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INVESTIGATIVE REPORT

Increased Skin Cancer Mortality in Chile Beyond the Effect of Ageing: Temporal Analysis 1990 to 2005

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Chile has a medium-to-high skin cancer mortality rate. Previous studies have shown an increasing rate of skin cancer mortality. We evaluated skin cancer mortality characteristics and their temporal evolution in Chile from 1990 to 2005 in a mixed ecological study using death certificate databases. Age, sex, year and region of residence were obtained for melanoma and non-melanoma deaths. Crude and age-sex-adjusted rates were calculated using the national projections and WHO 2000 standard population data. Descriptive and temporal analyses, using a Prais-Winsten regression, were computed. A total of 3588 deaths were registered, of which 55% were melanoma and 54% occurred in men (median age 71 years; women were older). The adjusted rate was 1.75 deaths per 100,000 inhabitants (2.22 in men vs. 1.39 in women). Melanoma skin cancer and non-melanoma skin cancer mortality had a tendency to increase. In conclusion, skin cancer mortality is rising beyond the rate predicted by ageing. An increased incidence due to changes in modifiable factors, such as exposure to ultraviolet radiation and arsenic, might explain the increase in skin cancer mortality. ***Key words: skin neoplasms; mortality; Chile.***

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Skin cancer is usually classified as malignant melanoma (MM) or non-melanoma skin cancer (NMSC), which includes basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), and is the most common cancer worldwide (1). The World Health Organization (WHO) estimates that between 2 and 3 million new cases of NMSC and 132,000 cases of MM are diagnosed each year (out of a total of 12 million new cancers), and they are together responsible for 66,000 deaths per year (1). According to the 2002 Global Burden Disease Report, New Zealand, Australia and Norway had the highest mortality rates from skin cancer (7.6, 7.4 and 6.4 deaths per 100,000 inhabitants, respectively). In this report, Chile was situated in the 71st percentile (2.0 deaths per 100,000 habitants) of the 192 countries examined (2).

Chile is a developing country located in South America. It is divided into 13 regions (counted from north to south, except for region XIII, which is situated approximately in the middle of the country). Copper extraction and agricultural product (cellulose, wine and fruit) exports are the main economic activities. In the last 40 years, Chile has experienced a rapid demographic and epidemiological transition towards chronic and degenerative diseases (3). Regarding skin cancer, previous studies have shown that skin cancer mortality rates in Chile have increased for both types of skin cancer (4–6).

In the evaluation of skin cancer epidemiology, it is important to acknowledge that external risk factors can change over time and that the distribution might not be homogeneous. Ultraviolet radiation (UV) and arsenic are among the external skin cancer risk factors that have been described in Chile, the latter mainly affecting NMSC (7–9), with a heterogeneous distribution of these risk factors. This situation could lead to differences in skin cancer mortality in Chile.

The main purpose of this study was to evaluate skin cancer mortality characteristics and their temporal evolution in Chile from 1990 to 2005 at national and regional levels.

METHODS

Study design

A population-based mixed ecological study (comparison of multiple groups and temporal series) was designed to evaluate the general characteristics and temporal evolution of skin cancer mortality in Chile between 1990 and 2005.

Variables and data sources

National death certificate databases from 1990 to 2005 were obtained from the Health Statistics and Information Department of the Chilean Ministry of Health. Information about sex, age at death (years), anatomical site (according to the International Classification of Diseases (ICD) code), region of residence and year of death were obtained for all recorded deaths from skin cancer: ICD-9: 172 (MM) and 173 (NMSC); ICD-10: C43 (MM) and C44 (NMSC) (both classifications are equivalent for skin cancer coding). ICD-9 and ICD-10 classifications, used in Chilean mortality registries, only include information regarding anatomical site; they do not identify the histological type of cancer as the International Classification of Diseases for Oncology (ICD-O) does. The WHO considers the Chilean

death registries to be of high completeness and coverage, but of medium quality because of the use of "garbage codes" and ill-defined conditions (10). Nevertheless, ill-defined conditions have decreased from 4.7% in 1997 to 2.8% in 2003 (11). Before being made available to the general public, death registries are validated by the Health Statistics and Information Department of the Chilean Ministry of Health.

