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ORIGINAL ARTICLE

The expression of the protein p53 is suggested as a risk factor for the development of multiple basal cell carcinomas

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ABSTRACT

Background: *The neoplastic transformation of cells is mediated by a set of genes known as oncogenes and tumor suppressor genes. Among these, the following stands out the p53 gene, known as the 'guardian of the genome', plays a crucial role in identifying and preventing the proliferation of cells whose DNA has been altered by mutagenic factors capable of inducing structural changes. By doing so, these factors contribute to the development of malignant transformation, making them carcinogenic agents.*

Objective: *To demonstrate that moderate-high expression of the p53 protein constitutes predictor of multi-localized basal cell carcinoma in patients.*

Patients and methods: *A case-control study was conducted. The population of the study consisted of 42 patients with BCC in different locations. Thus there were 84 patients diagnosed with BCC. single-location (control group) matched by age and by location of the injury (two controls for each patient) with the case group.*

Results: *42 patients with a diagnosis of multi-location BCC were included in the study, the average age at the group of cases was 76.5 years ± 13.8 and in the control group was 77.6 ± 12.4 years for which there was no difference statistically significant (p = 0.653) it should be noted that the variance of ages in both groups was homogeneous (p = 0.653). staining of cell nuclei in immunohistochemistry, it was found that in the case group was 65.3± 19.9 compared with the control group 31.4± 17.7for which there was a statistically significant difference (Student's t-test; p < 0.001).*

Conclusion: *the moderate-high expression of the protein p53 in the initial injury constitutes a risk factor for multiple localization in BCC, in Iraqi patients. Thus, the expression of the p53 protein could be a predictor of the emergence of new BCC.*

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Keywords: ***Basal cell carcinoma, p53 protein, risk factor.***

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1. INTRODUCTION

The neoplastic transformation of cells is mediated by a set of genes known as oncogenes and tumor suppressor genes. Among these, the following stands out the p53 gene, known as the 'guardian of the genome', plays a crucial role in identifying and preventing the proliferation of cells whose DNA has been altered by mutagenic factors capable of inducing structural changes. By doing so, these factors contribute to the development of malignant transformation, making them carcinogenic agents (1-3). The p53 gene is a transcription factor located on the short arm of chromosome (4). The levels increase when cells are exposed to harmful agents such as UV light, radiation, or chemicals that have the ability to cause damage to the DNA molecule. The transcription factor p53 serves as a sensor for this damage. If it determines that the damage is not severe, it initiates the repair process, allowing the cell cycle to continue. However, if the damage is significant, it triggers programmed cell death, also known as apoptosis. If p53 has mutations, these functions cannot be carried out, moreover, more than half of human neoplasms have acquired somatic mutations of p53 (5,6). Skin tumours are the most common type of human neoplasia. Skin cancer has exhibited a gradual increase globally and is a public health issue (7). More than 80% of them correspond to skin cancers not melanoma - basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)–, those who do not have high mortality but they produce a high disability in people (8). The malignant melanoma represents a low percentage, however, due to its aggressiveness it is responsible for the majority of the deaths caused by skin cancer (4,9). The development of non-melanoma skin cancer has three stages: initiation, promotion, and progression, in which UV radiation is implicated as a carcinogenic agent (10). During the initial phase, unrepaired photoproducts resulting from UV radiation can cause mutations in coding regions of oncogenes and tumor suppressor genes. Chronic UV exposure leads to the development of a benign tumor (such as actinic keratosis) formed by the clonal expansion of epidermal cells carrying alterations in several genes, such as the ras proto-oncogene or the p53 suppressor gene. Continuous UV irradiation accelerates tumor progression by selecting clones of cells that are resistant to apoptosis. Prolonged sun exposure also has a secondary carcinogenic effect due to the loss of Fas-l/Fas interaction resulting from the accumulation of mutations in

p53 (11). Ouhtit et al. in 1998 discovered in a case-control study that mutations affecting codons 247 and 248 of the p53 gene, caused by UV radiation, are associated with an increased risk of BCC (4). The conducted literature review has not found any studies that associate the expression of the p53 protein with multiple lesions in BCC.

