

It is worth noting the correlation that has been obtained with provincial GDP (positive with SMR MM, $r = 0.47$ and negative with SMR NMSC, $r = -0.50$). If we assume that provincial GDP is an indirect measure of provincial per capita income and economic wealth, these results contradict what is described in the literature. At a global level, numerous articles have been written on the influence of socioeconomic factors on the incidence and mortality of skin cancer, especially in MM. In the USA, Singh et al. in 2011[26] observed a higher incidence rate of MM in regions with less poverty, higher education, higher income, and lower unemployment. However, this higher incidence does not correspond to higher mortality, since Sitenga et al. in 2018[27] corroborated how the populations with the lowest income in the US percentile have lower survival and greater probability of dying from MM in all its stages, probably because of the delay in consulting a specialist and the difficulty of access to medical care in privatized health systems. At a European level, similar studies have been carried out in Denmark,[28] the Netherlands[24] and other northern countries[29] that reaffirm the higher incidence in populations with greater economic wealth, possibly because of intermittent recreational exposure to the sun of typical hobbies of higher economic status, coastal vacations in childhood, and a greater culture of tanning, activities that have been shown to increase the risk of MM.[6,12,30] Internationally, mortality and affluence show a similar relationship with patients with lower socioeconomic status (SES) having lower incidence[31–33] but being diagnosed at a later stage. In a 2015 meta-analysis where 32 studies were analyzed,[34] it was observed that although higher SES populations generally have a higher incidence of melanoma, lower SES populations have higher mortality from melanoma. However, in Spain at an ecological level, we observe that there is a higher mortality from MM in the provinces with higher income. This may be due to several factors, the main being the lower incidence of nodular melanoma that exists in Spain with respect to other nearby countries.[35] This subtype has been associated in several studies with a lower SES.[31,36] Other factors may also have contributed to explaining this difference, such as universal and free access to the healthcare system and the ecological nature of our study. Further analytical studies at the national level are needed to clarify this issue.

The relationship between NMSC and socioeconomic status has less been studied. Steding et al. in 2010[37] observed a higher incidence of SCC in the rural population with lower incomes, as well as higher mortality.[38] Similar results have been obtained in our analysis, obtaining a positive correlation with the agricultural development of each province. This may be explained by the fact that living in the countryside leads to an accumulation of smaller doses of UVR day by day, ultimately to a higher cumulated dose of UVR, and consequently to a higher risk of SCC. Likewise, this more chronic exposure would explain the lack of correlation with deaths from melanoma. The same can be said of the existing negative correlation with the number of hospital beds, since this is still an indirect measure of the economic development of each province.

The association between smoking and skin cancer is controversial. Our study obtained a positive correlation between melanoma mortality and provincial tobacco sales ($r = 0.33$), while no significant correlation was obtained with NMSC mortality. A recent meta-analysis[39] showed that smoking could moderately increase the risk of SCC but slightly reduce the risk of MM, contrary to our results. It may be explained as smoking encompasses many carcinogenic compounds, attenuates immune responses, and decreases the cutaneous blood flow, which increases the risk of SCC among smokers.[40,41] Smoking also hinders the growth of melanoma cells by downregulating the gene expression of the Notch pathway, which controls cell differentiation and produces the accumulation of nicotine in tissues containing melanin, thus suppressing inflammatory responses to UV radiation.[42,43] However, in agreement with our results, Pozniak et al.[44] observed a higher mortality from melanoma in heavy smokers. In this study, smoking had an adverse effect on melanoma-specific outcome by reducing the protective value of immune infiltration, with a greater detrimental effect of smoking on survival with the strength of the tumor immune signal of the patient. Smoking can also be a detriment to healing from skin cancer surgery. In fact, numerous scientific studies have shown that smoking cigarettes can significantly reduce the blood flow necessary for wounds to heal properly.[45] Finally, in another study carried out in Spain, using a propensity score matching analysis, the authors found no impact of smoking on survival of melanoma patients and that it should not influence treatment decisions.[46] With all these data, and given that our data show an association between smoking and mortality, we hypothesize that the smoking patients included in our study could present more aggressive melanomas.

The fundamental limitation of this study is that of analyses at the ecological level, where we can only establish correlations between variables, while the individual distribution of exposure and health remains unknown (ecological fallacy), which leads to a possible distortion of the association between exposure and outcome. However, they are an excellent way to establish hypotheses that can be confirmed later at the individual level.

Conclusion

The burden of skin cancer presents an urgent need for increased early detection and public education. Although skin cancer mortality in Spain is low compared to other nearby countries and has decreased in recent years, there are still important differences between each province that must be taken into account when planning health care and resource distribution. This ecological and province-wise study helps to elucidate the relationship between social and ambient exposure determinants and skin cancer mortality in Spain, with a higher mortality of melanoma in provinces of higher income and higher mortality of NMSC in the poorer and more agricultural-oriented provinces. To our knowledge, this is the first Spanish study that takes into account every province and may provide the foundation for more analytical studies to help clarify the complex relationship between skin cancer mortality and socioeconomic and environmental factors, leading to more effective targeted interventions and education on sun habits at the individual, community, province, and national level.

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