Population information for the period 1990 to 2005 was obtained from the Population Projections of the National Institute of Statistics, based on census data (12).

Statistical analysis

Median and percentiles (p25 and p75) were used as summary measures for age. Total number and proportions are reported for skin cancer type, sex and anatomical site. Age was categorized into five groups, 0–44, 45–54, 55–64, 65–74 and 75 years and older, for comparison with other investigations and for variable distribution reasons.

Crude mortality rates per 100,000 inhabitants were calculated using the population estimates for the country and each region per year. Sex- and age-adjusted mortality rates were also computed using the WHO 2000 Standard Population (WSP) (13) through direct standardization (14).

To compare regional rates, direct standardization was also computed using 1992 census data from Chile. This population has a higher percentage of people aged less than 75 years, allowing for a better representation of deaths in persons less than 75 years of age.

Temporal analysis was done using Prais-Winsten regression (15). This time-series regression model has the following characteristics that make it suitable for the present data analysis: (*i*) results are reported and interpreted as coefficients, similar to a linear regression estimating annual variations of the rates (magnitude of the coefficient). In this study, the coefficient represents the magnitude of the rate change per year. It also determines whether rates are decreasing (negative coefficient), increasing (positive coefficient) or stable (confidence interval includes zero). (*ii*) Permits the analysis of time series with few observations (minimal number of observations needed = 3). (*iii*) Corrects the autocorrelation existing in this type of data with the usual assumption that errors are not independent (it corrects a first-order autoregressive correlation, i.e. the value of an observation "at time i" is influenced by the value of an observation "at time i – 1" and affects the value "at time i + 1") reducing false positive results detected in data with autocorrelation (16).

Statistical analysis was conducted using STATA 10.1 (17). Statistical significance was defined as a *p*-value less than or equal to 0.05. ArcView 3.3 (18) was used to draw the Chilean map using cartographic boundary files from the National Congress Library.

RESULTS

A total of 3588 deaths from skin cancer were reported in Chile from 1990 to 2005. MM caused 55.1% ($n = 1975$) of the deaths. Men represented 54.4% ($n = 1953$) of the total deaths; this percentage was similar when analysing by type of skin cancer (Table I). In the present study, 99.9% of deaths were certified by a medical doctor, and 49.2% were registered by a doctor previously involved with the patient's care (50.6% for MM and 47.4% for NMSC).

The median age at death was 71 years (p25–p75: 57–82). All regions had a median age at death above 70 years, except for region II (66.5 years). The highest median age at death was observed in regions IV and XII (75 years). Deaths from MM occurred at a younger age (Median: 65; p25–p75: 50–65) vs. NMSC (Median 79; p25–p75: 67–85), and women were 5 years older than men. This difference was similar for both skin cancer types.

Table I. *Skin cancer deaths by type and sex, Chile 1990–2005*

	MM		NMSC		Both types	
Sex	*n*	%	*n*	%	*n*	%
Men	1,054	53.4	899	55.7	1,953	54.4
Women	921	46.6	714	44.3	1,635	45.6
Total	1,975	100	1,613	100	3,588	100

MM: malignant melanoma; NMSC: non-melanoma skin cancer

Regarding the anatomical site, 70% of death certificates were coded as "unspecified". This situation was more common in MM (81.3%) than in NMSC (58.5%). "Lower limb, including hip" was the most common anatomical site reported for MM. For NMSC, "other and unspecified parts of the face" had the highest frequency (Table II).

The 1990 to 2005 total crude mortality rate was 1.51 deaths per 100,000 inhabitants (1.66 for men, 1.36 for women, 0.83 for MM and 0.68 for NMSC). MM crude mortality rates were higher than NMSC in every age group, except for deaths of persons aged 75 years and older. Mortality rates in women were consistently lower. Independent of the type of skin cancer, as the age increased the death rates also increased, although the effect was more marked in NSMC rates, especially in the group aged 75 years and older (Fig. 1).

