Dermatology Practical & Conceptual

Impact of Rosacea on Keratinocyte Skin Cancers: A Prospective Case-Control Study of Basal and Squamous Cell Carcinoma Risk

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ABSTRACT

Introduction: The full range of cutaneous comorbidities associated with keratinocyte skin cancers remains to be elucidated.

Objectives: We aimed to examine other skin diseases in patients with keratinocyte cancer (KC) and to reveal potential associations between them.

Methods: Included in the study were 200 patients with KC and 200 disease-free controls. To identify any additional concomitant dermatological conditions, all study groups underwent examination by two dermatologists.

Results: In patients with KC, 87.5% were diagnosed with basal cell carcinoma and 13.5% were diagnosed with squamous cell carcinoma. There was no statistically significant difference between the two groups regarding sunscreen use habits (P =0.284). Patients with KC exhibited a significantly elevated odds ratio (OR) for the presence of rosacea (OR 5.13, 95% CI: 3.2–8.3, P=0.000) and especially erythematotelangiectatic rosacea (ETR) subtype (OR 5.03, 95% CI: 3.1–8.2, P=0.000). An Receiver Operating Characteristic (ROC) curve analysis was conducted to assess the efficacy of rosacea in differentiating between the control group and patients with KC. The sensitivity, specificity, negative predictive value, and positive predictive value for rosacea were 45.5%, 86%, 61.2%, and 76.5%, respectively (AUC 0.658, 95% CI: 0.604–0.711, P=0.000), while for ETR it was 44%, 86.5%,

60.7%, and 76.5%, respectively (AUC 0.653, 95% CI: 0.599–0.706, *P*=0.000). The presence of rosacea demonstrated a significant efficacy in differentiating patients with KC from the control group in all localizations (*P*< 0.05).

Conclusion: The risk of rosacea in patients with KC, particularly those with the ETR subtype, was found to be significantly elevated, irrespective of age, sex, or localization.

Introduction

Keratinocyte skin cancers represent the most prevalent form of cancer globally. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) collectively account for 99% of all keratinocyte cancers (KCs) [1]. The prevalence of KCs is higher among the elderly, and as the proportion of the global population aged 60 and above continues to grow, these cancers are becoming a significant burden on healthcare systems worldwide [2]. A more comprehensive understanding of the etiology of KCs may facilitate more effective treatment and prevention strategies. Predisposing factors include fair skin type, ultraviolet radiation (UVR), immunosuppression, and certain genetic syndromes as well as the human papilloma virus, particularly in the case of SCC. Additionally, exposure to chemicals such as arsenic, chronic ulcers, and burn scars may contribute to the development of these cancers [1]. However, the available data on the relationship between KCs and other cutaneous diseases are limited.

In recent years, studies have investigated the relationship between KCs and rosacea. However, the results of these studies were inconsistent. Egeberg et al. conducted an epidemiological study to investigate the incidence of cancer in patients with previously diagnosed rosacea compared with the general population [3]. Their 4-year follow-up revealed an increased risk of non-melanoma skin cancer (NMSC), breast cancer, and liver cancer in rosacea patients. In a systematic analysis of the association between rosacea and cancer in US women, Li et al. found that patients with a history of rosacea exhibited an elevated risk of thyroid cancer and BCC [4]. However, Dupont et al. identified no significant correlation between rosacea and the occurrence of skin cancers [5]. Furthermore, Lin et al. proposed that a history of rosacea may act as a protective factor against the development of facial BCC [6].

Objectives

In light of the inconclusive nature of these findings, our objective was to examine the presence of cutaneous comorbidities in patients with KC and ascertain whether they are associated.

Methods

Participants and Protocol

This prospective case-control study was conducted in a single center from September 2023 to May 2024, at the Department of Dermatology. The study was approved by the Institutional Ethics Committee (approval number: 4493). All aspects of the study were conducted in accordance with the latest version of the Helsinki Declaration and the Guidelines for Good Clinical Practice.

