



Expression of RXR- α in Cutaneous Squamous and Basal Cell Carcinoma

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Abstract

Non-melanoma skin cancer (NMSC) includes various tumors, mainly basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC), the most common skin cancers. NMSC are classified into high and low risk groups according to anatomical site and other histopathological criteria. Aim of Study: This study aimed to first: evaluate immunohistochemical (IHC) expression of retinoid x receptor- α (RXR- α) in BCC and cSCC. Second: correlate IHC expression of RXR- α to different clinico-pathological parameters including age, sex, associated inflammation, tumor site, BCC histopathological variants, and cSCC tumor grade. Patients and Methods: This study included 30 cases of BCC and 20 cases of cSCC were tested for RXR- α immune-reactivity scoring system (IRS) based on the percentage positivity and staining intensity. Results: RXR- α expression was detected in 37/50 of all studied cases. Thirty-seven cases showed variable degree of RXR- α expression which was localized to the nucleus. Reduction of RXR- α expression in BCC cases ≥ 60 years old and associated inflammation. No significant difference was found regarding patient's sex, nature of specimen, histo-pathological variants, risk of recurrence and anatomical sites (p-value >0.05). Reduction of nuclear RXR- α expression was observed in cSCC cases associated with sun exposure, high-risk features, and inflammation. No significant difference was found regarding patient's age, sex, nature of specimen (p-value >0.05). Conclusion: A significant negative linear correlation between nuclear RXR- α expression and cSCC tumor grade support it as a potential prognostic marker in cSCCs. No significant linear correlation was detected between nuclear RXR- α expression and BCC risk of recurrence.

Keywords : BCC, cSCC, RXR- α and NMSC.

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Introduction

Skin tumors represent 4.78% of primary malignant tumors among Egyptian patients.¹¹ NMSC comprises a heterogeneous group of tumors that is mainly represented by BCC and cSCC as the most common skin malignancies.) 2 (Ultraviolet radiation (UVR) exposure can activate various oncogenes while inactivating tumour suppressor genes, leading to gene mutations, which induces the survival and proliferation of keratinocytes.¹³

The RXR- α plays a crucial role as an obligatory partner of several nuclear receptors. Its role as a transcription factor is thus critical in many signalling pathways, such as metabolism, cell development, differentiation and cellular death.¹⁴ The ligands of RXR- α are retinoids, which are defined as either synthetic or natural derivatives of vitamin A.¹⁵

Retinoids promote apoptosis and regulate signaling pathways that are essential to the pathophysiology of BCC cells, which is how they achieve their anti-cancer effects.¹⁶ One way that retinoids can prevent the development of cSCC is through suppressing AP-1 activation.¹⁷

Patients and Methods

Sample collection: This retrospective analysis includes 50 cases: 20 of cSCC and 30 of BCC. From 2017 to 2021, all specimens were formalin-fixed paraffin-embedded tissue blocks that were gathered from the Pathology Department Lab at Sohag University's Faculty of Medicine. The 50 patients under study were divided into two groups: low-risk and high-risk. Among the low-risk lesions, which accounted for 34 out of the 50 cases, there were 13 cases of nodular BCC, 6 cases of pigmented BCC, 1 case of superficial spreading BCC, 7 cases of well-differentiated cSCC, and 7 cases of moderately differentiated cSCC. Among the high-risk lesions (16/50), there were 6 cases of poorly differentiated cSCC, 4 cases of micronodular BCC, 4 cases of morpheiform BCC and 2 cases of basosquamous BCC.

Immunohistochemistry: Reagents used were RXR- α (3B5) monoclonal antibody (Bioss,

Catalog number bsm-54427R, Boston, USA) at a dilution of 1:100, overnight at 4 °C. The Universal Staining Kit (UltraTek HRP Anti-Polyvalent Lab Pack; #UHP125; ScyTek Laboratories, Inc.) contains a biotinylated goat anti-polyvalent secondary antibody. Streptavidine peroxidase, hydrogen peroxide block, diaminobenzidine (DAB) chromogen, and DAB substrate are among its constituents. Mayer's hematoxylin was used for staining, and DPX was used as the mounting medium.

