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Bacterial colonization of skin profile and their relation with non-melanoma skin cancers

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ABSTRACT

The skin is the largest physical barrier between attacking pathogens and the body. This study aimed to find the relationship between some popular characteristics or behaviors, and bacterial prevalence in causing different types of skin cancer. Therefore, specimens of 64 cases of different cutaneous tumors including bacterial swabs (tumor and healthy sites) are collected from each patient. The results showed that the randomly collected 64 specimens included 45 (70.3%) males and 19 (29.7%) females with no wide differences between males and females in the mean of age for both sexes. As well as, the results revealed that the difference was substantial among skin tumors which are restricted to 5 types including Squamous Cell Carcinoma (SCC), Basal Cell Carcinoma (BCC), Mycoses Fungoides (MF), Kaposis sarcoma, and Dermato fibroma in percentages 46.9%, 25.0%, 20.3%, 6.3%, and 1.6% respectively, and BCC (73.3%), SCC (75%), and KS (53.8%) are higher significantly in males than females 26.7%, 25%, 0.0% respectively. Simultaneously, the results elucidated that various non-melanoma skin cancer kinds are more prevalent in married patients 93.74%, than in unmarried 6.25%. Moreover, the findings demonstrated that there are no substantial differences among tumor patients who had chronic diseases and those who do not, in both males and females in general, but females with chronic diseases recorded a significant increase in the case of BCC only. On the other hand, the bacteriological status of both the tumor and healthy areas of each patient was investigated and the results showed no significant difference between positive and negative bacterial growth in tumor sites, while the negative growth recorded significantly increasing results in the case of healthy areas. Significant differences were found between tumor and healthy areas in the same context. Furthermore, gram-positive bacteria such as different species of the *Staphylococcus* genus are more dominant than gram-negative bacterial isolates which are restricted into two genera including *Acinetobacter lwoffii*, and *Pseudomonas aeruginosa* only.

Keywords: Nonmelanoma skin cancer; BCC; SCC; Kaposis sarcoma; Dermato fibroma

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INTRODUCTION

The skin is the body's biggest organ. Due to the complexity of their structures with various cell types, over 100 kinds of tumors are known to be clinically observable on the skin. At different phases of their differentiation, these cell types may convert malignantly, resulting in tumors with unique histologies and a range of clinical behaviors [1]. The prevalence of skin cancers has risen considerably in recent decades, owing in part to increased solar exposure, demanding close monitoring [2]. However, both genetic and environmental variables might be important [3].

Skin cancer is the most serious health issues in the world because of its high prevalence when compared to other kinds of cancers [4]. Skin tumors are spread everywhere and might be benign or cancerous, and they can impact people of various ages [5]. The incidence of cancer of the skin rises by aging [6]. Skin cancers can have numerous causes, including genetic, chemical, hormonal, nutritional, viral, and environmental elements that interact with a vulnerable person. Skin tumors may arise from the surface epithelium, epidermal appendages, or dermis. According to their origin, they are categorized by the WHO as keratinocyte, melanocytic, appendageal, and hematolymphoid tumors [7]. As a whole, Nonmelanoma Skin Cancer (NMSC) and Melanoma Skin Cancer (MSC) are the two main types of skin cancer. Squamous cell carcinoma and basal cell carcinoma are two kinds of Non-Melanoma Skin Cancer (NMSC) [8].

The first line of defense against pathogenic microbial invasion is the skin. A physical barrier is created by the stratum corneum's tight connections between corneocytes, while a chemical barrier is produced by the antimicrobial peptides and lipids released by keratinocytes and glands [9]. Furthermore, commensal skin microbes can inhibit pathogen growth, either directly by releasing antimicrobial compounds, or indirectly by taking up space and vying for sources of nutrition [10,11].

Numerous different species, including bacteria and fungus, constitute the skin microbiome. In adults, the microbial population makeup is consistent throughout time, although persistent exposition to exogenous microorganisms from other people and the environment [12]. However, the microbiota's makeup varies with puberty, with children's microbiotas being more diverse than adults' [13,14]. Bacteria make up the majority of the microbiota, accounting for more than 70% of the species in most skin regions [15].