The study population comprised the KCs group, which was recruited from patients admitted to the dermatology outpatient clinic. The control group consisted of age- and sex-matched volunteers consisting of patients' relatives.

The diagnosis of the KC in patients was made based on clinicopathological criteria. The following details were recorded: the histological type of BCC, the site of localization, the number of lesions, the patient's skin type, their family history, and their habits concerning using sunscreen. Both the patient group with KC and the control group underwent examination by two dermatologists to identify any additional concomitant dermatological conditions. The study included participants aged 18 years and above. Participants with a syndrome known to cause KC, a history of organ transplantation, a confirmed HIV diagnosis, a history of arsenic and chemical exposure, users of photosensitizing drugs, patients with a history of phototherapy, and patients receiving immunosuppressive therapy were excluded from the study.

Statistical Analysis

The statistical analyses were conducted using the SPSS 28.0 software. Descriptive statistics were performed on the data using mean, standard deviation, median, minimum, maximum, frequency, and ratio values. The distribution of the variables was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Mann-Whitney U test was employed to analyze quantitative independent data exhibiting a non-normal distribution. The chi-squared test was employed to analyze qualitative independent data, while the Fischer test was utilized in instances where the conditions for the chi-squared test were not met. The effect level and cutoff value were subjected to analysis via the ROC curve. The effect level

was analyzed using univariate and multivariate logistic regression. Statistically significant was defined as $P<0.05$.

Results

A total of 200 patients and 200 controls were included in the study. There were no significant differences between cases and controls regarding age, sex, skin type, or race/ethnicity (all $P>0.05$). In patients with KC, 175 patients (87.5%) were diagnosed with BCC and 27 patients (13.5%) were diagnosed with SCC. Subtype analysis revealed that 132 (66.0%) of patients with BCC had nodular BCC, 34 (17.0%) had infiltrative BCC, 19 (9.5%) had superficial BCC, five (2.5%) had adenoid BCC, one (0.5%) had morpheaform BCC, one (0.5%) had pigmented BCC, and four (2.0%) had basosquamous carcinoma. Eighteen of these patients (9.0%) had multiple BCC with different histological types. Three (1.5%) patients also had both BCC and SCC. The majority of KCs were localized on the face (n=153, 76.5%), followed by the trunk (n=22, 11.0%), scalp (n=15, 7.5%), ear (n=6, 3.0%), neck (n=6, 3.0%), lower extremity (n=6, 3.0%), and upper extremity (n=5, 2.5%). The majority of the patients presented with a single lesion (n=165, 82.5%), while 23 (11.5%) had two lesions, 10 (5.0%) had three lesions, one (0.5%) had four lesions, and one (0.5%) had five lesions. While 188 (94.0%) of the patients had no family history, 12 (6.0%) of the patients had a family history of KC. There was no statistically significant difference between the two groups regarding sunscreen use habits ($P=0.284$) (Table 1). Table 2 illustrates the prevalence of other dermatological conditions observed in patients with KC and control subjects. In comparison to the control group, those with KC were more likely to have rosacea (54.5% vs 14%, $P=0.000$), dysplastic nevi (2.5% vs 0%, $P=0.024$), and Bowen's disease (2.5% vs 0%, $P=0.024$). Patients with KC exhibited a significantly elevated odds ratio for the presence of rosacea (OR 5.13, 95% CI: 3.2–8.3, $P=0.000$) and erythematotelangiectatic rosacea (ETR) (OR 5.03, 95% CI: 3.1–8.2, $P=0.000$) (Table 2). In the control group, solar lentigo, xerosis cutis, dermal nevi, and lichen simplex chronicus were significantly higher ($P=0.013$, $P=0.000$, $P=0.043$, and $P=0.044$, respectively). A ROC curve analysis was conducted to assess the efficacy of rosacea in differentiating between the control group and patients with KC. The sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) for rosacea were 45.5%, 86%, 61.2%, and 76.5%, respectively (AUC 0.658, 95% CI: 0.604–0.711, $P=0.000$), while for ETR it was 44%, 86.5%, 60.7%, and 76.5%, respectively (AUC 0.653, 95% CI: 0.599–0.706, $P=0.000$) (Figure 1).

