Original Article

Clinical prediction rule for nonmelanoma skin cancer

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ABSTRACT

Background: Skin cancer is the most frequent neoplasia in the world. Even though ultraviolet radiation is the main cause, established prevention campaigns have not proved to be effective for controlling the incidence of this disease. **Objective:** To develop clinical prediction rules based on medical consultation and a questionnaire to estimate the risk of developing nonmelanoma skin cancer. **Methods:** This study was developed in several steps. They were: Identifying risk factors that could be possible predictors of nonmelanoma skin cancer; their clinical validation; developing a prediction rule using logistic regression; and collecting information from 962 patients in a case and control design (481 cases and 481 controls). We developed independent prediction rules for basal cell and squamous cell carcinomas. Finally, we evaluated reliability for each of the variables. **Results:** The variables that made up the final prediction rule were: Family history of skin cancer, history of outdoor work, age, phototypes 1–3 and the presence of poikiloderma of civatte, actinic keratosis and conjunctivitis in band. Prediction rules specificity was 87% for basal cell carcinomas and 92% for squamous cell carcinomas. Inter- and intra-observer reliability was good except for the conjunctivitis in band variable. **Conclusions:** The prediction rules let us calculate the individual risk of developing basal cell carcinoma and squamous cell carcinoma. This is an economic easy-to-apply tool that could be useful in primary and secondary prevention of skin cancer.

Key words: Basal cell carcinoma, clinical prediction rule, dermatology, prevention, skin cancer, squamous cell carcinoma

INTRODUCTION

In Caucasian populations, nonmelanoma skin cancer is the most frequent neoplasia in the world.[1] Basal cell carcinoma is the most common, followed by squamous cell carcinoma. These neoplasias do not lead to a high mortality rate, however, they generate an important morbidity load and high costs for health systems.[2,3]

The main cause of nonmelanoma skin cancer is ultraviolet radiation exposure.[4-6] For this reason, various prevention campaigns have been developed in different parts of the world to teach patients about topics related to photoprotection. Despite these efforts, recent studies show that these measures have not managed to lower the incidence of the disease.[7,8] These campaigns usually include information regarding skin self-examination and skin examination done by the general physician aiming at the early detection of nonmelanoma skin cancer; nevertheless, there is no evidence to indicate that the implementation of self-examination has been useful.[9]

For this reason, it is necessary to look for alternative or additional measures to prevent primary and secondary nonmelanoma skin cancer. One alternative is to use prediction rules to identify variables that give an approximation of the risk of developing nonmelanoma skin cancer. Clinical prediction rules are tools that use the information obtained during medical history, physical exam and paraclinical exams to establish the diagnosis or prognosis of a disease.[10]

The objective of this study was to develop a clinical prediction rule to evaluate the risk of an individual of developing nonmelanoma skin cancer at the time of the medical consultation.

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METHODS

Population

This study was developed in the third level hospital specializing in dermatology, where > 40,000 dermatological

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consults take place. The facility is located in Bogota, Colombia, a city with an elevation of 2600 m above the sea level and an average 14°C temperature all year. Since Colombia is located in the tropics, it has no seasons. The data were collected by dermatologists and students from the dermatology program, who had been previously trained. The measurements were standardized.

The study was developed in several phases. First, we carried out an extensive literature search to identify the risk factors of developing nonmelanoma skin cancer. Then, we created a focal group with experienced dermatologists to clinically validate the risk factors that could be important predictors in our population. After that, using a case and control design, we created a questionnaire that included the selected variables, all of which could be obtained by questioning and by the physical exam. This questionnaire was given to 962 patients, 481 of which had a nonmelanoma skin cancer history (cases) and 481 were controls. We developed a prediction rule for patients with basal cell carcinoma (302 patients) and another one for patients with squamous cell carcinoma (179 patients).

In each case, we obtained the approval and informed consent form from all patients. The study, which complied with national and international ethics regulations, was approved by an Independent Ethics Committee. For the statistical analysis, we performed a descriptive analysis of all the variables and afterwards, a bivariate analysis. To identify the predictors we used logistic regression. We calculated sensitivity and specificity for each one of the proposed models (basal cell carcinoma and squamous cell carcinoma) and we evaluated inter- and intra-observer reliability for each of the variables that made up the prediction rule using kappa statistics.