2. METHODOLOGY

A case-control study was conducted. The population of the study consisted of 42 patients with BCC in different locations. Thus there were 84 patients diagnosed with BCC.

single-location (control group) matched by age and by location of the injury (two controls for each patient) with the case group. The selection criteria they were the following:

A. Case group

Inclusion criteria: Patients of any age and sex with two or more confirmed BCC diagnosed by anatomo-pathological study. Cases with measurement of expression of the p53 protein in the first lesion.

Exclusion criteria: Result of incomplete pathological anatomy, patients with Gorlin syndrome.

B. Control group

Inclusion criteria: Patients with a diagnosis of Single-location BCC confirmed by study anatomo-pathological matched by age and location in a 2:1 ratio with the cases. Cases with measurement of expression of the p53 protein in the single BCC lesion.

Exclusion criteria: Result of pathological anatomy incomplete. No sampling was carried out, we worked with the entire patients in the case-control group who complied with the inclusion and exclusion criteria.

Technique and method

The results of pathological anatomy of lesions were reviewed of skin in the many hospitals, in the period from January 2019 to May 2023, of which 305 cases were obtained that had diagnosis of BCC. Subsequently, the search was made of the patients who had been diagnosed with more of a basal cell carcinoma, which occurred in different locations and at different time periods, a total of 42 cases of multiple BCC were obtained.

The anatomo-pathological reports with diagnosis were reviewed of BCC and the age, gender, location of the injury and the histological type. Then, the sheets were checked anatomo-pathological and the measurement of the expression was carried out of the p53 protein from both the cases and the controls by immunohistochemistry.

For the group of cases is considered the measurement of the expression of the p53 protein in the first of the lesions to appear; while, for the control group the measurement at the single lesion.

Immunohistochemistry

The samples were stained with the strept-avidina biotin method- peroxidase, and the slices were subjected to sequentially to the following:

1) 3% hydrogen peroxide for 10 min;

2) Blocking with inert proteins for 10 min:

3) Murine anti-p53 antibody diluted 1/100 per 20 min;

4) Biotinylated anti-IgG antibody for 10 min;

5) Complex streptavidin-peroxidase for 10 min;

6) Developed with addition of di-amino-benzidine (DAB)-hydrogen peroxide for a long enough time until color change was observed in the controls (about 2 min).

The sheets were washed with distilled water after steps 1 and 6, and with PBS-Triton after steps 3, 4 and 5.

Finally, it was counterstained with Mayer's hematoxylin, dehydrated, rinsed and mounted with Canada balsam.

The positive reaction was evidenced by a brown intranuclear staining. 10 fields were read at 400x magnification and the reactivity was classified as negative (absence of stained nuclei), mild positive (staining of less than 50%), moderate positive (from 50% to 74% of nuclei) and high positive (staining of more than 75%).

Data processing and analysis

The statistical analysis was carried out in the SPSS program version 22.0. A statistical analysis was performed univariate and frequencies were obtained, percentages, measures of central tendency and dispersion. For the analysis bivariate, Pearson's chi-squared test was used and the student's test, after completion of the homogeneity test of Levene variances.

For multivariate analysis, it is a binary logistic regression model was used and it was obtained the adjusted odds ratio (OR) with variable control potentially confusing. The calculations were made with a confidence level of 95%.

Ethical aspects Regarding the ethical aspects, the study did not imply procedures in patients but consisted of the revision of medical records, results of pathological anatomy and reading of the expression of the p53 protein, which is why no informed consent was required. It was guaranteed respect and confidentiality of the information obtained the which has been used only for the purposes of the present study.