The effectiveness of the presence of rosacea in terms of age, sex, family history, skin type, tumor type, and localization in differentiating patients with KC from the control group was examined. The results demonstrated a significant efficacy of rosacea in differentiating patients with KC from the control group in both patients under and those over 65 years of age (OR 4.5, 95% CI: 2.1–9.6, $P=0.000$ and OR 5.5, 95% CI: 2.9–10.4, $P=0.000$, respectively). Significant efficacy of rosacea in differentiating between KC patients and the control group was observed in both females and males (OR 4.67, 95% CI: 2.4–9.1, $P=0.000$ and OR 5.99 95% CI: 2.9–12.4, $P=0.000$, respectively). In the group with a family history, the presence of rosacea was found to be significantly effective in differentiating between the KC and control groups (OR 12.29, 95% CI: 3.5–43.5, $P=0.000$). In the group with skin types II and III, the presence of rosacea was found to be significantly effective in differentiating between patients with KC and the control group (OR 5.72, 95% CI: 2.9–11.1, $P=0.000$ and OR 5.27, 95% CI: 2.0–13.7, $P=0.001$, respectively). The presence of rosacea in BCC, nodular BCC, infiltrative BCC, adenoid BCC, and SCC, as determined by histopathological type, demonstrated a significant efficacy in differentiating between patients with cancer patients and the control group (OR 4.8, 95% CI: 2.9–7.9, $P=0.000$; OR 4.67, 95% CI: 2.8–7.9, $P=0.000$; OR 6.14, 95% CI: 2.8–13.4, $P=0.000$; OR 24.57, 95% CI: 2.6–58, $P=0.005$; OR 10.44, 95% CI: 4.3–25.1, $P=0.000$, respectively). The presence of rosacea demonstrated a significant efficacy in differentiating between patients with KC and the control group in all localizations ($P<0.05$) (Figure 2).

Discussion

The present study revealed a robust positive association between KCs and rosacea. It is established that UVR represents a significant risk factor for the development of skin cancers. Furthermore, there is compelling evidence to suggest that UVR plays an important role in the pathogenesis of rosacea, with the production of reactive oxygen species and the expression of cathelicidin (in particular, LL-37) being of particular importance [7]. LL-37 may modulate the pro-inflammatory effects of UVR, thereby contributing to increased sensitization to sun exposure in rosacea patients [8]. It is hypothesized that patients with rosacea have an altered skin barrier and are more susceptible to higher levels of UV exposure at an early age, which may increase their risk of developing skin cancers such as SCC and BCC [3,4,9]. Chronic sunlight exposure has been demonstrated to impair the capacity of cells to repair damage to their DNA. Patients with KC have been shown to exhibit a decreased capacity for DNA repair. Pathogen-associated molecular patterns (PAMPs) derived from Bacillus oleronius or Demodex mites have been proposed to contribute to the pathogenesis of

Table 1. Demographic and Clinical Characteristics of the Study Groups.