RESULTS

During the first phase, we identified 19 variables as potential predictors of nonmelanoma skin cancer risk, are shown in Table 1.

We collected information for these variables from 962 patients. The average age was 67 years and 66% of the patients were women. From the total, 63% corresponded to patients with a history of basal cell carcinoma and the other 37% to squamous cell carcinoma. The variables that after the logistic regression were identified as predictors of risk for developing basal cell carcinoma and squamous cell carcinoma are shown in Tables 2 and 3.

The index of prediction for the risk of developing basal cell carcinoma had a sensitivity (measures the proportion of actual positives, which are correctly identified) of 40% and a specificity (measures the proportion of negatives, which are correctly identified) of 87%. This rule correctly identifies 69% of patients at risk of developing basal cell carcinoma.

The index of prediction of the risk for developing squamous cell carcinoma had a sensitivity of 39% and a specificity of 92%, and it correctly identifies 78% of patients at risk.

The reliability for the variables that make up the index are shown in Tables 4 and 5.

Table 1: Variables

Living in a rural area during childhood
Living in a rural area during adulthood
Number of years living a rural area
Outdoor jobs during childhood
Outdoor jobs during adulthood
No use of a hat during outdoor jobs
No use of long-sleeved shirts during outdoor jobs outdoor sports after 30 years of age
Hours per week of sport practice
Number of years of sport practice
No use of physical photoprotection elements (hat and long-sleeved clothes) during sport practice
History of sunburn
Use of sunscreen
Personal history of actinic keratosis
History of treatment of actinic keratosis
Phototype
Presence of actinic conjunctivitis[11]
Presence of poikiloderma
Family history of skin cancer

Table 2: Prediction rule for the risk of developing basal cell carcinoma

Variable	OR[a]	95% CI[b]	*P*
Family history of skin cancer	3.7	1.7-7.9	0.00
Phototype 1-3	4.2	2.5-7.2	0.00
Presence of actinic keratosis	2.7	1.9-4	0.00
Presence of actinic conjunctivitis	2.4	1.5-3.6	0.00
Presence of poikiloderma	1.4	1.0-2.0	0.03
Working outdoors during adulthood (30+years old)	1.4	1.3-2.6	0.00

[a]Odds ratio, [b]95% confidence interval. Hosmer-Lemeshow goodness of fit test: 0.01

Table 3: Clinical prediction rule for the risk of developing squamous cell carcinoma

Variable	OR[a]	95% CI[b]	*P*
Family history of skin cancer	5.7	2.5-13	0.00
Phototype 1-3	1.9	1.1-3.3	0.02
Presence of actinic keratosis	4.9	3.1-7.6	0.00
Presence of actinic conjunctivitis	2.8	1.7-4.7	0.00
Presence of poikiloderma	2.7	1.8-4.1	0.00
Age	1.0	1.0-1.0	0.00

[a]Odds ratio, [b]95% confidence interval. Hosmer-Lemeshow goodness of fit test: 0.35

DISCUSSION

Clinical prediction rules are constructs that combine multiple predictors from the medical history, physical examination or laboratory tests to estimate the probability

Table 4: Inter-observer reliability of the variables that make up the prediction rules

Variable	% agreement	% expected agreement	Kappa
Working outdoors between 15 and 30 years old	86	50	0.72
Presence of actinic keratosis	87	66	0.63
Presence of actinic conjunctivitis	77	65	0.19
Presence of poikiloderma of civatte	70	50	0.41
Family history of skin cancer	97	84	0.85
Phototype	86	76	0.43

Table 5: Intra-observer reliability of the variables that make up the prediction rules

Variable	% agreement	% expected agreement	Kappa
Working outdoors between 15 and 30 years old	86	50	0.72
Presence actinic keratosis	85	64	0.59
Presence of actinic conjunctivitis	84	72	0.43
Presence of poikiloderma of civatte	80	52	0.58
Family history of skin cancer	96	85	0.77
Phototype	87	73	0.54

a certain result has of being present in (diagnosis) or happening to an individual (prognosis).[10,11] In this case, we developed prediction rules related to prognosis (the risk of developing nonmelanoma skin cancer).[12]

There is extensive medical literature regarding prediction rules, but in dermatology it is limited. Concerning skin cancer, there are two prediction rules for early recognition of melanoma: The Asymmetry, Border, Color, Diameter (ABCD) rule (checking moles or growths for ABCD, and Evolving [changing]) and the seven-point checklist developed in the United Kingdom.[13,14] From these, only the ABCD rule has shown a good sensitivity, especially when applied by dermatologists.[15] During the literature review, we did not find publications of prediction rules for nonmelanoma skin cancer, which implies that the rules, we present, are, in all probability, the first rules developed for this pathology.