The microenvironment of cancer, which signifies tumors and non-cancerous cells such fibroblasts, immune cells, and endothelial cells, influences how the disease develops and responds to therapy. Cancer is characterized by persistent inflammation, where suggesting that it generates a carcinogenic milieu [16].

Therefore, this research is aimed to find the relationship between some popular characteristics, and bacterial prevalence in causing different types of skin cancer.

MATERIALS AND METHODS

The patients' subjects

Sixty-four specimens of randomly selected patients including 45 males and 19 females participated in this study, which was obtained from the dermatology center in the city of medicine in Baghdad/ Iraq, for the period starting March 2022 to December 2022. The diagnosis of skin tumors was carried out by a professional consultant dermatologist, based on the clinical findings and histological examination. Patients' ages ranged from 15 to 90 years. Accordingly, they were divided into five groups depending on the diagnosed skin tumor type. Patients' case histories are regulated throughout the questionnaire form included; (name, age, sex, medication, chronic disease with a type of medication, smoking, and marital case).

Isolation and characterization of bacterial isolates

Patients' skin swabs from both tumor and healthy areas were activated for 24 hours at 37°C in Brain Heart Infusion Broth (BHIB)/Himedia. The activated bacterial growth was cultivated on primary isolation media, such as Blood agar base/oxoid, MacConkey agar, mannitol agar, and nutrient agar/himedia, and then incubated aerobically for 24-48 hours at 37°C. Samples cultivated on both nutrient agar and chocolate agars were incubated in a candle jar with CO_2 at the same temperature and time as described previously [17].

Bergey's manual of systematic bacteriology was used to diagnose the isolates microbiologically (morphological and biochemical assays) [18]. Secondary identification was done using VITEK 2 COMPACT as a quick identification system for diverse bacterial isolates, according to the supplying company's contained instructions.

Statistical analysis

The data were analyzed using the following software, Microsoft excels used for graphics and IBM SPSS V26 for statistical investigation. The study's findings were presented as mean standard deviation SD., Z-test was used to contrast the two ratios. The chi-square goodness-of-fit test was used to test more than two proportions, and the *chi-square* test of association adapted to describe the observations' analytical perspective for the two study groups. Probability values less than 0.05 was deemed significantly different [19].

RESULTS AND DISCUSSION

Data were collected on 64 cases of patients diagnosed with different types of skin tumors during the period of the research. These patients include 45 (70.3%), and 19 (29.7%) were men and women respectively. The patients' sex percentages are given in Table 1, with a significant difference between both sexes. Skin cancer statistics show an obvious alteration between males and females. Dependent to the Skin Cancer Foundation (SCF), more than half (57%) of those identified with BCC are men. As the number of BCCs rises, 62% of persons established with 2-5 BCCs are men [20]. As well as reported that men are more predominant with skin tumors than women.

Tab. 1. The ratio of males and females in skin tumors.

Type of sex	No. of cases (%) from skin tumors
Males	45 (70.3%)
Females	19 (29.7%)
P value©	0.001**
Total no. of cases	64
Note: © Z-test of two proportions was used, **P≤0.001.	

The age of patients at diagnosis was range 15-90 years. Table 2 illustrated there are no wide differences between males and females in the mean of age for both sexes, except Kaposis sarcoma, and Dermato fibroma both are characterized by a low rate frequency among patients. While, reported that the percentage of alteration in malignancies of the skin varied among countries. SCC increased directly through 17 years. Men skilled more age-specific occurrence rates of keratinocyte cancer throughout all ages, but women had a more incidence of melanoma till nearly the age of 50 years, following which the tendency upturned till the age of 85 years. Males with experience more death rates by age group for all ages. Both melanoma and keratinocyte carcinoma raised significantly with age in terms of disability-adjusted life years.

Tab. 2. Range and mean of age for experimental patients.