		KCs (n=200)					Controls (n=200)				P	
Age (years) mean±SD (med)		68.2	±	13.3	(70.0)		65.5	±	14.2	(67.0)	0.059	[m]
Age (years) (n/%)	≤ 50	24		12.0%			27		13.5%		0.419	X^2
	51-65	56		28.0%			66		33.0%			
	66-96	120		60.0%			107		53.5%			
Sex (n/%)	Female	87		43.5%			106		53.0%		0.057	X^2
	Male	113		56.5%			94		47.0%			
Skin type (n/%)	II	94		47.0%			79		39.5%		0.098	X^2
	III	87		43.5%			89		44.5%			
	IV	19		9.5%			32		16%			
Sunscreen use (n/%)	(-)	194		97.0%			198		99.0%		0.284	X^2
	(+)	6		3.0%			2		1.0%			
Family history (n/%)	(-)	188		94.0%								
	(+)	12		6.0%								
Type of KCs (n/%)												
BCC		175	87.5%									
Nodular BCC		132	66.0%									
Infiltrative BCC		34	17.0%									
Morpheaform BCC		1	0.5%									
Superficial BCC		19	9.5%									
Adenoid BCC		5	2.5%									
Pigmented BCC		1	0.5%									
Basosquamous		4	2.0%									
SCC		27	13.5%									
Localization (n/%)												
Scalp		15	7.5%									
Face		153	76.5%									
Ear		6	3.0%									
Neck		6	3.0%									
Trunk		22	11.0%									
Upper extremity		5	2.5%									
Lower extremity		6	3.0%									
Number of KCs (n/%)												
I		165	82.5%									
II		23	11.5%									
III		10	5.0%									
IV		1	0.5%									
V		1	0.5%									

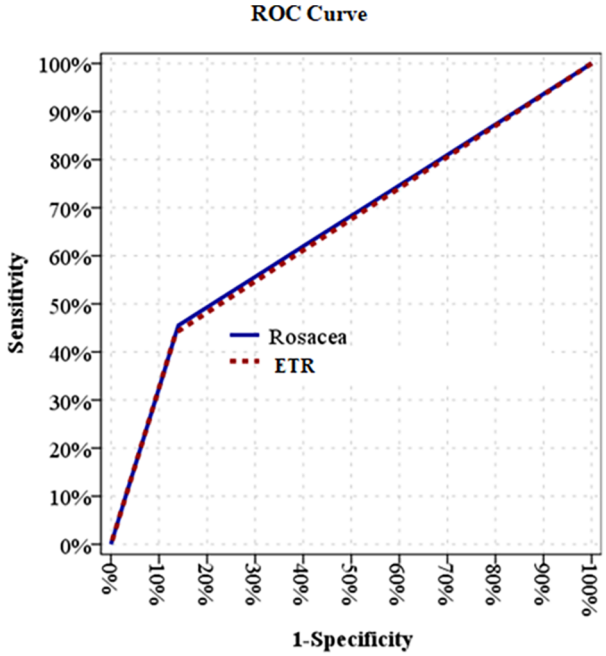
[m] Mann-Whitney U test / X^2 Chi-squared test (Fischer test). Abbreviation: KC: Keratinocyte cancer, SD: Standard deviation

rosacea [7,10]. These biological triggers are known to activate Toll-like receptors (TLRs), including TLR-2. TLR stimulation results in the activation of the nuclear factor kappa B (NF-κB) pathway, which in turn leads to the production of cytokines, chemokines, and antimicrobial peptides [11]. The Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway plays a role in the LL-37-mediated inflammatory mechanism of rosacea [12]. In a recent study, Deng and colleagues reported that the mechanistic target of rapamycin complex 1 (mTORC1) pathway is

Table 2. Cutaneous Comorbidities Accompanying the KC and Control Groups and their Comparison.

