Risk factors for non-melanoma skin cancer in Taubaté, São Paulo, Brazil: a case-control study

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Summary

Objective: To identify factors associated with non-melanoma skin cancer in the city of Taubaté, São Paulo, Brazil. **Methods:** Hospital-based case-control study with individuals residing in Taubaté, treated between January 2005 and December 2006. The subjects were matched 1:1 according to gender and age. Age, gender, phototype, European descent, time of residence, sun exposure, time (in years), number of hours and time of occupational and non-occupational sun exposure, photoprotection, family history and photodamage were independent variables. A hierarchical logistic regression was used at three levels. The model adjustment was performed using the Hosmer-Lemeshow test and its accuracy was verified by ROC curve. The significance level was $p < 0.05$. **Results:** There were 132 cases and 132 controls. Phototype with OR = 3.14 (95% CI 1.79-5.49), hours of occupational 1.76 (1.04-2.99) and non-occupational sun exposure 1.80 (0.98-3.29) and family history 2.10 (1.13-3.93) were the variables in the final model. Hosmer-Lemeshow test, $p = 0.97$. Accuracy 70% (95% CI 63-76). **Conclusion:** We concluded that fair skin, family history and occupational and non-occupational sun exposure were associated with non-melanoma skin cancer in Taubaté-São Paulo.

Keywords: Skin neoplasms; risk factors; multivariate analysis; neoplasms, basal cell; neoplasms, squamous cell.

Study conducted at Universidade de Taubaté – UNITAU, Taubaté, SP, Brazil

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Introduction

Cancer is a disease with a multifactorial etiology, resulting mainly from genetic alterations, environmental factors and lifestyle[1].

Among the several types of cancer, skin cancer is one of the most important, presenting as melanoma skin cancer (MSC) and non-melanoma skin cancer (NMSC), which includes the basocellular carcinoma and the spinocellular carcinoma[2].

The expression "skin cancer epidemics" has been broadly used, as the disease incidence has been increasing, affecting from 900,000 to 1,200,000 individuals a year in the USA, with the cost of NMSC treatment in the years 1994 and 1995 being over 500 million dollars for health insurance agents[3].

In Brazil, the number have been equally increasing, especially in the state of São Paulo and the South Region, due to multiple epidemiological factors: direct exposure to sunlight, predominance of Caucasian individuals and large numbers of Caucasian immigrants[3,4].

National epidemiological data show that NMSC is the malignant neoplasm with the highest incidence in Brazil, in spite of the under-notification acknowledged even by the Ministry of Health, constituting a severe public health problem as the disease, despite the low lethality, in some cases can lead to physical deformity and severe ulcerations, consequently generating high costs to the health services[5-7]. MSC, in spite of its high mortality, represents only 4% of all skin cancers[5,8].

Risk factors such as fair skin, hair and eyes, propensity to sunburn and sunlight sensitivity, and presence of photodamage have been associated with a higher risk for development of NMSC. Other factors that have been studied are age, time of sun exposure, rural activity and family history[3]. Alcohol consumption and tobacco smoking, in the case of spinocellular carcinoma of the lip, genodermatoses (xeroderma pigmentosum, basocellular nevus syndrome), chronic immunosuppression, exposure to arsenic, and ionizing radiation and chronic irritative dermatologic processes are other factors that, albeit less common, can increase the risk for NMSC[2,4,9].

Skin cancer results from a close and complex association of several dimension factors and thus, the objective of this research to use a hierarchical model in the study of its determinants and interrelations. In this model, distal factors (antecendents) influence intermediate factors, which in turn influence proximal factors (those acting more directly on the outcome). Thus, by using a hierarchical structure, it is possible to consider and model distinct factors according to its precedence in time and its relevance for determining the outcome[10].

Prevention and early diagnosis of skin cancer, while knowing the risk factors and markers are of utmost importance to reduce its morbimortality and impact in public health[1,3,7].

The objective of the present study was to identify factors associated with non-melanoma skin cancer (NMSC) in the city of Taubaté, state of São Paulo (SP), Brazil, using a hospital-based case-control study and a hierarchical logistic regression technique.