3. RESULTS

42 patients with a diagnosis of multi-location BCC were included in the study, the average age at the group of cases was 76.5 years ± 13.8 and in the control group was 77.6 ± 12.4 years for which there was no difference statistically significant (Student's test, p = 0.653) it should be noted that the variance of ages in both groups was homogeneous (p = 0.653). In the case group, the percentage of males and females was 64.3% and 35.7%, respectively; while, in the control group was 76.2% of males and 23.8% of women for which there was no statistical difference significant between the two groups (**Figure 1**). The proportion of patients who by immunohistochemistry had moderate-high intensity of expression of the p53 protein in the case group was 93% (39/42) in comparison with the control group 68% (57/84) for there was a statistically significant difference (p < 0.001). The multivariate analysis with control of the variables age and sex found that the moderate-high expression of the p53 protein was significantly higher in patients with BCC of multiple location, a ratio of possibilities was obtained adjusted of 5.9 (95% CI: 1.6-21.02) (**Table 1**). staining of cell nuclei in immunohistochemistry, it was found that in the case group was 65.3± 19.9 compared with the control group 31.4± 17.7for which there was a statistically significant difference (Student's t-test; p < 0.001) (**Table 2 and Figure 2**).

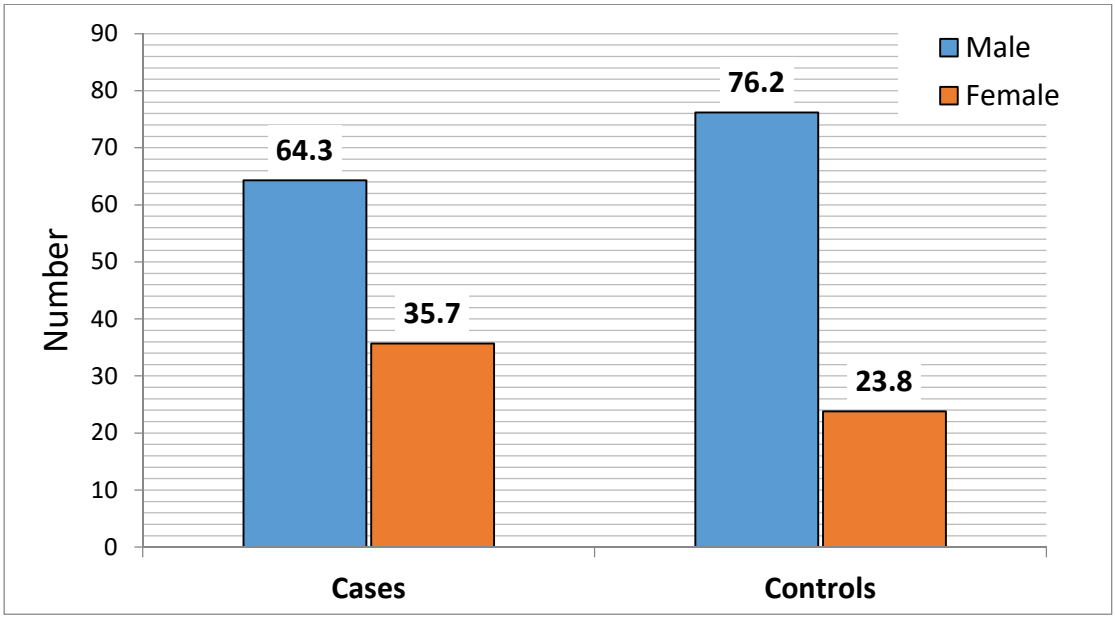

Figure 1. Gender distribution of the studied groups

Table 1. Multivariate analysis of p53 protein expression and potentially confounding variables.

Variable	β	SE	OR	95% CI	
				Lower	Upper
Age	0.573	0.8	1.7	0.3	9.2
Sex	-0.5	0.45	0.6	0.3	1.5
Expression p53 moderate-high	1.8	0.6	5.9	1.6	21.02

Table 2. Difference between P53 protein expression in the studied groups.