	Controls	KCs		
	N (%)	N (%)	OR (95% CI)	P*
Rosacea	28 (14.0)	91 (54.5)	5.13 (3.2-8.3)	**0.000**
Erythematotelangiectatic rosacea	27 (13.5)	88 (44)	5.03 (3.1-8.2)	**0.000**
Papulopustular rosacea	0 (0.0)	3 (1.5)	-	0.248
Phymatous rosacea	1 (0.5)	4 (2.0)	4.06 (0.5-36.7)	0.177
Seborrheic keratosis	62 (31.0)	79 (39.5)	1.45 (1.0-2.2)	0.075
Cherry angioma	42 (21.0)	32 (16.0)	0.72 (0.4-1.2)	0.198
Actinic keratosis	24 (12.0)	33 (16.5)	1.45 (0.8-2.6)	0.198
Solar lentigo	28 (14.0)	13 (6.5)	0.43 (0.2-0.9)	0.013
Skin tag	20 (10.0)	15 (7.5)	0.73 (0.4-1.5)	0.376
Xerosis cutis	22 (11.0)	4 (2.0)	0.17 (0.1-0.5)	0.000
Dermal nevi	18 (9.0)	8 (4.0)	0.42 (0.2-1.0)	0.043
Dermatofibroma	8 (4.0)	7 (3.5)	0.87 (0.3-2.5)	0.792
Seborrheic dermatitis	4 (2.0)	5 (2.5)	1.26 (0.3-4.8)	0.736
Verruca vulgaris	3 (1.5)	5 (2.5)	1.68 (0.4-7.1)	0.425
Psoriasis vulgaris	5 (2.5)	3 (1.5)	0.59 (0.1-2.5)	0.475
Stasis dermatitis	5 (2.5)	2 (1.0)	0.39 (0.1-2.1)	0.253
Tinea unguium	5 (2.5)	2 (1.0)	0.39 (0.1-2.1)	0.253
Sebaceous hyperplasia	3 (1.5)	3 (1.5)	1.0 (0.2-5.0)	1,000
Dysplastic nevi	0 (0.0)	5 (2.5)	-	**0.024**
Bowen disease	0 (0.0)	5 (2.5)	-	**0.024**
Lichen simplex chronicus	4 (2.0)	0 (0.0)	-	0.044
Acne vulgaris	2 (1.0)	1 (0.5)	0.50 (0.1-5.5)	1,000
Urticaria	1 (0.5)	2 (1.0)	2.01 (0.2-22,4)	1,000
Vitiligo	2 (1.0)	1 (0.5)	0.50 (0.1-5.5)	1,000
Post-inflammatory hyperpigmentation	2 (1.0)	1 (0.5)	0.50 (0.1-5.5)	1,000
Keratoacanthoma	0 (0.0)	3 (1.5)	-	0.248
Xanthelasma	0 (0.0)	2 (1.0)	-	0.499
Pityriasis versicolor	2 (1.0)	0 (0.0)	-	0.499
Tinea pedis	2 (1.0)	0 (0.0)	-	0.499
Callus	1 (0.5)	1 (0.5)	1 (0.1-16.1)	1,000
Lichen sclerosus	0 (0.0)	1 (0.5)	-	1,000
Melasma	0 (0.0)	1 (0.5)	-	1,000
Melanoma	0 (0.0)	1 (0.5)	-	1,000
Diabetic foot infection	1 (0.5)	0 (0.0)	-	1,000
Decubitus ulcer	1 (0.5)	0 (0.0)	-	1,000
Epidermal cysts	0 (0.0)	1 (0.5)	-	1,000
Angiokeratoma	0 (0.0)	1 (0.5)	-	1,000
Hidradenitis suppurativa	0 (0.0)	1 (0.5)	-	1,000
Milia	0 (0.0)	1 (0.5)	-	1,000
Nevus spilus	0 (0.0)	1 (0.5)	-	1,000
Recurrent aphthous stomatitis	0 (0.0)	1 (0.5)	-	1,000
Pemphigus vulgaris	0 (0.0)	1 (0.5)	-	1,000
Granuloma annulare	0 (0.0)	1 (0.5)	-	1,000
Frontal fibrosing alopecia	0 (0.0)	1 (0.5)	-	1,000
Syringoma	1 (0.5)	0 (0.0)	-	1,000
Prurigo nodularis	1 (0.5)	0 (0.0)	-	1,000
Herpes zoster	1 (0.5)	0 (0.0)	-	1,000

* Chi-squared test (Fischer test). Abbreviation: KC: Keratinocyte cancer.