Adjusted mortality rates (using WSP) were 1.39 deaths per 100,000 inhabitants for women and 2.22 for men. MM and NMSC adjusted mortality rates were 0.95 and 0.80, respectively.

According to the region of residence, an uneven distribution of skin cancer adjusted death rates (using WSP) was observed. The highest mortality (adjusted rate) was

Table II. *Anatomical site reported in the skin cancer death records, Chile 1990 to 2005*

Anatomical site (according to ICD)	MM		NMSC		Both types	
	n	%	*n*	%	*n*	%
Lip	7	1.8	25	3.6	32	3.0
Eyelid, including canthus	3	0.8	20	2.9	23	2.1
Ear and external auricular canal	8	2.1	107	15.6	115	10.7
Other and unspecified parts of face	79	20.3	262	38.2	341	31.7
Scalp and neck	27	6.9	114	16.6	141	13.1
Trunk	59	15.2	64	9.3	123	11.4
Upper limb, including shoulder	26	6.7	27	3.9	53	4.9
Lower limb, including hip	173	44.5	57	8.3	230	21.4
Overlapping	7	1.8	10	1.5	17	1.6
Total	389	100	686	100	1,075	100

"Unspecified site" registries according to the International Classification of Diseases (ICD) codification (C43/4–9 and 172/3–9) were not included. MM: malignant melanoma; NMSC: non-melanoma skin cancer.

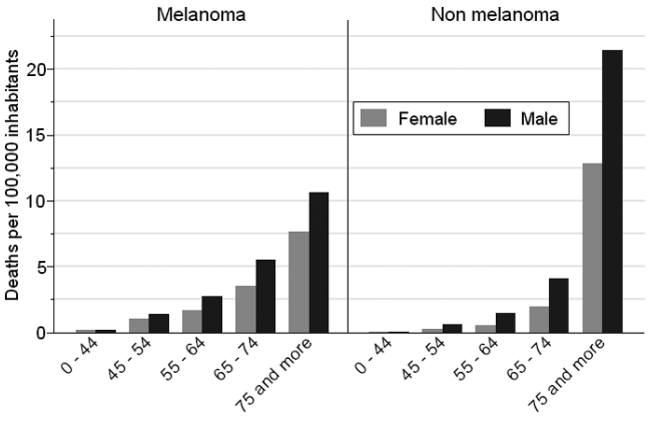

Fig. 1. Age-adjusted skin cancer mortality rates (using WHO 2000 Standard Population) by sex and type of cancer, Chile 1990 to 2005.

observed in region II (2.99 per 100,000 inhabitants), followed by region XII (the most southern region) with 1.83. The lowest rates were observed in region XI (0.97) and region VI (1.10) (Fig. 2).

Temporal analysis showed that adjusted mortality rates varied from 1.40 to 2.07. For MM, adjusted rates ranged from 0.79 to 1.14, and for NMSC, the rates ranged from 0.45 to 1.02.

