Head and Neck Cutaneous Squamous Cell Carcinoma Clinicopathological Risk Factors according to Age and Gender: A Population-based Study

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ABSTRACT: **Background:** Clinicopathological risk factors for cutaneous squamous cell carcinoma of the head and neck (CSCCHN) are associated with local recurrence and metastasis.

Objectives: To compare the incidence and risk factors of CSCCHN by age and gender in order to help refine the clinical evaluation and treatment process.

Methods: Clinical and pathological data of all patients diagnosed with CSCCHN during 2009–2011 were obtained from a central pathology laboratory in Israel. Estimated incidence rate calculation was standardized to the 2010 Israeli population. Independent risk factors for poorly differentiated CSCCHN were analyzed using logistic regression.

Results: CSCCHN was diagnosed in 621 patients. Mean age was 75.2 years; mean tumor horizontal diameter was 11.1 ± 6.8 mm. The overall estimated incidence rate in males was higher than in females (106.2 vs. 54.3 per 1,000,000, $P < 0.001$). Twenty cases (3.2%) had poorly differentiated CSCCHN. Scalp and ear anatomic locations were observed more often in males than in females (22.1% vs. 6.1% and 20.3% vs. 3.3%, respectively, $P < 0.001$). Per 1 mm increment, tumor horizontal diameter increased the risk for poorly differentiated CSCCHN by 6.7% (95%CI 1.3–12.4%, $P = 0.014$).

Conclusions: CSCCHN clinicopathological risk factors are not distributed evenly among different age and gender groups.

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KEY WORDS: cutaneous squamous cell carcinoma (SCC), head and neck, risk factors, anatomic location

Cutaneous squamous cell carcinoma (SCC) is the second most common non-melanoma skin cancer after basal cell carcinoma in white populations [1,2], with an estimated lifetime risk of 7–11% [3]. The incidence of squamous cell carcinoma has been increasing rapidly and universally [4]. Australia has the highest annual incidence, approximately 1% per year [5], and in Europe, incidence rates are estimated at 15.8 cases per 100,000 [6].

The risk of developing squamous cell carcinoma is related to age and gender. The mean patient age at first occurrence is approximately 70 years and is twice as common in men as women [3,5,7,8]. The annual age-adjusted incidence rate for squamous cell carcinoma has been reported to be 8–136/100,000 for Caucasian men and 26–59/100,000 for Caucasian women [9].

Cutaneous squamous cell carcinoma of the head and neck (CSCCHN) accounts for 50–75% of all cases of cutaneous squamous cell carcinoma [7,8]. This anatomic region also portends the highest risk for unfavorable outcomes. While invasive cutaneous squamous cell carcinoma (SCC) has an overall 5 year local recurrence rate of 8% and a 5 year risk of metastasis of approximately 5%, a CSCCHN that emerges on the ear or lip has a twofold risk of local recurrence and metastasis [10]. In addition, the risk of local recurrence of SCC and metastasis is related to pathological attributes of the malignancy, such as degree of differentiation and level of invasiveness [11]. However, intraoperative frozen section positive margins did not correlate with the anatomic location of the primary tumor [12].

Early detection and surgical removal of SCC offer the best chance of cure. However, data on the association between CSCCHN anatomic location and patients' age and gender are currently insufficient and require ongoing updates due to the dynamic nature of SCC incidence trends [13]. Therefore, a more accurate description of high risk CSCCHN subpopulations would refine targets for skin cancer screening and treatment efforts. To this end, the present study undertook to compare the estimated incidence and risk factor distribution of CSCCHN by age and gender subgroups.

Table 1. Cutaneous squamous cell carcinoma baseline characteristics by gender*

Characteristic	Female (N=213)		Male (N=408)		Total (N=621)		*P* value
Mean age in years (SD)	76.9	(11.3)	74.3	(11.0)	75.2	(11.2)	0.005
Mean size in mm (SD)	10.7	(7.1)	11.4	(6.6)	11.1	(6.8)	0.25
Differentiation (% of gender)							0.63
Well	181	(85.0%)	338	(82.8%)	519	(83.6%)	
Moderate	27	(12.7%)	55	(13.5%)	82	(13.2%)	
Poor	5	(2.3%)	15	(3.7%)	20	(3.2%)	
Risk area (% of gender)							0.07
Medium	137	(64.3%)	232	(56.9%)	369	(59.4%)	
High	76	(35.7%)	176	(43.1%)	252	(40.6%)	
Risk grade (% of gender)							0.10
Low risk	84	(39.4%)	134	(32.8%)	218	(35.1%)	
High risk	129	(60.6%)	274	(67.2%)	403	(64.9%)	