Sensitivitv 45.5%, specificity 86.0%, NPV 61.2%, PPV 76.5%, AUC 0.658 for rosacea

Sensitivity 44.0%, specificity 86.5%, NPV 60.7%, PPV 76.5%, AUC 0.653 for ETR

Figure 1. ROC curve of rosacea and ETR for predicting KCs. (AUC Area under curve; NPV, negative predictive value; PPV, positive predictive value; ROC: receiver operating characteristic; ETR: erythematotelangiectatic rosacea; KC: keratinocyte cancer

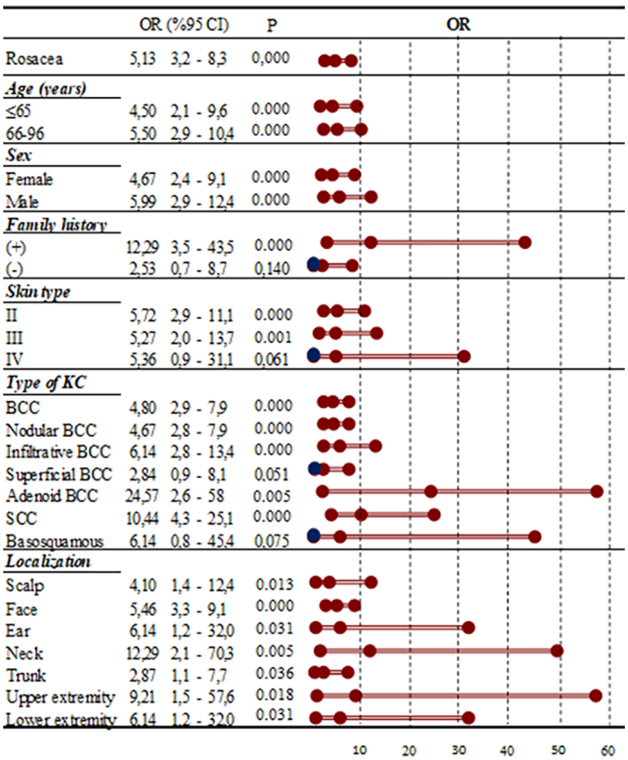


Figure 2. Forest plot for the effect of the presence of rosacea on keratinocyte cancers in terms of age, sex, family history, skin type, cancer subtype, and localization.

hyperactivated in rosacea [13]. mTOR is a key regulator of several fundamental cellular processes, including cell growth, proliferation, differentiation, survival, autophagy, and motility as well as angiogenesis and lymphangiogenesis. The authors observed a positive correlation between epidermal activation of the mTORC1 pathway and the severity of the rosacea, thereby identifying a mechanism linking the dysregulation of the innate immune system and the inflammatory response in the disease.

A substantial body of evidence indicates that the PI3K/AKT/mTOR/S6K1 pathway can be activated by UVR exposure in the development of skin cancers [14,15]. Hyperactivation of the PI3K/AKT/mTOR axis was identified in both SCC and BCC skin tissues, indicating a potential involvement in the pathogenesis and malignant progression of these tumors [16,17]. Furthermore, the activation of the STAT3 and NF-κB pathways is also a significant factor in the development of KC [18]. The expression of Vascular Endothelial Growth Factor (VEGF), a crucial regulator of angiogenesis and tumor growth, is elevated in both rosacea and KCs. The observation that these two diseases share common pathogenic mechanisms may be associated with the increased prevalence of KC in patients with rosacea.