Methods

This is a hospital-based case-control study, in which the study subjects were immunocompetent individuals of both genders, living in the city of Taubaté, state of São Paulo, Brazil, treated and followed at the Service of Dermatology of Hospital Universitário de Taubaté in the period of January 2005 to December 2006 and diagnosed for NMSC through biopsy and histopathological analysis. Controls were also immunocompetent individuals of both genders treated and followed at the same service and within the same period of time, but who did not have the disease and had never had it, who had had other dermatological diagnoses such as psoriasis, seborrheic eczema, other types of eczema, dermatophytosis, seborrheic and viral warts, among others. Control selection was carried out using a convenience sample. For both groups, minimum age was 25 years, with no upper age limit.

The individuals were combined according to gender and age; sample size was calculated based on an odds ratio (OR) = 2.1, alpha of 5% and test power of 80% (beta = 20%). This calculation was conducted using the Epi-info 6.04 resulting in 127 individuals for each group. A standardized questionnaire was used, which was applied by the author.

Independent variables were: age, gender, phototype, European descent, time of residence in Taubaté, occupational exposure to sunlight (related to professional activity with sunlight exposure), time of occupational exposure to sunlight, hour of the day during occupational exposure to sunlight, number of hours of occupational exposure, non-occupational exposure to sunlight (related to leisure, either daily – such as during walks – or sporadic – such as fishing in the weekends), hour of the day during non-occupational exposure to sunlight, number of hours of non-occupational exposure to sunlight, photoprotection (sunscreen use), family history of skin cancer and photodamage (melanosis and actinic keratosis, solar leucoderma, poikiloderma and solar elastosis).

The independent variables were categorized and codified as 1 = RISK and 0 = NO RISK, as follows:

- Age (in years): up to 50 years = 0; 51 years and older = 1
- Phototype (according to Fitzpatrick): up to 2 = 1; 3 and higher = 0
- European descent: yes = 1; no = 0
- Time of residence in Taubaté (in years): up to 10 years = 0; 11 years and longer = 1
- Occupational exposure to sunlight: yes = 1; no = 0

- Time of profession with occupational exposure to sunlight (in years): up to 10 years = 0; 11 years and longer = 1
- Number of hours (per day) of occupational exposure to sunlight: up to 5 hours = 0; 6 hours and longer = 1
- Non-occupational exposure to sunlight: yes = 1; no = 0
- Number of hours (per day) of non-occupational exposure to sunlight: up to 2 hours = 0; 3 hours and longer = 1
- Photoprotection: yes = 0; no = 1
- Family history of skin cancer: yes = 1; no = 0
- Photodamage: yes = 1; no = 0

The cutoffs were obtained by univariate analysis for each independent variable according to the intensity of effect.

Variables hour of the day during occupational and non-occupational exposure to sunlight and gender were not included above due to codification criteria.

These variables were included in the univariate analysis according to their presence or absence and the case or control situation and the respective OR, 95% confidence intervals (CI) and p-values were obtained.

Mean values of the quantitative variables were compared according to the case and control situation using Student's *t* test.

These variables were hierarchical in three levels: distal, intermediate and proximal in relation to the outcome, which was skin cancer. Variables that were the most distant from the outcome were included in distal level; those intermediate to the outcome were included in intermediate level and variables closest to the outcome were included in proximal level, as shown in Figure 1.

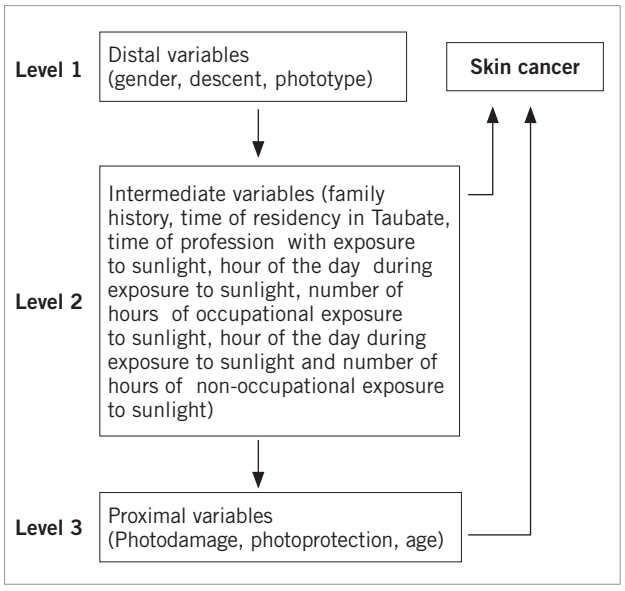

Figure 1

The univariate and multivariate analyses were carried out by conditional logistic regression, according to the hierarchical model. All variables were included in the model according to the hierarchical levels, which allowed adjustment for confounding factors. At each level, variables with $p < 0.20$ were maintained and the others were eliminated. In the final model, variables that reached a significance of $p < 0.05$ were considered significant.