Type of skin tumor of patient	Range of age		Mean of age
	Males (years)	Females (years)	Males (years)
Basal Cell Cancer (BCC)	39-83	21-85	60.9 ± 14.3
Squamous Cell Cancer (SCC)	15-90	51-80	58.2 ± 21.7
Mycoses Fungoides (MF)	29-58	31-67	47.7 ± 10.7
Kaposi sarcoma	31-60	0	46.0 ± 12.9
Dermato fibroma	0	32	0 ± 0

On another hand, Table 3 revealed the percentages of different skin tumors which varied among patients including BCC, SCC, MF, Kaposi sarcoma, and Dermato fibroma in percentages 46.9%, 25.0%, 20.3%, 6.3%, and 1.6% respectively.

Tab. 3. Determining the type of skin tumor and its proportion of the patients.

Type of skin tumor of the patients	No. of cases (%) from skin tumors
Basal Cell Cancer (BCC)	30 (46.9%)
Squamous Cell Cancer (SCC)	16 (25.0%)
Mycoses Fungoides (MF)	13 (20.3%)
Kaposi Sarcoma (KS)	4 (6.3%)
Dermato Fibroma (DF)	1 (1.6%)
P value	0.001**
Total no. of skin tumors cases	64

Note: The *Chi-square* goodness of fit test was applied.**P ≤ 0.001.

Documented that both BCC and SCC are more prevalent among skin cancer patients, and this data was improved by the American cancer society last revised in January 2023. In spite of these types of skin cancers are common than others, death is uncommon. Most individuals who die from these malignancies are older people who may not have been monitored by a doctor until the cancer has spread. Other persons are more probably to die of these, whose body's defense system is suppressed, such as people with organ transplants.

Moreover, to find the type of skin tumors more prevalent between males and females, the results in Table 4 showed each BCC (73.3%), SCC (75%), and KS (53.8%) are higher significantly in males than females (26.7%, 25%, 0.0% respectively). World Studies have described an elevating occurrence of NMSC (Non-Melanoma Skin Cancer). The World Health Organization estimates that 2 to 3 million NMSCs occur annually worldwide. Elucidated that, the frequencies of BCC and SCC are increasing, and there is a disproportionate rise in women of these tumors and shifting of anatomical spreading.

Tab. 4. The comparison of skin tumor types with sex.

Diagnosed skin tumor types	Sex		P-value©
	No. of males (%)	No. of females (%)	
Basal Cell Carcinoma (BCC)	22 (73.3%)	8 (26.7%)	0.001**
Squamous Cell Carcinoma (SCC)	12 (75%)	4 (25%)	0.001**
Mycoses Fungoides (MF)	7 (53.8%)	6 (46.2%)	$0.694^{N.S}$
Kaposi Sarcoma (KS)	4 (100%)	0 (0.0%)	0.029*
Dermato Fibroma (DF)	0 (0.0%)	1 (100%)	$1.00^{N.S}$
P value	0.001**	0.019*	
Total no. of skin tumors cases	45 (70.3%)	19 (29.7%)	100

Note: *Chi-square* test of goodness of fit was used, © Z-test of two proportions was used.
N.S: Non-Significant results, *P ≤ 0.05, **p ≤ 0.001.

In the same context, MF results in the present study revealed no significant difference between males and females. It is the most prevalent kind of skin. T-cell lymphoma and constitutes practically about 50% of all major cutaneous lymphomas, frequently affecting adult/elderly patients with a ratio of 1.6-2.0:1 for male-to-female. Cases of children and adolescents have also been described.

As well this study followed the marital status of each patient in Table 5. The findings revealed that the proportion of married patients was 93.74%, while the unmarried was 6.25%. These results are confirmed by that published globally, they considered married marital status as a positive thing in the first discovery and treatment of cancer mentioned that patients who were married had a considerably lower chance of death from cancer than patients who are divorced. The best overall and cancer-specific survival rates were found in female patients and younger age groups. Concluded that married marital status was related to the primary stage at diagnosis and extended persistence compared with unmarried or divorced patients with MF.

Tab. 5. Marital status of patients.