Immunohistochemical scoring: In each example, the nuclear expression of RXR- α was assessed independently from the immune-stained tissue sections. An established immune-reactivity scoring method (IRS) was used to assign scores to the immunostained sections. The RXR- α immune-expression intensity was graded as follows: 0 for negative staining, 1 for weak, 2 for moderate, and 3 for strong. The following scores were assigned to the percentage of positive tumor cells: 0 = 0%, 1 < 10%, 2 (10–50%), 3 (51–80%), and 4 (>80%). The intensity score and the percentage score of positive cells were multiplied to determine the final result. The IRS that resulted was classified as mild (1–4), moderate (6–8), intense staining (9–12), and negative (0).¹⁸

Statistical analysis: Data was analyzed using Statistical Package for Social Sciences (SPSS) 16 for Windows.

Results:

Demographic data:

The mean $\pm$ SD for patients' age was 59.74 $\pm$ 11.4. Most of the patients were males 29/50 (58%) while 21/50 (42%) were females, with male: female ratio (M/F) 1.4: 1.

IHC expression of RXR- α in the studied cases:

Among 50 studied cases, normal stratified squamous epithelium was included in 11 cases. Thirty-seven cases showed variable degree of RXR- α expression which was localized to the nucleus.

Table 1: Histopathological findings

Cases	Risk of recurrence	Histological classification		Frequency	Total	Percent %
BCC (n=30)	Low risk	Nodular	Classic nodular	5	20	40%
			Keratotic	3		
			Nodulocystic	3		
			Adenoid cystic	2		
		Pigmented		6		
		Superficial spreading		1		
	High risk	Micronodular		4	10	20%
		Morphoeic		4		
		Basosquamous		2		
SCC (n=20)	Low risk	Well differentiated		7	14	28%
		Moderately differentiated		7		
	High risk	Poorly differentiated		6	6	12%

Table 2:RXR- α expression and immunohistochemical findings

Risk of recurrence	Score				Total
	Negative	Mild	Intermediate	High	
Low risk BCC	5	3	10	2	20
High risk BCC	3	2	3	2	10
Low risk SCC	1	2	3	8	14
High risk SCC	4	1	1	0	6
Total	13 (26%)	8 (16%)	17 (34%)	12 (24%)	50 (100%)

Table 3: The relation between RXR- α expression in the studied BCC and clinicopathological findings

Parameters	Score				Total	p-value
	Negative	Mild	Moderate	Strong		
Age						
<60	1	2	10	1	14	0.025*
≥60	7	3	3	3	16	
Sex						
Male	4	3	8	3	18	0.868 (NS)
Female	4	2	5	1	12	
Nature						
Mass	2	1	2	1	6	0.948 (NS)
Ulcer	6	4	11	3	24	
Inflammation						
Absent	8	2	9	4	23	0.05*
Present	0	3	4	0	7	
Risk of recurrence						
Low risk	5	3	10	2	20	0.734 (NS)
High risk	3	2	3	2	10	
Anatomical sites						
- Cheek	3	2	3	0	8	0.509 (NS)
- Forehead	1	1	2	2	6	
- Eye canthus	3	1	4	0	8	
- Nose	1	0	2	2	5	
- Ear	0	1	2	0	3	

Chi-square test was used, * = Significant, NS= Not significant.

Table 4: The relation between RXR- α expression in the studied cSCC and clinicopathological findings

Parameters	Score				Total	p-value
	Negative	Mild	Moderate	Strong		
Age						
<60	1	1	2	4	8	0.708 (NS)
≥ 60	4	2	2	4	12	
Sex						
Male	4	2	1	4	11	0.397 (NS)
Female	1	1	3	4	9	
Nature						
Mass	2	1	0	2	5	0.563 (NS)
Ulcer	3	2	4	6	15	
Inflammation						
Absent	0	0	2	6	8	0.022*
Present	5	3	2	2	12	
Site						
Sun exposed	5	3	3	2	13	0.018*
Non sun exposed	0	0	1	6	7	
Risk of recurrence						
Low risk	0	3	3	8	14	0.001*
High risk	5	0	1	0	6	

Chi-square test was used, * = Significant, NS= Not significant.