Interactions between variables of the final model were tested. The model adjustment was estimated by Hosmer-Lemeshow test and a ROC curve was constructed to verify its accuracy. Level of significance was set at alpha = 5%.

Results

A total of 264 individuals were included in the study and divided in two groups: case (individuals with non-melanoma skin cancer) and control (individuals without non-melanoma skin cancer/with other dermatoses) combined 1:1, comprising 132 cases and 132 controls, treated and/or followed at the Service of Dermatology of Taubaté from January 2005 to December 2006, being 106 (40.2%) males and 158 (59.8%) females.

Mean age of the sample was 68.5 years (SD = 12.9), minimum age was 35 years and maximum age was 96 years. For the case group, mean age was 69.5 years and for the control group it was 67.4 years ($p = 0.18$) showing that the ages of case and control groups did not show a statistically significant difference.

Of the 132 individuals in the case group 90 (68.2%) had basocellular carcinoma and 42 (31.8%) had spinocellular carcinoma. Phototype of the sample varied from 1 to 5 according to Fitzpatrick's classification. European ascendency was positive in 105 individuals (39.8%). Mean profession time of the sample was 38.0 years (SD = 15.0) varying from 3 to 75 years. Occupational exposure to sunlight was reported by 185 individuals (70.1%) and time of occupational sunlight exposure varied from 0 to 73 years. The hour of the day during sunlight exposure that predominated in the sample was that corresponding to the whole day as reported by 153 individuals (58.0%), whereas 79 individuals (29.9%) denied exposure to sunlight. Regarding the duration (in hours) of occupational exposure to sunlight, 65 individuals (24.6%) were exposed for 10 hours and 34 individuals (12.9%) for 8 hours.

Regarding the non-occupational exposure to sunlight, 108 individuals (40.9%) reported it. Of the 108, 71 individuals (65.7%) reported the exposure was not daily, but sporadic (weekends). Also considering the 108 individuals that reported exposure to sunlight, 43 (39.8%) were exposed for up to 2 hours.

Sunscreen use was reported by 126 individuals (47.7%) in this sample. Values obtained for OR, CI and p-values are shown in Table 1.

Table 1 – Univariate analysis with the respective OR and 95% confidence intervals Taubaté, SP, Brazil – 2009

	Case (n)	Control (n)	OR	(95%) IC	p-value
Age					
Up to 50 years	10	19	2.05	0.92-4.60	0.08
51 years and older	122	113			
Phototype (according to Fitzpatrick)					
Up to 2	102	68	3.20	1.88-5.44	< 0.001
3 and higher	30	64			
European descent					
Yes	57	48	1.33	0.81-2.18	0.26
No	75	84			
Time of residence in Taubaté					
Up to 10 years	14	18	1.33	0.63-2.80	0.45
11 years and longer	118	114			
Occupational exposure to sunlight					
Yes	95	90	1.20	0.71-2.03	0.50
No	37	42			
Time of occupational exposure to sunlight					
Up to 10 years	63	62	0.97	0.60-1.57	0.90
11 years and longer	69	70			
Hour of the day during occupational exposure to sunlight					
Whole day or up to 3 PM	78	79	1.03	0.63-1.69	0.90
Other hours	54	53			
Number of hours of occupational exposure to sunlight					
Up to 5 hours	93	106	1.40	0.86-2.28	0.18
6 hours and longer	39	26			
Non-occupational sunlight exposure					
Yes	55	53	1.06	0.65-1.74	0.80
No	77	79			
Number of hours of non-occupational exposure to sunlight					
Up to 2 hours	93	106	1.71	0.97-3.02	0.065
3 hours and longer	39	26			
Photoprotection					
Yes	88	38	0.20	0.12-0.34	< 0.001
No	44	94			
Family history of skin cancer					
Yes	43	21	2.55	1.41-4.62	0.002
No	89	111			
Photodamage					
Yes	132	107	2.10^9	< 0.001- ∞	0.99
No	0	25			

Associations were identified for the following variables: age, phototype, number of hours of occupational sunlight exposure, number of hours of non-occupational sunlight exposure, photoprotection and family history of skin cancer.