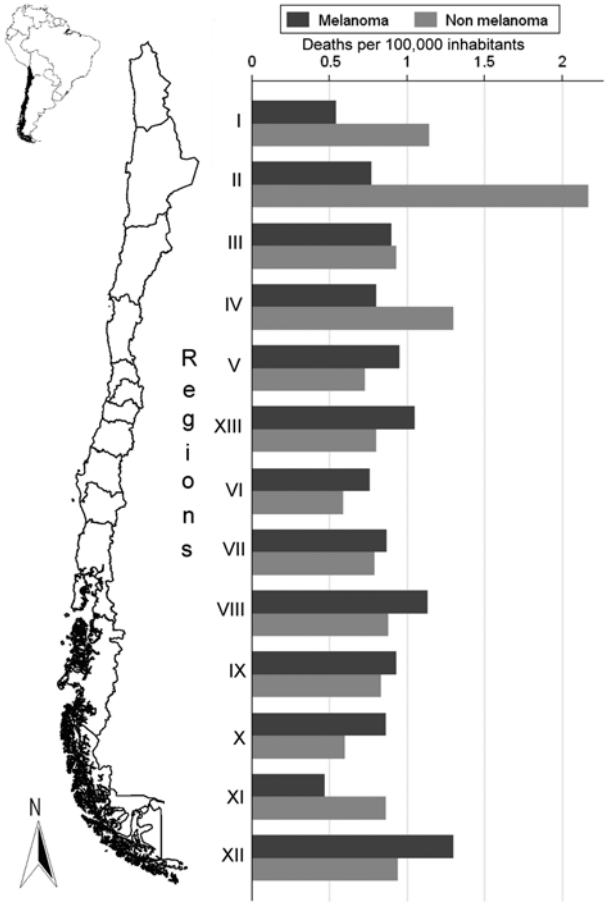

Fig. 2. Age-sex adjusted skin cancer mortality rates (using 1992 Chilean census data) by region and type of skin cancer, Chile 1990 to 2005.

Prais-Winsten regression demonstrated that the mortality for both skin cancer types had a tendency to increase: for MM, the coefficient was 0.014 (95% confidence interval (CI): 0.006; 0.022); for NMSC, the coefficient was 0.020 (95% CI: 0.007; 0.034); and for both skin cancer types, the coefficient was 0.034 (95% CI: 0.015; 0.053) (Fig. 3).

According to sex, analysis of age-adjusted mortality rates in men showed an increase that was slightly higher for MM (coefficient: 0.028 (95% CI: 0.017; 0.039)) than for NMSC (coefficient: 0.025 (95% CI: 0.006; 0.044)). For women, the situation was different; NMSC showed a tendency to increase (coefficient: 0.016 (95% CI: 0.04; 0.028)), while MM showed a tendency to decrease that was not statically significant.

The evaluation of mortality time trends by age group showed an increase in the following groups in men: 0–44 years (coefficient: 0.009 (95% CI: 0.004; 0.014)), 45–54 years (coefficient: 0.06 (95% CI: 0.001; 0.011)) and 75 years and older (coefficient: 1.098 (95% CI: 0.588; 1.609)). The only significant trend in women was found in the group aged 75 years and older (coefficient: 0.531 (95% CI: 0.252; 0.81)). The analysis by skin cancer type revealed an increase in mortality rates for MM in the group aged 45–54 years (coefficient: 0.034 (95% CI: 0.001; 0.06)), 55–64 years (coefficient: 0.06 (95% CI: 0.014; 0.10)) and 75 years and older (coefficient: 0.22 (95% CI: 0.13; 0.32)). For NMSC, the only group showing a statistically significant increase in mortality rates was the group aged 75 years and older (coefficient: 0.51 (95% CI: 0.29; 0.74)).

The analysis of mortality rates from skin cancer according to region of residence showed different patterns. When using the WSP, the mortality rates in regions I, IV, V, VII and VIII had a tendency to increase with coefficients of 0.08 (95% CI: 0.01; 0.015), 0.07 (95% CI: 0.012; 0.13), 0.04 (95% CI: 0.002; 0.075), 0.07

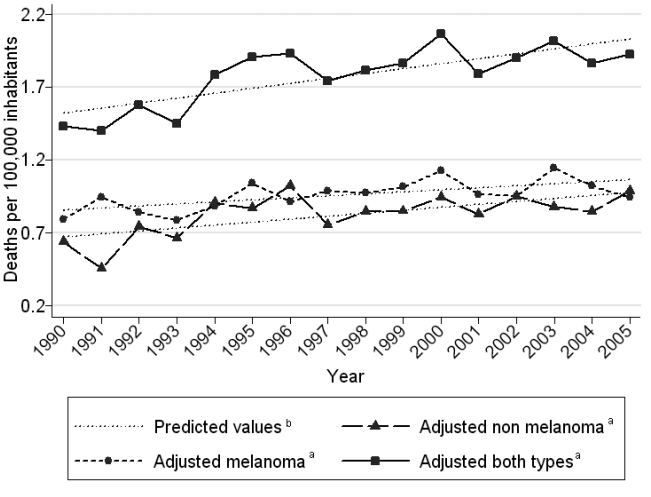

Fig. 3. Temporal evolution of skin cancer mortality rates, Chile 1990 to 2005.
[a]Adjusted for age and sex, according to the WHO 2000 standard population.
[b]Predicted using Prais-Winsten regression.