After identifying the risk factors that could be useful for us as risk predictors reported in the literature, we underwent the process of clinical validation. In other words, we had the participation of experienced dermatologists who evaluated, from the clinical point of view, which of the reported predictors could be the most relevant. In the literature, the importance of clinical validation is emphasized, since there could be a statistically validated rule that is not useful in practice or does not seem to be useful for clinicians.[16] Another advantage, we had, was having risk factors studies performed in our population, which allowed us to come close to the most useful predictors in our context.[6,17]

There were four major groups among the selected predictors: The first is related to sun exposure while working; the second, to recreational sun exposure; the third one, to the use or lack of solar protection physical elements (hats and clothes) for solar protection; and the last one, related to the signs of chronic solar damage detected during the physical exam (poikiloderma of civatte, conjunctivitis in band and actinic keratosis). Multivariate analysis allowed us to identify the strongest predictors. Among these the more prevalent were solar damage signs and sun exposure associated with work; chronic solar damage signs and sun exposure while working taking prevalence. The variables that were not directly related to solar exposure were important predictors for both tumors: Phototypes 1–3 and a family history of skin cancer. In addition, it is possible that the weight of the family history as a predictor is even greater than the one found in this study, taking into account that the interviewed patients are senior citizens and many of them did not know if a family member had had skin cancer.

Even if the predictors were very similar in the case of basal cell carcinoma and squamous cell carcinoma, variables like age were important only for the latter. In addition, the coefficients obtained were different, which made the rule behave differently for each tumor. The prediction rule has an intermediate sensitivity for both basal cell carcinoma and squamous cell carcinoma. Although the specificity is high for both tumors, it is better for squamous cell carcinoma. Thus, the prediction rule for squamous cell carcinoma would be more useful to rule out patients at risk (identifying the individuals with low or minimal risk of developing the tumor).

Based on the foundations of logistic regression, we were able to use its coefficients to turn them into probabilities. As such, if during clinical consultations, we applied the prediction rule, we would be able to obtain the probability (risk) of developing basal cell carcinoma or squamous cell carcinoma for each patient. For example, the patient who answers affirmatively to all the variables that compose the model for basal cell carcinoma has a 95% probability of developing this tumor in the future. On the other hand, the patient that does not have any of the characteristics of the basal cell carcinoma rule has a 4% probability of developing this tumor. This means that doctors could use the prediction rule for each patient in the daily medical and dermatology practice, to identify subjects at a high risk for developing nonmelanoma skin cancer, and teach them about photoprotection. Once they are identified they should be followed closely to detect nonmelanoma skin cancer at an early stage. We considered that this tool would be more useful for general and family physicians who work in primary care, because most of the patients do not have access to a specialist. Dermatologists, having more clinical experience, have a higher probability

of detecting patients at risk without having to use this prediction rule.

This study provides recommendations regarding the development of clinical prediction rules.[10,12,16,18-21] We used a case and control design (possible at this phase), classified cases by histopathology and examined all patients to avoid misclassification biases (undiagnosed nonmelanoma skin cancer controls). One of the weaknesses of this study was the lack of standardization of the variables, which reflects on the low reliability of some of these, especially for an actinic conjunctivitis. This implies that further work is required to accurately define and standardize each of the variables to achieve a better performance of the prediction rules.

Prediction rules are very useful instruments during clinical practice; nonetheless, the development of the rule is just the first step to attain its implementation. In our case, the prediction rule presented herein will need to be evaluated in other contexts (external validation), other hospitals, by other doctors and with other patients. As a conclusion, it is possible to have a low-cost, practical and easy-to-use tool that provides a better approximation to patients concerning primary and secondary prevention of nonmelanoma skin cancer. Nevertheless, we know that this conclusion can only be consolidated if this prediction rule works well in other scenarios.

CONCLUSION

In the construction of the prediction rule the identified predictors are: Outdoor work throughout life, living in rural area after 30 years of age, family history of skin cancer, presence or history of actinic keratosis, presence of band conjunctivitis and presence of poikiloderma of civatte. It was possible to create a prediction rule for risk of nonmelanoma skin cancer associated with sun exposure, with good predictive ability and good reliability.