*Chi-square test was used to compare nominal variables and independent Student *t*-test for numerical variables

Table 2. Number of cutaneous squamous cell carcinoma cases stratified by gender and anatomic location*

Anatomic location	Gender†				Age (years)‡		Tumor size (mm)§	
	Female (N=213)**		Male (N=408)**		Mean	SD	Mean	SD
Scalp	13	(6.1%)	90	(22.1%)	75.2	(11.5)	12.4	(7.0)
Forehead	24	(11.3%)	45	(11.0%)	75.2	(11.8)	12.5	(6.9)
Temple	22	(10.3%)	33	(8.1%)	75.4	(11.6)	10.7	(6.6)
Ear	7	(3.3%)	83	(20.3%)	74.3	(10.5)	9.0	(5.8)
Brow	5	(2.3%)	10	(2.5%)	74.6	(10.4)	10.4	(7.3)
Eyelid	4	(1.9%)	4	(1.0%)	76.0	(10.6)	10.7	(6.5)
Nose	24	(11.3%)	22	(5.4%)	71.0	(11.8)	8.8	(5.6)
Cheek	83	(39.0%)	79	(19.4%)	66.8	(15.2)	4.2	(1.5)
Lip	10	(4.7%)	22	(5.4%)	75.5	(10.3)	11.9	(6.8)
Chin	4	(1.9%)	2	(.5%)	74.9	(12.1)	12.2	(8.2)
Neck	17	(8.0%)	18	(4.4%)	79.2	(10.3)	11.0	(6.9)
Total	213	(100.0%)	408	(100.0%)	75.2	(11.2)	11.1	(6.8)

*Chi-square test was used to compare categorical variables and ANOVA for numerical variables
†$P < 0.001$, ‡$P = 0.35$, §$P = 0.007$
**Column percentage

PATIENTS AND METHODS

DATA SOURCE AND INCLUSION CRITERIA

This retrospective cohort study was conducted at Patho-Lab Diagnostics, Ltd., Ness Ziona, Israel. The laboratory complies with OECD (Organisation for Economic Co-operation and Development) Principles of Good Laboratory Practice according to directive 88/320/EEC in histopathology testing by the Israel Laboratory Accreditation Authority and is audited by the College of American Pathologists.

Data from all patients primarily diagnosed with CSCCHN from 1 January 2009 to 31 December 2011 were retrospectively obtained. Patients with recurrent disease were excluded from the database. Among patients who underwent surgery for more than one CSCCHN during the study period, only the primary tumor was included in the study, based on the maximum horizontal diameter and degree of differentiation.

The study was approved by the Institutional Review Board at Assaf Harofeh Medical Center, Israel. Informed consent was waived due to the retrospective nature of the study. Data were de-identified.

VARIABLES

Variables collected for each case included age at CSCCHN resection, gender, specific anatomic location, horizontal tumor diameter, and degree of pathological differentiation. Age was further divided into seven subgroups. National Comprehensive Cancer Network (NCCN) guidelines [14] were used to calculate CSCCHN risk grade and risk area.

STATISTICAL ANALYSIS

Estimated incidence rates were calculated for overall and specific age, gender and anatomic location subgroups. Compatible age/gender population groups taken from Israeli population data in 2010 were used as the denominator [15]. The estimated incidence rate is presented as the number of new CSCCHN cases per 1,000,000 persons.

Statistical analyses were conducted using SPSS software v.18 (SPSS technologies, IBM, USA). Continuous variables were presented as averages and standard deviations and were compared using independent Student *t*-tests. Differences in categorical variables were compared using the chi-square or Fisher exact test. Linear correlation was assessed by means of Pearson's correlation. A conditional logistic regression model was used to assess the risk of finding a poorly differentiated CSCCHN.