Research group	Cases (n= 42)	Control (n=84)	P. value
Mean± SD	65.3± 19.9	31.4± 17.7	< 0.001

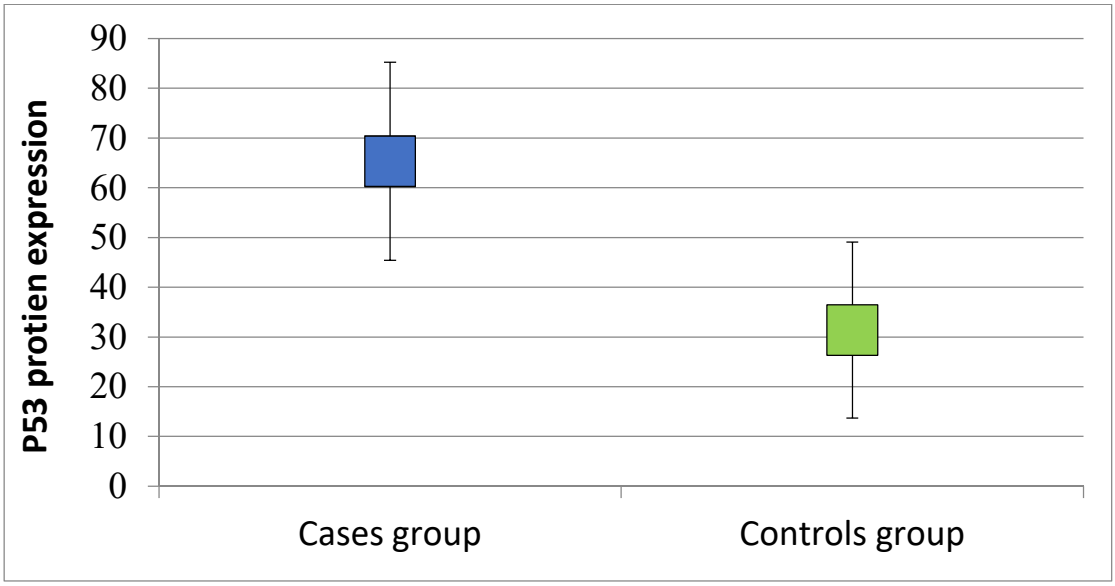

Figure 2. Line-Marker graph for the comparison of P53 in the studied groups

4. DISCUSSION

Skin neoplasms are pathologies of considerable frequency in the dermatological consultation. In Iraq and according to a study carried by AL-Hashimi MM revealed that it ranks 10th among cancers diagnosed in establishments of the Ministry of Health, which entails to patients' disability and high costs for the state (12). Basal cell cancer arises from versatile epithelial cells that have p53 mutations. Activation of the "aberans sonic hedgehog signaling " pathway can leading to mutations in the PTCH gene (13). The p53 gene is very susceptible to alterations caused by sun exposure, leading to the development of skin cancer, particularly basal cell carcinoma. Between the ages of 17 and 20, the protein p53 is involved in regulating the cell cycle. It carries out its tasks by preventing the cell cycle from progressing, promoting programmed cell death (apoptosis), and facilitating DNA repair (14-17). Overexpression of p53 can be triggered by UV light exposure which causes DNA damage. Disruptions in the cell cycle, such as uncontrolled cell proliferation and suppression of the DNA repair mechanism, occur when p53 undergoes mutation or sustains damage. (18,19)

The results indicate that p53 expression can serve as a marker for analysing basal cell carcinoma patients (20,21). Multiple studies have demonstrated the presence of p53 expression in many forms of Basal Cell Carcinoma, each exhibiting varying degrees of aggressiveness. According to the findings, the aggressive group exhibited higher levels of p53