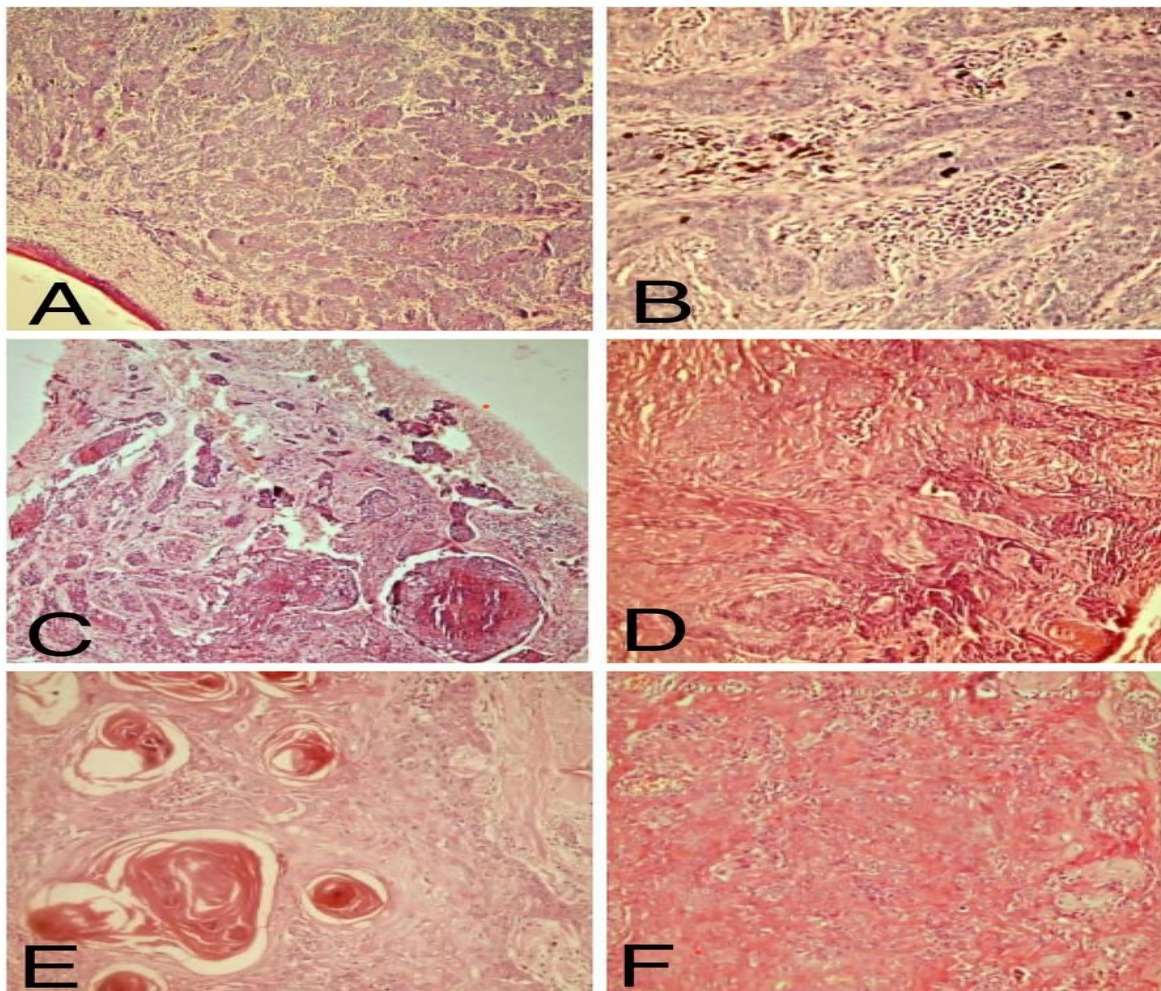


Figure (1): H&E stain of nodular BCC (x100) (A), pigmented BCC (x200) (B), micronodular BCC (x100) (C), basosquamous BCC (x200) (D), well differentiated cSCC (x200) (E) and moderately differentiated cSCC(x200) (F).