RESULTS

A total of 1199 consecutive new cases of cutaneous SCC were pathologically diagnosed during the study period. Of these, 621 patients with CSCCHN were included in the study. Their baseline characteristics are presented in Table 1. The patients' mean age was 75.2 ± 11.2 years, and 408 (65.7%) were males. The mean tumor diameter was 11.1 ± 6.8 mm. Of the 621 cases, 252 tumors (40.6%) were located in the high risk area of the face, and 403 (64.9%) were graded as high risk according to NCCN criteria. On histopathological analysis, 20 cases (3.2%) were poorly differentiated CSCCHN. On average, female patients were 2.6 years older than males at diagnosis (76.9 ± 11.3 vs. 74.3 ± 11.0, $P = 0.005$). No significant gender differences were found in tumor diameter or degree of differentiation on histopathology [Table 1].

Anatomic distribution of CSCCHN by age and gender of patients is presented in Table 2. No significant differences were

found in patients' mean age when comparing CSCCHNs at different anatomic locations ($P = 0.35$). The most commonly affected anatomic locations in females were the cheek (39%), nose and forehead (11.3% each) ($P < 0.001$) [Table 2]. In males, the most common anatomic locations were the scalp, ear and cheek (22.1%, 20.3% and 19.4% respectively, $P < 0.001$). Significant differences were found in the anatomic location of CSCCHN by gender ($P < 0.001$). CSCC on the scalp and ear were observed more often in males than in females (22.1% vs. 6.1% and 20.3% vs. 3.3%, respectively, $P < 0.001$). However, there were no significant gender differences in the overall tendency of CSCCHN to be localized in high risk anatomic areas [Table 1]. The mean tumor diameter for each anatomic location is also shown [Table 2], varying among anatomic locations ($P = 0.007$). The smallest mean tumor diameter was found on the cheek (4.2 ± 1.5 mm) and the largest on the forehead (12.5 ± 6.9 mm).

The overall estimated CSCCHN incidence rate was 80 per 1,000,000 (106.2 in males and 54.3 in females). The estimated incidence rates stratified by anatomic location, gender and age groups are summarized in Table 3. The largest gender differences in estimated incidence rates were in the scalp and ear (23.4 vs. 3.3 and 21.6 vs. 1.8 per 1,000,000, respectively) [Figure 1]. Very low estimated incidence rates were found in the 0–39 and 40–49 year age groups. A steady increase in estimated incidence rates with age was found in overall gender and anatomic location-specific rates.

A logistic regression model controlled for age and gender found tumor diameter to be an independent risk predictor for poorly differentiated CSCCHN ($P = 0.014$): an increment of 1 mm in tumor diameter increased the risk for poorly differentiated CSCCHN by 6.7% (confidence interval1.3%–12.4%).

DISCUSSION

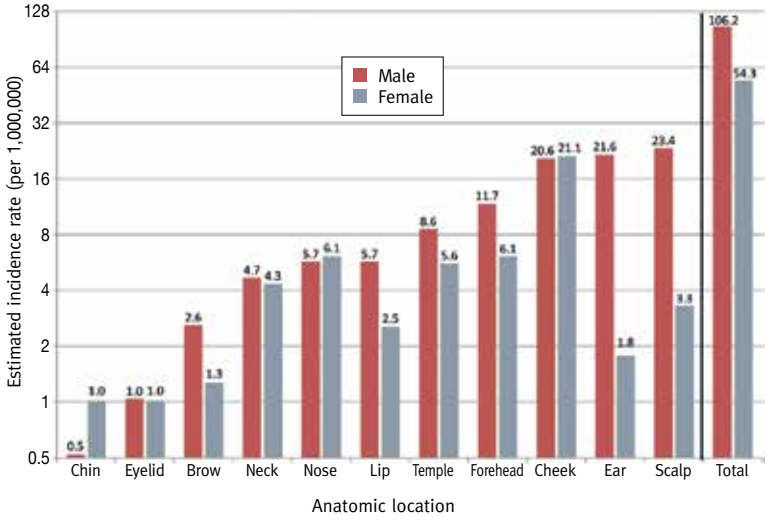
This study describes differences in age, gender and anatomic location regarding poor prognostic markers for CSCCHN tumors. We found an approximately 2:1 male to female incidence ratio. Estimated incidence rates of scalp and ear tumors were significantly higher in males compared to females in all age groups.