expression. Aupemkiete et al. provided additional support for this study by demonstrating a correlation between p53 expression and the aggressive nature of Basal Cell Carcinoma. Research conducted by Zagrodnik et al. supports the use of p53 expression as a means to assess recurrence following radiation. The presence of this immunoreactivity has been linked to factors that increase the danger of sun exposure and the ageing process. De Rosa et al. discovered no association between p53 immuno-reactivity and either patient age or lesion site. De Rosa and Barrett et al. discovered a notable correlation between the aggressiveness of clinicopathological characteristics and the presence of p53 immuno-reactivity. However, Healy et al. found no notable disparity in the reactivity % among primary basal cell carcinomas that experienced recurrence (22-25). Ultraviolet radiation A and B are involved in the genesis of these neoplasms it is observed that more of 90% of squamous cell epithelial tumors and more than 50% of the BCCs of the population of some countries they have mutations caused by UV radiation in the p53 gene, responsible for tumor suppression (26,27). The present study contrasts the expression of the protein p53 with the appearance of multiple BCC. It was found that patients with moderate-high expression had higher possibility of presenting a BCC with multiple injuries in compared to those who had low expression what could indicate that the expression of the p53 protein could to constitute a predictor of the emergence of new BCC. Although there are studies where it is well evidenced the role of the p53 gene in the genesis of skin tumors in none the mutation is compared in single BCC cases versus multiple (4,28,29). This could justify conducting the study of the expression of the p53 protein to all patients with BCC on his first injury allowing him to take a therapeutic decision in premalignant injuries as well as the closest follow-up program. Prospective research is required that will allow to establish its use as a predictor of multiple injuries of BCC as well as its diagnostic value in terms of sensitivity, specificity and predictive values. A limitation of the study is that, given the retrospective of the research it is not possible to establish that patients with a single lesion have developed additional injuries in the future and that these have been under-registered when being attended to in another establishment. On the other hand, the small number of patients although it is enough has influenced the confidence intervals of the estimates; however, this does not alter the associations found.

5. CONCLUSIONS

The moderate-high expression of the protein p53 in the initial injury constitutes a risk factor for multiple localization in BCC, in Iraqi patients. Thus, the expression of the p53 protein could be a predictor of the emergence of new BCC.

Ethical Approval:

All ethical issues were approved by the author. Data collection and patients enrollment were in accordance with Declaration of Helsinki of World Medical Association , 2013 for the ethical principles of researches involving human. Signed informed consent was obtained from each participant and data were kept confidentially.

6. BIBLIOGRAPHY

1. *Rivlin N, Brosh R, Oren M, Rotter V. Mutations in the p53 tumor suppressor gene: important milestones at the various steps of tumorigenesis. Genes & cancer. 2011 Apr;2(4):466-74.*
2. *Martínez-Jiménez F, Muiños F, Sentís I, Deu-Pons J, Reyes-Salazar I, Arnedo-Pac C, Mularoni L, Pich O, Bonet J, Kranas H, Gonzalez-Perez A. A compendium of mutational cancer driver genes. Nature Reviews Cancer. 2020 Oct;20(10):555-72.*
3. *Feroz W, Sheikh AM. Exploring the multiple roles of guardian of the genome: P53. Egyptian Journal of Medical Human Genetics. 2020 Dec;21(1):1-23.*
4. *Ouhtit A, Nakazawa H, Armstrong BK, Kricker A, Tan E, Yamasaki H, et al. UVradiation-specific p53 mutation frequency in normal skin as a predictor of risk of basal cell carcinoma. J Natl Cancer Inst. 1998;90(7):523-31.*
5. *Ghaderi R, Haghighi F. Immunohistochemistry Assessment of p53 protein in basal cell carcinoma. Iran J Allergy Asthma Immunol. 2005;4(4):167-71.*
6. *Salamanca-Gómez F. Células troncales, cáncer y p53. Gac. Méd Mex. 2009; 145(5):441-2.*
7. *Gallagher RP. Sunscreens in melanoma and skin cancer prevention. CMAJ.2005;173(3):244-5.*
8. *Miller DL, Weinstock MA. Nonmelanoma skin cancer in the United States: incidence. J Am Acad Dermatol. 1994;30:774-8.*
9. *Nova Villanueva JA. Carcinoma basocelular, un problema de salud pública. Bol Dermatol. 2013;11(1):2-3.*
10. *Trager MH, Geskin LJ, Samie FH, Liu L. Biomarkers in melanoma and non-melanoma skin cancer prevention and risk stratification. Experimental dermatology. 2022 Jan;31(1):4-12.*

11. Cabrera-Morales CM, Lopez-Nevot MA. Efectos de la radiación ultraviolet en la inducción de mutaciones de p53 en tumores de piel. Oncología. 2006;29(7):291-8.