(95% CI: 0.02; 0.11) and 0.04 (95% CI: 0.001; 0.08), respectively. Only region II had a tendency towards decreased mortality (coefficient: –0.1 (95% CI: –0.2; 0.001)) that was marginally not statistically significant (*p*-value 0.07). Other regions did not show any trend that was statistically significant.

When used as a standard population, the 1992 Chilean census data had lower mortality rates, but a rising tendency was also detected. The weight of mortality in the group aged less than 75 years was not underestimated, because this population is younger than the WSP. Temporal analysis showed that only regions VII and VIII had a tendency towards increasing mortality that was statistically significant (coefficient: 0.042 (95% CI: 0.013; 0.07) and coefficient: 0.031 (95% CI: 0.009; 0.053), respectively). On the contrary, the mortality tendency in region II to decrease was statistically significant (coefficient: –0.073 (95% CI: –0.136; –0.01)).

DISCUSSION

This study demonstrated that skin cancer mortality had a tendency to increase in Chile from 1990 to 2005. Until the year 2000, previous studies in Chile came to similar conclusions, implying that skin cancer mortality has been increasing since at least 1980 (4, 5, 19).

Studies in other countries showed dissimilar results. A global study showed that MM mortality is rising (20), although this situation varies depending on the country being analysed. For example, countries such as Spain, Mexico and the Netherlands showed an increase in MM mortality rates (21–23), whereas other countries, including the UK, Finland, Canada, Germany, USA, Sweden and Australia, reported a recent stabilization or even a decrease in MM and/or NMSC mortality rates (24–30).

The high percentage of deaths from NMSC (44.96%) differs from that reported in developed countries such as the USA (22.8%) (31), Australia (24.1%) (32) and Germany (19.33%) (28). On the other hand, the Chilean figure is similar to that reported in Argentina, where NMSC represented 43.6% (33), or lower than that in Mexico at 71.3% (23). A dissimilar distribution of skin cancer risk factors or survival profiles might explain this situation.

Through standardization, we eliminated the effect of ageing in the population that might be the first theory to explain the Chilean skin cancer mortality trend.

The temporal evolution analysis using the WSP aimed to permit international comparisons. However, the Chilean 1992 census data seemed a better choice, because it is a standard population more similar to the population analysed in this study. Although adjusted rates in older people were underrepresented using the Chilean 1992 census data when compared with the WSP standardization, it had a better representation of the younger population that is less affected by the cumulative effect of age (affecting especially NMSC) and external factors.

For a long time, the accuracy of death certificates has been a subject of discussion (34), and an underestimation or overestimation of cases could be a source of information bias. Although there are no specific studies known to us on the accuracy of skin cancer death certificates in Chile, Percy et al. (35) described death certificate detection and confirmation rates of 87.5% and 90.5% for MM and 35.3% and 26.9% for NMSC, respectively, in the USA. Lewis & Weinstock (36) reported a 44% rate of misclassified NMSC death records in a study in Rhode Island, USA. Chile has a high rate of deaths certified by doctors, but those certified by non-treating doctors might be less reliable, especially for NMSC. Nevertheless, the percentage certified by non-treating doctors was similar for both types of skin cancer, and the anatomical site report was even higher in NMSC. This could reflect a more exhaustive investigation of the cause of death in this type of skin cancer. Because of the data quality and consistency through time, an unexpected increase in mortality through a change in the registry of "false cases" seems not be the answer to the increase in skin cancer mortality.

Sex-related differences in age at death and mortality rates have also been reported previously for MM (37–39). Less knowledge in prevention and higher risk related to an increased exposure to environmental factors, such as (intermittent) UV radiation and others related to occupational activities, have been proposed to be related to these differences (21, 37).