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REFERENCES

1. Leiter U, Garbe C. Epidemiology of melanoma and nonmelanoma skin cancer – The role of sunlight. Adv Exp Med Biol 2008;624:89-103.
2. Lucas R, McMichael T, Smith W, Armstrong B. Solar Ultraviolet Radiation: Global Burden of Disease from Solar Ultraviolet Radiation. Environmental Burden of Disease Series, No 13. Geneva: World Health Organization; 2006.
3. Viola KV, Jhaveri MB, Soulos PR, Turner RB, Tolpinrud WL, Doshi D, *et al.* Mohs micrographic surgery and surgical excision for nonmelanoma skin cancer treatment in the Medicare population. Arch Dermatol 2012;148:473-7.
4. Narayanan DL, Saladi RN, Fox JL. Ultraviolet radiation and skin cancer. Int J Dermatol 2010;49:978-86.
5. Vlajinac HD, Adanja BJ, Lazar ZF, Bogavac AN, Bjekic MD, Marinkovic JM, *et al.* Risk factors for basal cell carcinoma. Acta Oncol 2000;39:611-6.
6. Sánchez G, Nova J, de la Hoz F. Risk factors for basal cell carcinoma: A study from the national dermatology center of Colombia. Actas Dermosifiliogr 2012;103:294-300.
7. Dodd L, Forshaw M. Assessing the efficacy of appearance-focused interventions to prevent skin cancer: A systematic review of the literature. Health Psychol Rev 2010;4:93-111.
8. Kasparian NA, McLoone JK, Meiser B. Skin cancer-related prevention and screening behaviors: A review of the literature. J Behav Med 2009;32:406-28.
9. Choudhury K, Volkmer B, Greinert R, Christophers E, Breitbart EW. Effectiveness of skin cancer screening programmes. Br J Dermatol 2012;167 Suppl 2:94-8.
10. Toll DB, Janssen KJ, Vergouwe Y, Moons KG. Validation, updating and impact of clinical prediction rules: A review. J Clin Epidemiol 2008;61:1085-94.
11. Rebora I. Actinic prurigo Clinical, histopathologic and considerations of immunology, photobiology and genetics part I. Arch Argent Dermatol 2009;59:89-95.
12. McGinn TG, Guyatt GH, Wyer PC, Naylor CD, Stiell IG, Richardson WS. Users' guides to the medical literature: XXII: How to use articles about clinical decision rules. Evidence-Based Medicine Working Group. JAMA 2000;284:79-84.
13. McGovern TW, Litaker MS. Clinical predictors of malignant pigmented lesions. A comparison of the Glasgow seven-point checklist and the American Cancer Society's ABCDs of pigmented lesions. J Dermatol Surg Oncol 1992;18:22-6.
14. Healsmith MF, Bourke JF, Osborne JE, Graham-Brown RA. An evaluation of the revised seven-point checklist for the early diagnosis of cutaneous malignant melanoma. Br J Dermatol 1994;130:48-50.
15. Strayer SM, Reynolds PL. Diagnosing skin malignancy: Assessment of predictive clinical criteria and risk factors. J Fam Pract 2003;52:210-8.
16. Wallace E, Smith SM, Perera-Salazar R, Vaucher P, McCowan C, Collins G, *et al.* Framework for the impact analysis and implementation of Clinical Prediction Rules (CPRs). BMC Med Inform Decis Mak 2011;11:62.
17. Sánchez G, Nova J. Risk factors for squamous cell carcinoma, a study by the National Dermatology Centre of Colombia. Actas Dermosifiliogr 2013;104:672-8.
18. Wasson JH, Sox HC, Neff RK, Goldman L. Clinical prediction rules. Applications and methodological standards. N Engl J Med 1985;313:793-9.
19. Laupacis A, Sekar N, Stiell IG. Clinical prediction rules. A review and suggested modifications of methodological standards. JAMA 1997;277:488-94.
20. Altman DG, Royston P. What do we mean by validating a prognostic model? Stat Med 2000;19:453-73.
21. Reilly BM, Evans AT. Translating clinical research into clinical practice: Impact of using prediction rules to make decisions. Ann Intern Med 2006;144:201-9.

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