12. AL-Hashimi MM. Trends in skin cancer Incidence in Iraq during the period 2000-2019.

13. Janic A, Valente LJ, Wakefield MJ, Di Stefano L, et al. DNA repair processes are critical mediators of p53-dependent tumor suppression. Nature Med. 2018; 24(7): 947- 53.

14. Kim S, Seong SA. Role of p53 isoforms and aggregations in cancer. Medicine. 2016; 95(26): 1345-9.

15. Mondal, Abdul M, Hua Zhou, Izumi Horikawa, Frank A., et al. "Δ133p53α, a natural p53 isoform, contributes to conditional reprogramming and long-term proliferation of primary epithelial cells." Cell death & disease. 2018; 9(7): 1-14.

16. Martens, Marie Christine, Christina Seebode, Janin Lehmann, and Steffen Emmert. "Photocarcinogenesis and skin cancer prevention strategies: an update." Anticancer research. 2018; 38(2): 1153-1158.

17. Chen, J. The cell-cycle arrest and apoptotic functions of p53 in tumor initiation and progression. Cold Spring Harbor perspectives in medicine. 2016; 6(3):145-9.

18. Perri, Francesco, Salvatore Pisconti, and Giuseppina Della Vittoria Scarpati. "P53 mutations and cancer: a tight linkage." Annals of translational medicine. 2016; 16(4):110-8

19. Batinac T, Zamolo G, Jonjić N, Gruber F, Petrovecki M. P53 protein expression and cell proliferation in non-neoplastic and neoplastic proliferative skin diseases.Tumori. 2004; 90(1): 120-7.

20. Khodaeiani E, Fakhrjou A, Amirnia M, Babaei Nezhad S, Taghvamanesh F, et al. Immunohistochemical evaluation of p53 and Ki67 expression in the skin epithelial tumors.Indian J Dermatol. 2013; 58(3): 181- 7.

21. Sunjaya, AP, Sunjaya, AF, & Tan, ST The use of BEREP4 immunohistochemistry staining for detection of basal cell carcinoma. Journal of Skin Cancer. 2017; 32(4):123-8.

22. Zagrodnik B, Kempf W, Seifert B, et al. Superficial radiotherapy for patients with basal cell carcinoma: recurrence rates, histologic subtypes, and expression of p53 and Bcl-2. Cancer 2003; 98: 2708-14.

23. De Rosa G, Staibano S, Barra E, Donofrio V, Salvatore G, Vessecchia G, Boscaino A. p53 protein in aggressive and non-aggressive basal cell carcinoma. Journal of cutaneous pathology. 1993 Oct;20(5):429-34.

24. Monsef A, Ansar A, Behnoud S, Monsef F, & Esmaeili R. Frequency of P53 immunohistochemical expression in all histopathological types of basal cell carcinoma and its correlation with clinicopathological features. Life Sci J. 2012; 9:106-111

25. Chakramurty A, Astuti MD, Istiadi H, Prasetyo A, Puspasari D. Profile of p53 Protein Expression in Basal Cell Carcinoma Low-Risk and High-Risk Subtype. Bioscientia Medicina: Journal of Biomedicine and Translational Research. 2022 May 9;6(6):1951-8.

26. Autier P. Skin cancer and enviromental factors. Rev Medic Brux. 1998;19(4):A346-50

27. Brash De, Ziegler A, Jonason AS, Simon JA, Kunala S, Leffell DJ. Sunlight and sunburn in human skin cáncer: p53, apoptosis and tumor promotion. J Invest Dermatol Symp Proc. 1996;1(2):136-42.

28. McGregor JM, Harwood CA, Brooks L, Fisher SA, Kelly DA, O'nions J, et al. Relationship between p53 codon 72 polymorphism and susceptibility to sunburn and skin cáncer. J Invest Dermatol. 2002;119(1):84-90.

29. Sánchez Vanegas G, Nova J, de la Hoz F. Factores de riesgo de carcinoma basocelular. Un estudio del Centro Nacional de Dermatología de Colombia. Actas Dermosifiliogr. 2012;103(4):293-300.

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