	Marital status				Total	
	Single		Married			
	N	(%)	N	(%)	N	(%)
BCC	2	50.00%	28	10.00%	30	46.90%
SCC	2	50.00%	14	23.30%	16	25.00%
MF	0	0.00%	13	21.7	13	20.30%
Kaposi sarcoma	0	0.00%	4	6.70%	4	6.30%
Demato fibroma	0	0.00%	1	1.70%	1	1.60%
P-value	0.000**		0.001**		0.0003**	
Total	4	100	60	100	64	100
Chi-square tests			P-value		$0.685^{N.S}$	

Chronic diseases including Diabetes Mellitus (DM) and high blood pressure are considered the predisposing factor that may encourage skin tumor development. The results in Table 6 elucidated that there are no notable differences among tumor sufferers who had chronic diseases and those who do not, in both males and females generally, but females with chronic diseases elucidated a significant increase in the case of BCC only. Whilst, reviewed that DM, low-grade chronic inflammation, oxidative and her colleagues, stress, environmental factors, and genetic lifestyle partially clarify the crosslink between skin tumors and this metabolic disorder. Additionally, DM and its correlated complications may interact with the suitable management of skin malignancies. Anti-diabetic drugs seem to have an antineoplastic effect. Furthermore, research studies have revealed raised the possibility of emerging SCC in diabetic patients. A reviewing research exhibited the prevalence of increasing generalized cutaneous tumor (skin cancer without melanoma) could be 1.29 times more likely in diabetes patients over the age of 60 years.

Tab. 6. Distribution of patients according to chronic diseases.

Type of skin tumor of the patient	Males without chronic disease		Males with chronic disease		p-value
Basal cell carcinoma (BCC)	N	%	N	%	
Squamous cell carcinoma (SCC)	11	50	11	50	0.461
Mycoses Fungoides (MF)	7	58.3	5	41.7	0.82
Kaposi sarcoma	4	57.1	3	42.9	0.927
Dermato fibroma	3	75	1	25	0.389
Total	0	0	0	0	1
Chi-square tests	25	55.6	20	44.4	-
	P-value			0.12	

Type of skin tumor of patients	Females without chronic disease		Females with chronic disease		p-value
	N	%	N	%	
Basal Cell Carcinoma (BCC)	1	12.5	7	87.5	0.006
Squamous Cell Carcinoma (SCC)	2	50	2	50	0.723
Mycoses Fungoides (MF)	4	66.7	2	33.3	0.133
Kaposi sarcoma	1	100	0	0	0.285
Dermato fibroma	0	0	0	0	1
Total	8	42.1	11	57.9	-

The bacteriological status of the tumor and healthy areas are investigated to find the correlation between bacterial existence and cutaneous tumors. In general, the results in Table 7 showed that there is no statistically significant difference between positive and negative bacterial growth in tumor sites, while the negative growth recorded significant results in the case of healthy areas. Simultaneously, important variations were discovered between the tumor and the healthy areas. Although the results do not record substantial distinctions between healthy skin and tumors, the gram-positive bacterial isolates especially *Staphylococcus* spp. are more prevalent than others including *Staphylococcus aureus* (20.3% and 7.8%), *Staphylococcus epidermidis* (14.1%and 9.4%), *Staphylococcus hominis* (3.1% and 3.1%), *Staphylococcus haemolyticus* (1.6% and 1.6%). Whereas gram-negative bacterial isolates are restricted to two genera including *Acinetobacter lwoffii* (6.3% and 3.1%), and *Pseudomonas aeruginosa* (1.6% and 0%) for tumor site and healthy skin respectively.

The automatic method VITEK2 (Table 7) effectively recognized 3 genera and 6 species in this research from skin swab of patients with skin tumors. VITEK2's capacity to diagnose more than 150 fermentative and non-fermentative gram-negative bacilli and up to 120 significant non-spore-forming gram-positive bacteria with a high discrimination between species and a low rate of multiple choice or misidentification enables the diagnosis at the level of genus and species among the isolates.

Tab. 7. Bacterial species isolated from tumor and healthy skin of patients.