The multivariate analysis was then carried out using the hierarchical logistic regression technique, where the first level (distal level) consisted of a single variable, which was phototype, considering the variable European descent had a $p > 0.20$ at the univariate analysis (Table 1).

At the second level (intermediate level), multivariate analysis included number of hours of occupational and non-occupational sunlight exposure and the family history of skin cancer. The other variables were not included as $p > 0.20$, as shown in Table 1.

Variables number of hours of occupational exposure to sunlight and number of hours of non-occupational exposure to sunlight were kept in model given their clinical importance, even though their intralevel significance was 0.09 and 0.07, respectively.

Table 2 shows the variables of intermediate level adjusted by the variables of distal level. After this adjustment, p-values of variables number of hours of occupational sunlight exposure and number of hours of non-occupational sunlight exposure reached the limit of significance, which justifies their being maintained in the model.

Among the variables of the third level (proximal level), photodamage was not maintained in the model, as it did not have statistical significance (Table 1). The variable photoprotection was excluded from the final model, although it was highly significant, possibly due to the fact that patients in case group only used sunscreen after skin cancer diagnosis; the exclusion can be explained by the difficulty to quantify/estimate photoprotection before development of NMSC. In the case group, sunscreen use was reported by 70% of the individuals, whereas only 30% of the individuals in the control group reported using it. When inserted in the model, variables family history of skin cancer and age lost their significance. A correlation was made between the variable photoprotection and the variables family history of skin cancer and age, resulting in a highly significant correlation ($p < 0.001$), justifying the exclusion of the variable photoprotection from the model.

The variable age showed borderline significance ($p = 0.06$) and was maintained by the same criterion adopted in the second level for the variables number of hours of occupational sunlight exposure and number of hours of non-occupational exposure to sunlight. However, when adjusted for the variables of first and second levels, this variable lost all of its significance ($p = 0.18$), having been permanently excluded from the model.

Summarizing the results of multivariate analysis by the technique of hierarchical logistic regression, risk factors found for non-melanoma skin cancer in Taubaté, São Paulo, were:

- Phototype
- Number of hours of occupational sunlight exposure
- Number of hours of non-occupational exposure to sunlight
- Family history of skin cancer

The interactions for these variables were tested, but they were not significant.

The Hosmer-Lemeshow test showed a Chi-square of 1.74 ($p = 0.97$). Model accuracy was then established by the ROC (receiver operating characteristics) curve.

The area under the curve represented 70% of the total area, with CI between 63 and 76% ($p < 0.001$).

Discussion

This is the first study conducted in Vale do Paraíba on risk factors for non-melanoma skin cancer.

High morbidity of NMSC and high mortality of melanoma in advanced stages are a major public health problem. Prevention and early diagnosis, through the knowledge of their risk factors and markers, are essential to reduce the morbimortality.

However, the understanding of epidemiological risk factors for skin cancer comes mainly from studies conducted in other countries: Australia, North America and Europe. This lack of data related to the Brazilian population justifies carrying out this type of investigation in our country.

This study provides data on the influence of constitutional characteristics and environmental factors for development of non-melanoma skin cancer that corroborate or contradict the findings found in the literature.

Findings regarding gender were controversial (59.8% women and 40.2% men) similar to those found by Machado et al.[11] and Santos et al.[12] and in opposition to those found by Castro et al.[13], all performed in the metropolitan region of São Paulo.

Mean age of the sample was 68.5 years, with minimum age being 35 years and maximum, 96 years. In the case group, mean age was 69.5 years similar to the data in the literature, with most cases occurring after the age of 60[3,11-13]. In the control group, mean age was 67.4 years, showing that the ages of the two groups were statistically similar ($p = 0.18$).