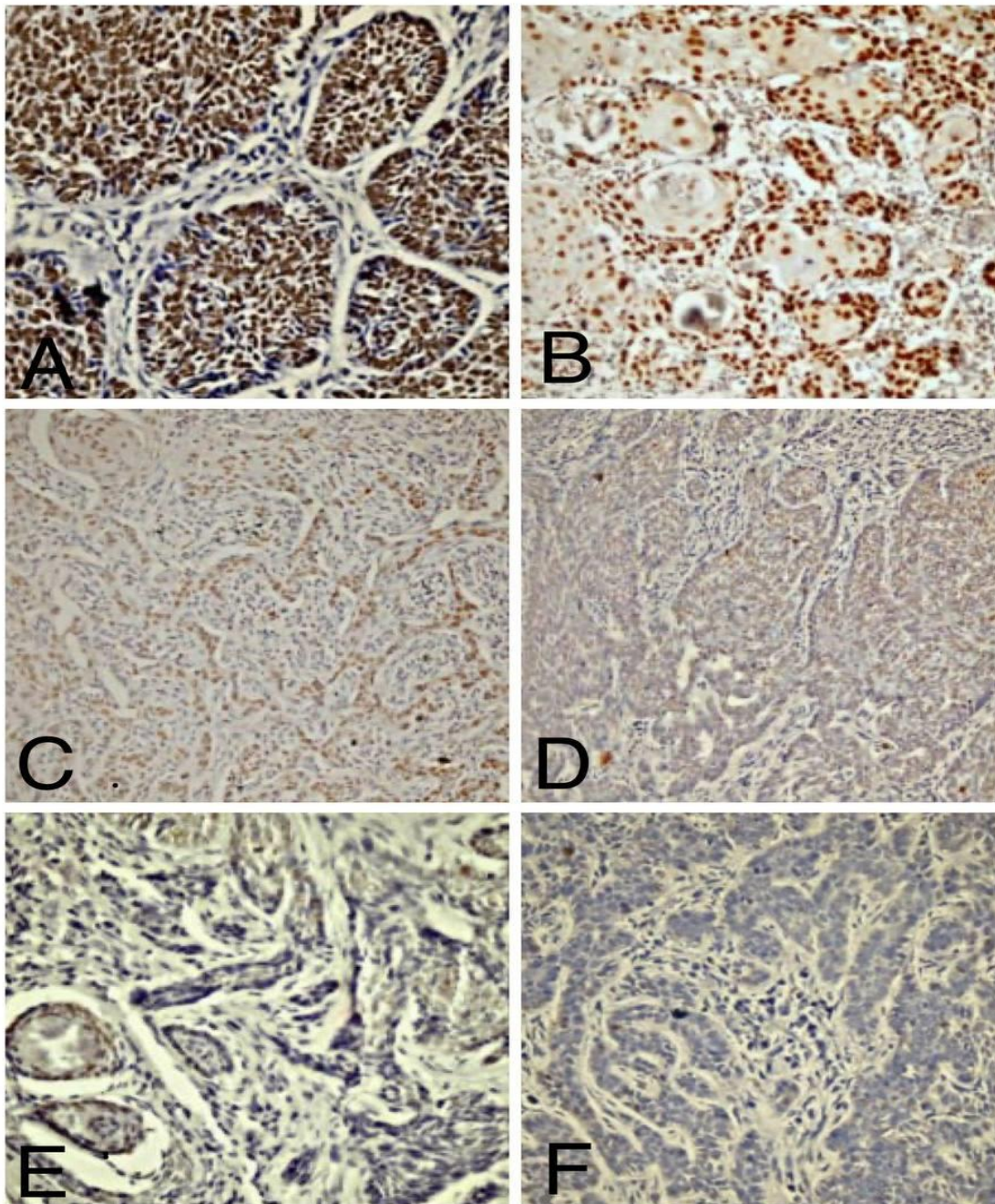


Figure (2): Nodular BCC (x400) (A) and moderately differentiated cSCC (x200) (B), Strong nuclear RXR- α expression. Moderately differentiated cSCC (x200) (C) and morphoeic BCC (x200) (D), moderate expression. Basosquamous BCC (x400) (E), mild expression. Micronodular BCC (x400) (F), negative nuclear expression.