Gender differences in SCC presentation might be attributable to genetic, behavioral and occupational factors. Lifestyle is believed to play a major role in gender disparity. Historically, men tended to have occupations that required them to spend more time in the sun, and men are generally less likely to use sun protection than women [16,17]. Occupational exposure to ultraviolet light was previously reported to have a strong relationship with cumulative sunlight exposure and SCC risk [18]; however, no clinical studies have examined gender differences in the development of non-melanotic skin cancers following exposure to equivalent ultraviolet doses.

Table 3. CSCCHN estimated incidence rate (per 1,000,000 persons) stratified by anatomic location, gender and age

Location	Gender	Age group (years)						
		0–39	40–49	50–59	60–69	70–79	80–89	90+
Brow	Female	0.00	0.00	0.00	0.00	10.35	8.82	95.24
	Male	0.00	0.00	2.72	7.53	0.00	96.82	0.00
Cheek	Female	0.00	0.00	5.05	50.56	118.99	291.01	476.19
	Male	0.00	2.37	24.47	60.24	203.41	262.79	227.27
Chin	Female	0.00	0.00	5.05	0.00	5.17	0.00	47.62
	Male	0.00	0.00	2.72	0.00	6.56	0.00	0.00
Ear	Female	0.00	0.00	2.52	10.11	5.17	17.64	0.00
	Male	0.00	0.00	13.59	79.07	170.60	345.78	454.55
Eyelid	Female	0.00	0.00	2.52	3.37	0.00	17.64	0.00
	Male	0.00	0.00	0.00	3.77	13.12	13.83	0.00
Forehead	Female	0.40	0.00	2.52	13.48	15.52	114.64	95.24
	Male	0.00	2.37	5.44	41.42	98.43	207.47	75.76
Lip	Female	0.00	0.00	7.57	6.74	15.52	17.64	0.00
	Male	0.00	2.37	5.44	22.59	45.93	55.33	151.52
Neck	Female	0.00	0.00	2.52	16.85	15.52	61.73	47.62
	Male	0.00	2.37	2.72	15.06	32.81	69.16	151.52
Nose	Female	0.00	0.00	2.52	16.85	51.73	61.73	47.62
	Male	0.00	0.00	8.16	18.83	39.37	82.99	151.52
Scalp	Female	0.00	2.31	2.52	3.37	20.69	52.91	0.00
	Male	0.39	0.00	8.16	94.13	118.11	497.93	530.30
Temple	Female	0.00	0.00	5.05	10.11	25.87	88.18	95.24
	Male	0.00	0.00	16.31	30.12	39.37	165.98	75.76

Figure 1. Estimated incidence rate (per 1,000,000 persons) of CSCCHN by anatomic location



In our study, the highest estimated incidence rates of CSCCHN in males were observed on the scalp, ear and cheek. In females, the highest occurrence was observed on the cheek, forehead and nose. The differences in gender incidence can be explained by facial hair distribution, such as the relatively lower ear incidence of CSCCHN in females due to long hair covering the ear, or to androgenic alopecia in males that exposes the scalp and contributes to the relatively high incidence compared with females.

Another gender-related difference was that females were on average 2.6 years older at presentation than males. Age was correlated with tumor size, and a 1 mm incremental increase in tumor size increased the risk for poorly differentiated CSCCHN by 6.7%.

LIMITATIONS

Although a substantial number of CSCCHN cases are included in this study, it represents cases accumulated in only one pathology laboratory. Another limitation is the lack of data regarding predisposing risk factors. Patient data such as skin type, history of occupational exposure [19] and immunosuppression [20] could not be obtained in the present study; therefore, confounding cannot be excluded. Nonetheless, the data presented are consistent with previous epidemiological observations, which lend validity to the results, at least regarding the selected study population.

CONCLUSIONS

The increasing incidence of non-melanoma skin cancer [21-25] among light-skinned individuals who live in high ultraviolet radiation exposure areas [21] requires meticulous assessment of the clinicopathological characteristics in order to properly evaluate the urgency and incidence of recurrence and metastasis [10]. Our study results in terms of age and gender distribution are in accordance with the literature [3,5,7,8].

Gender differences in SCC presentation might be attributable to genetic, behavioral and occupational factors which may be attributed to local lifestyle. However, no clinical studies have examined gender differences in the development of non-melanotic skin cancers following exposure to equivalent ultraviolet doses. In this study, differences in gender incidence can be explained by facial hair distribution, or to androgenic alopecia in males that exposes the scalp and contributes to the relatively high incidence in males compared with females.

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