In relation to the phototype, a statistically significant association was observed for non-melanoma skin cancer in individuals with phototype up to II, according to Fitzpatrick's classification. These findings are consistent with the findings of Maia et al.[3,14] and Bariani et al.[15], which in epidemiological studies conducted in São Paulo, SP in 1995 and 2006, respectively, found as susceptibility factors

Table 2 – Second-level variables (intermediate level) adjusted by first-level variables (distal level). Taubaté, SP, Brazil – 2009

	OR	CI (95%)	p-value
Phototype	3.14	1.79-5.49	< 0.001
Number of hours of occupational exposure to sunlight	1.76	1.04-2.99	0.03
Number of hours of non-occupational exposure to sunlight	1.80	0.98-3.29	0.06
Family history of skin cancer	2.10	1.13-3.93	0.02

for development of non-melanoma skin cancer fair skin (types I and II of the Fitzpatrick classification). Higher incidence of malignant and premalignant lesions in Caucasians is almost a consensus in the literature[1,3-5,8-10,12], except for work of Prado[16], where there was a predominance of mulatto individuals.

European descent (up to the 2nd generation) was positive in 105 individuals (39.8%) of the sample, but there was no statistically significant difference between the groups and it was not possible to establish an association between presence of this variable and higher risk for developing NMSC.

Considering that the cities of Vale do Paraíba have high UV levels, ranging from 5 (winter months) to more than 13 (summer months)[17], the variable time of residence in Taubaté was included in the study, in an attempt to identify an association between this and a higher risk of developing non-melanoma skin cancer. There was no statistically significant difference between the groups; most individuals (more than 86%) of both groups had lived in Taubaté for more than 10 years and therefore, no association could be established between living in Taubaté and a higher chance of developing NMSC.

Sunlight exposure as a risk factor shows contradictory findings in the literature.

In this study the variables occupational sunlight exposure and non-occupational sunlight exposure were not statistically significant.

On the other hand, the number of hours of occupational sunlight exposure and the number of hours of non-occupational sun exposure showed to be statistically significant, allowing identification of a positive association between these and skin cancer. The variable number of hours of non-occupational exposure to the sunlight, not studied previously, showed to be important, almost doubling the chance of developing non-melanoma skin cancer. It is noteworthy the fact that permanence of these variables, scarcely studied before, differentiates this study from previous ones.

Photoprotection was reported by approximately 48% of the studied sample, a number that is consistent with the findings of Bakos et al.[18], which found similar positivity for sunscreen use in the adult population of their sample. Much of this percentage in this study, however, was due to the use of sunscreen by individuals in the case group (70%), in contrast with only 30% of positivity for sunscreen use by individuals in the control group. This is possibly due to the fact that patients in the case group only use sunscreen after the skin cancer diagnosis.

Family history of skin cancer was highly significant in this study. This finding is similar to those found by Gon[9] and opposes to those of Maia et al.[3]. Two aspects might be involved in this association. First, the genetic factor itself, which is involved in determining the risk of developing these tumors (phenotypic characteristics, hereditary syndromes, genes that determine these tumors). Second, one must consider that by living in the same environment, individuals from the same family are exposed to the same environmental factors and are therefore susceptible to developing the same diseases.

Photodamage was not statistically significant in this sample, contrary to the findings of Rocha et al.[3], where the studied risk markers (*cutis rhomboidalis nuchae*, elastosis, poikiloderma and solar melanosis) were significantly associated with premalignant lesions and NMSC.

The final model included the variables: phototype, number of hours of occupational sunlight exposure, number of hours of non-occupational sunlight exposure and family history of skin cancer.

The variables age, gender and European descent were not included in the final model in spite of their known clinical significance, as we sought to comply with the statistical significance adopted in the methodology.

The model presented very good adjustment, as demonstrated by the Hosmer-Lemeshow test and good accuracy, shown by the ROC curve.

Hence, the present study was able to identify and estimate risk factors: fair skin, number of hours of occupational and non-occupational exposure to sunlight, photoprotection and positive family history for skin cancer as being associated with development of nonmelanoma skin cancer in the city of Taubaté, state of São Paulo, Brazil and identification of a scarcely studied variable, i.e., the number of hours of non-occupational exposure to sunlight.

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