Deaths from NMSC are caused mainly by SCC (40) which is related to chronic UV exposure. This fact might explain why NMSC is the main cause of death from skin cancer in the northern area of Chile (where subtropical and desert climates predominate).

The uneven distribution of mortality rates, according to the region of residence, could be evidence of the existence of other environmental factors beside UV radiation exposure that could be associated with the increased incidence of MM and NMSC reported in some areas in Chile (41–43). Changes in exposure habits might partially explain this situation, but environmental and occupational-related exposures cannot be dismissed as important factors. Regarding NMSC, arsenic was, for several years, an important public health problem in the northern area of Chile because of its carcinogenicity. Antofagasta and its surroundings (region II) were exposed to very high concentrations of arsenic through tap water contamination and air pollution until the 1970s (7). Many studies have reported an increase in lung and bladder cancer mortality, along with other health problems in the same area (7, 8, 44–47). Although nowadays arsenic concentrations in the northern area of the country are below WHO recommendations (48),

the consequences are still seen, especially in diseases with long latent periods, such as cancer.

The fact that region II skin cancer mortality rates (standardized with 1992 Chilean census data) had a decreasing tendency and that the rate in region I was lower than that in regions II or even III might support the argument that arsenic had a more relevant role than UV radiation in skin cancer mortality in the northern area of Chile through a higher incidence of NMSC. The decreasing mortality tendency in that region might be explained by a decreasing incidence, but there are no temporal analysis studies in that region. There is scarce information regarding the skin cancer incidence in Chile; only limited data is available. The Local Cancer Registry in region II (International Agency of Research on Cancer Associate) reported an incidence of skin cancer (not differentiated by type) of 74.7 and 59.5 cases per 100,000 inhabitants for men and women, respectively, for the period 1998 to 2002 (43). The incidence rate in region II was higher than those reported in region XIII (21.73 cases per 100,000 inhabitants in 1998) (41), region VIII (9.7 for men and 7.5 for women for the period 2002 to 2005) or region X (19.1 for men and 20.9 for women for the period 1998 to 2002) (43).

Other exposures, especially those related to occupational activities in the metal and agricultural industries, such as pesticide and herbicides and polycyclic aromatic hydrocarbons (49), might explain the situation in regions VII and VIII. Even though there seems to be a paradox with the information mentioned previously about the incidence in region VIII, that registry represents only 69% of the population, and present information might not represent what happened in the past.

This study has some limitations. Although the study was carried out using validated databases, we cannot assume that information bias was absent (mainly generated in the registration process). Actions were taken to address this issue, such as training of doctors and exhaustive revision of death certificates. It would be of great interest to have more information regarding the incidence, risk factor distribution and survival from skin cancer in different areas of Chile in order to draw more detailed conclusions. Another limitation was the small number of deaths in some regions. This fact limited the temporal analysis by producing unstable mortality rates when doing separate analyses by skin cancer, especially in regions with small populations (data not shown). Conclusions drawn from those hypothetical analyses would possibly be erroneous; thus we had to limit the regional temporal analysis to skin cancer as a whole and not make separate analyses for MM and NMSC. This would have been of great interest due to the fact that risk factors are not equal. A possible solution would be to smooth the rates, but that technique would require a longer period of time.

The reader should bear in mind the ecological fallacy that arises from ecological studies. This could lead to incorrect conclusions when inferring that community-level findings are also observed at a personal level.

Even if the Chilean population is ageing (3), in the long term, skin cancer mortality rates should stabilize or even decrease for both MM and NMSC. This argument is supported by the fact that screening campaigns were implemented to promote early detection (50) and that there is a better control of risk factors. However, it is mainly due to the ease of access to effective treatments that improve overall survival (51–55).

The analysis of mortality trends is a strong tool for assessing the relevance of a disease in public health. Although skin cancer mortality is lower than stomach, lung, gallbladder, cervix or prostate cancer mortality in Chile, its high incidence, especially in the northern area of Chile (43), represents a high cost to the health system. This cost could be lowered by empowering people with knowledge, preventive activities and improving early detection, especially in men.

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