In our study, the sensitivity, specificity, NPV, and PPV of the effectiveness of the presence of rosacea in differentiating between patients with KC and the control group were 45.5%, 86.0%, 61.2%, and 76.5%, respectively. For ETR, the corresponding values were 44.0%, 86.5%, 60.7%, and 76.5%. Recent studies have indicated that there is an association between rosacea and numerous comorbidities, including hypertension, autoimmune disease, cardiovascular disease, gastrointestinal disorders, dyslipidemia, and psychiatric disorders [19,20]. Furthermore, numerous studies have investigated the potential link between rosacea and various forms of cancer. In a two-sample bidirectional Mendelian randomization study, Luo et al. identified a positive association between rosacea and glioma, NMSC, and breast cancer [21]. In a cohort study by Egeberg et al. analyzing data from nationwide Danish registries, a statistically significant association was observed between rosacea and NMSC [3]. Patients with rosacea were more likely to develop NMSC compared to patients in the reference population (HR 1.36, 95% CI: 1.26–1.47). In another study, Cho et al. conducted a nationwide, population-based retrospective cohort study of 11,420 patients in South Korea [22]. The results demonstrated a notable correlation between rosacea and NMSC incidence in comparison to the reference population (HR 2.66, 95% CI: 1.53–4.61). In contrast, in the study by Lin et al., 2453 of the 4537 patients diagnosed with BCC had facial BCC, and 267 of them had a history of rosacea [6]. The results of the study demonstrated that the prevalence of facial BCC in patients with a history of rosacea was markedly lower than in patients without rosacea (3.80 vs 5.07 per 100 patients; $P< 0.001$). A comparison of BCC of the body revealed no significant difference between patients with and without a history of rosacea. Lazzeri et al. presented a case series and a literature review of a total of 46 patients with rhinophyma who subsequently developed skin cancer [23]. Of the patients in question, 28 were diagnosed with BCC, 11 with SCC, four with both SCC and BCC, and one with angiosarcoma. With regard to SCC, 577 cases of SCC were identified in a population of 90,238 women in the USA [24]. The results demonstrated a significant association between rosacea and SCC (RR 1.40. 95% CI: 1.02–1.93). In this study, the location of SCC was also divided into two groups: head and neck and non-head and neck. These groups were then compared in terms of the history of rosacea. The results demonstrated a significant association between rosacea and head and neck SCC (RR 1.71, 95% CI: 1.09–2.69). The findings of our study indicate that the presence of rosacea is associated with an increased risk of KC in all localizations. Furthermore, the majority of patients with rosacea were observed to belong to the ETR subgroup. Concerning the risk of BCC subgroups, a significant and positive association was observed for nodular, infiltrative, and adenoid BCCs. Conversely, no significant risk was identified for superficial BCCs and basosquamous carcinomas. Morpheaform and pigmented BCC were observed in a single patient. The findings of our study indicate that the presence of rosacea is an independent risk factor for KCs, irrespective of age and sex, and in patients with skin types II and III.

Regarding other cutaneous comorbidities, the prevalence of dysplastic nevus and Bowen's disease was significantly higher in the group of patients with KC compared to the control group. However, the number of cases was limited to five patients in the KC group, with no case observed in the control group. In a cohort of 11,420 patients with rosacea, Cho et al. reported an increased risk of actinic keratosis and KC [22]. The present study did not find an increased risk of actinic keratosis.

Limitations

The study's key strengths are its prospective case-control design and its ability to compare tumor localization and subtype. However, it has several limitations. First, it was conducted at a single center, which may have introduced some bias. Second, due to the demographic characteristics of our region, there was no patient with Fitzpatrick skin type I.

Conclusion

This prospective case-control study investigated cutaneous comorbidities in patients with KC in detail. The risk of rosacea in patients with KC, particularly those with the ETR subtype, was found to be significantly elevated, irrespective of age, sex, or localization. We recommend that individuals with rosacea undergo regular examinations for the development of KC and that patients be made aware of the importance of sun protection.

Ethics Approval: The clinical study was approved by the University of Health Sciences, Şişli Hamidiye Etfal Training and Research Hospital local ethics committee (Approval number: 4493), and was performed in accordance with the ethical standards of the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from all patients and control participants included in the study.

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