Discussion

This study was concerned with studying the expression of RXR- α in BCC and cSCC in a group of Egyptian patients. In the current study, thirty-four cases were low risk, twenty BCC cases and fourteen cSCC cases. According to low-risk BCC, nodular type BCC cases were 13/30, pigmented 6/30 and only one case was superficial spreading. This is close to some researchers who

revealed that the nodular variant accounts for the majority of cases.⁹⁽

Regarding the anatomical site, 13/20 of the cSCC cases were discovered in places exposed to sunlight, whereas all 30 BCC cases were limited to the head region. Similar results were shown by previous studies, indicating that the face was the most afflicted area (69.5%) and that sun-exposed

skin also had 67.9% of all cSCCs, with the face being the most affected (30.5%).^{10,11} Similar findings were made by another study, which found that outdoor workers had a 77% higher risk of cSCC and a 43% higher risk of BCC than populations that were not exposed to outdoor employment.¹²

The severity of cSCC was shown to be significantly correlated with sun exposure in this study (p-value = 0.002). This can be explained by the fact that long-term exposure to the sun results in changes in cellular DNA that may eventually induce unchecked growth, tumor formation, and cutaneous immune suppression that may prevent tumor rejection.¹³

In the current study, there was a significant relationship between cases of BCC above 60 years old and reduction of RXR- α expression (p-value = 0.039). According to previous reports, the face and neck areas show the most obvious aging symptoms throughout time because they experience a mix of photoaging and chronological aging.¹⁴ Additionally, epidermal and dermal thinning is a noticeable aspect of aging in older people, which significantly impairs skin functionality and reduces the response of keratinocytes due to fewer nuclear retinoid receptors.¹⁵

The current study revealed that 22/30 BCC cases showed variable RXR- α expression localized in cell nuclei, with mild expression in 5 cases, moderate in 13 cases and strong in 4 cases. This result is close to what was reported by another study, which found positive expression of RXR- α in 73.5% of BCC cases.¹⁶

This study showed a significant relationship between the reduction of RXR- α nuclear expression and the presence of severe inflammation in BCC cases (p-value = 0.05) and cSCC cases (p-value = 0.022). It was reported that the activation of inflammatory processes is involved in carcinogenesis of NMSC as well as stimulation of cancer cell proliferation and invasion.¹⁷ Another study found that nuclear RXR- α protein levels were significantly reduced in hepatocytes in association with inflammation.¹⁸ In contrast, others found no significant relationship between inflammatory cytokines and alteration of RXR- α intracellular distribution in Schwann cells.¹⁹

Regarding cSCC cases, the current study showed a significant relationship between RXR- α

expression and sun exposure (p-value = 0.018). There is a reduction in RXR- α nuclear expression in sun-exposed areas. These results were close to what was reported previously, that UVR affects the function of nuclear retinoid receptors and significantly reduces both the mRNA and protein levels of RXR- α .²⁰

RXR- α nuclear expression was shown to be lower in high-risk and poorly differentiated SCC cases in the current investigation. Similar results were also reported by other researchers, who found that retinoid receptors and retinoic acid (RA) are altered in cSCC, with higher amounts observed in the early stages of the disease and lower levels as it advances.²¹ Less differentiation, increased proliferation, and eventually more severe cSCC could result from this decreased RA.

Conclusion:

A significant negative linear correlation between nuclear RXR- α expression and cSCC tumor grade support it as a potential prognostic marker in cSCCs. No significant linear correlation was detected between nuclear RXR- α expression and BCC risk of recurrence.

Abbreviation list:

NMSC: Non-melanoma skin cancer

BCC: Basal cell carcinoma

cSCC: Cutaneous squamous cell carcinoma

IHC: Immunohistochemistry

RXR- α : Retinoid x receptor- α

IRS: Immune-reactivity scoring system

UVR: Ultra violet radiation

DAB: Diaminobenzidine

SD: Standard deviation

RA: Retinoic acid.

Ethical consideration:

Ethical approval was taken from the Ethical Committee of Faculty of Medicine, Sohag University with approval number is (IRB00013006), and registration number of clinical trial is Soh-Med-22-09-05.

Consent for publication:

Informed consent for publication was obtained from all authors

Availability of data and material:

All data are included within the article

Conflict of interest

All authors have approved this article and declare no conflicts of interest

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