Type of bacterial isolates	No. of cases (%) from tumor skin	No. of cases (%) from healthy skin	P value
Staphylococcus aureus	13 (20.3%)	5 (7.8 %)	0.411
Staphylococcus epidermidis	9 (14.1%)	6 (9.4 %)	0.61
Staphylococcus haemolyticus	1 (1.6%)	1 (1.6%)	0.672
Staphylococcus hominis	2 (3.1%)	2 (3.1%)	0.537
Acinetobacter lwoffii	4 (6.3%)	2 (3.1%)	0.936
Pseudomonas aeruginosa	1 (1.6%)	0 (0.0%)	0.309
P value	0.001**	0.068 N.S	
No. of +ve growth culture	30 (46.9%)	16 (25.0%)	0.008
No. of -ve growth culture	34 (53.1%)	48 (75.0%)	0.008
P value	$0.479^{N.S}$	0.001**	
Total no. of cases	64	64	

Reported that an alteration of skin microbiota besides pathogen-related molecular patterns and patterns linked with damage with bacterial Toxins can stimulate long-term inflammation. The chronic case a characteristic of cancer when the suggestion that it creates a cancer-promoting milieu of the cutaneous layers and cells injury that could result in to the beginning and development of cancer of the skin. In the same context, mentioned microorganisms that home in the human body are closely related to the progress and treatment of cancers. Recently, Tumor Microbiome (TM) has been recognized in different cancers such as breast cancers, lung, and pancreatic. TM has diverse compositions in different tumors and has variable effects on tumors. TM had a vital role in the development of the tumor microenvironment, instruction of local immunity, and alteration of tumor cell biology, and directly on the efficacy of drug action for tumors.

Consistent with present findings, found a correlation between S. aureus and SCC using swab specimens and tumor biopsies, respectively. SCC biopsies showed a higher incidence of *S. aureus* than normal skin biopsies. Additionally, the frequency of *S. aureus* in swab specimens from SCC was higher than in normal skin swab specimens. They concluded that a raised incidence of *S. aureus* DNA was closely related with Squamous Cell Carcinoma (SCC) and Actinic Keratosis (AK) of the skin through attacking *S. aureus*. However, the increased establishment of *S. aureus* in AK indicates that S. aureus is related to the carcinogenesis mechanism that causes AK to cause SCC.

As well as, found an increase in the expression of human Beta Defensin-2 (hBD-2) in SCCs was associated with *S. aureus* abundant. In a cultivation experiment utilizing Hecate cells, SCC cell lines from cutaneous SCCs, and *S. aureus*, the hBD-2 expression was increased through the *S. aureus* test, in addition to a rise in tumor cell proliferation. Furthermore, the direct contest of SCC cell treatment by hBD-2 caused a proliferation of tumor cells also but there is a scarcity of advances on the actual causative connection of SCCs and *S. aureus*.

Whereas documented that pathogens had a function in cancer in numerous circumstances, the most common links among mass tumors and microorganisms are opportunistic rather than causal agents. An experiment done by observed that microorganisms are normally able to reside in cancers if systematic injected, and subsequent large amounts of replicating particularly occurred. It was initially recognized after species IV delivery of *Vibrio cholerae, Clostridium, Escherichia coli, Salmonella, Listeria monocytogenes,* and *Bifidobacterium*. Moreover, numerous clinical studies have revealed that capability of different strains of bacteria to invade and duplicate selectively throughout cancers. On other hand, found that gram negative Bacterial Lipopolysaccharide (LPS), Both BIA-ALCL cell lines and tumor cells from patients responded differently to LPS stimulation. A peptide inhibitor of the Toll-Like Receptor 4 (TLR4) dramatically reduced this response.

CONCLUSION

Moreover, the results showed that there are no statistical differences between oncology patients with chronic diseases and those who do not suffer from them, in both males and females in general, but females with chronic diseases recorded a significant increase in the case of basal cell carcinoma.

On the other hand, the bacteriological status of both the tumor and healthy areas for each patient was examined, and the results showed that there was no significant difference between positive bacterial growth and no growth in the tumor sites, while the absence of growth recorded a significant increase in the case of healthy areas. In the same context, statistically significant differences were found between tumor areas and healthy areas. In addition, gram-positive bacteria, represented by the different types of the genus *Staphylococcus*, are more prevalent than gram-negative bacterial isolates, which are limited to *Acinetobacter lovii* and *Pseudomonas aeruginosa* only.

ETHICAL APPROVAL

The college of sciences local ethics committee approved the trials detailed in this research, and all of the volunteers signed off on them. Patients were also given information and benefits based on the research.

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