

ANALYSIS OF HEAD AND NECK CANCER RISK FACTORS IN PUNJAB, PAKISTAN: A CASE CONTROL STUDY

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Abstract

Aim: The aim of this study was to assess the prevalence of head and neck cancer (HNC) risk factors in Punjab, Pakistan including demographic and behavioral risk factors, socioeconomic status and diet pattern.

Materials and methods: A total of 640 subjects including 320 HNC patients and 320 controls (healthy subjects) were enrolled. Data of recruited patients was gathered from different hospitals of Punjab, Pakistan. Ethical approval and informed consent were taken and a standardized questionnaire was designed. **Results:** Results of demographic risk factors revealed that regarding age, smoking, chewing habits, diet pattern, consumption of fruits and vegetables, anemic status, socioeconomic status, monthly income, type of occupation and living area, there was highly significant difference ($p < 0.001$) between patients and controls. Location ($p = 0.002$) and marital status ($p = 0.043$) were also found to be significantly different. Results of the behavioural risk factors between patients and controls were significantly different for smoking habit, smoking frequency, chewing habits ($p < 0.001$), sun exposure ($p = 0.010$) and poor oral hygiene ($p = 0.004$). Multiple Logistic Regression analysis showed patients age > 37 to 87, unmarried, unemployed patients, students, patients living in rural area and belonging to central Punjab were found to be significantly associated with HNC.

Keywords: Head and Neck Cancer, Smoking, Chewing Habits, Family History, Oral Hygiene, Occupation, Diet.

1. INTRODUCTION

The most complex anatomical structure in human body is region of head and neck. Speech, hearing, swallowing and breathing are the basic functions of this region which are essential for life. HNCs include all these structures where the mentioned mechanisms occur and is recognized by the area where it arise [1].

Annually, 9 million cases of HNC are reported worldwide [2]. According to epidemiological classification of HNC into subsites such as oropharynx, hypopharynx, nasopharynx, oral cavity, tongue and lip, separate frequencies are found for each subsite, so frequency of HNC may be considered as low but when all the subsites are combined, HNC rate is very

high and found to be 5th most frequent cancer in men. These findings suggest that this is a very common disease [3].

Based on the GLOBOCAN database (2020), 10% of all new cases of cancer and 5.4% of all cancer deaths are due to HNC [2]. According to another study, there were 5.7% of deaths due to HNC worldwide that is comparable to frequency of deaths of breast cancer (6.1%) followed by pancreatic cancer (4.5%). In the countries with low and middle income, a very high percentage (82%) was seen where approximately 67% of HNC cases were present [4]. It might be increased in developing countries in future [5].

Among HNC cases worldwide, 57.5% HNC cases were observed in Asia, of which 30% were in India. [6], [7]. A study showed significantly high frequency (12%) of smokers use tobacco in any form by chewing were 7.7% and 69.1% were passive or second hand smokers found in Pakistan [8]. Pakistan is next to India, where people have adopted chewing habits of areca nut and its different products, with a frequency of 21.3% in males and 19.3% in females of Pakistan. In largest city of Pakistan (Karachi) 40% of the inhabitants were using areca nut and its products on daily basis. Pan, gutka, sweet supari, betal quid, main puri, mawa are the main products of areca nut. Gutka was more prevalent chewing substance in 46% of karachi population [9]. These chewing substances are used in Asian countries but in South Asian and US countries smokless tobacco is also used as traditional culture which are considered to be associated with oral carcinogenesis [10].

The current study was designed with the aim to establish the figure among different risk factors (demographic, behavioural, socioeconomical status and diet pattern) in patients and controls.

2. MATERIALS AND METHODS

2.1 Data collection

In current study, 320 blood samples were collected from healthy persons who were willing to participate and 320 biopsy verified HNC patients from Nishtar Institute of Dentistry (NID), Oncology ward No. 25 of Nishtar Medical Hospital Multan and Multan Institute of Nuclear Medicine and Radiotherapy (MINAR), Pakistan. Age range was 12-85 years for healthy controls and 13-87 years for patients. Questionnaire included questions about age, gender, marital status, smoking, chewing habits, diet, consumption of fruit and vegetables, anemic status, socioeconomic status, monthly income, type of occupation, living area, poor oral hygiene, sun exposure, location and family history of cancer.

2.2 Statistical analysis

Collected data was arranged in Microsoft Excel sheet 2016 and mentioned as mean \pm SD. on categorical data chi-square test was applied and to determine association multiple logistic regression analysis was applied using SPSS version (16.0). p-value \leq 0.05 was considered to be statistically significant for all tests.

3. RESULTS

Demographic characteristics (age, gender, marital status, socioeconomic and occupational status, monthly income, type of occupation, living area and location) were compared between patients and controls. The study subjects were divided into 3 groups with respect to age (12-37 years, >37-62 years, >62-87 years).

The highest frequency was observed in age group >37-62 years consisting of 187(58.4%) patients compared to 127(39.7%) controls followed by 12-37 age group comprised of 59(18.4%) patients and 187(55.6) controls, while lowest in >62-87 age group 74(23.1%) patients and 15(55.6%) controls. Statistically significant difference was observed between the groups ($\chi^2_{(2)} = 1.103$; $p < 0.001$).

The multiple logistic regression analysis showed that patients in age group >37-62 (OR 4.44; 95% CI; 3.06-6.44; $p < 0.001$) and in age group >62-87 years (OR 14.88; 95% CI; 7.94-27.90; $p < 0.001$) were significantly at increased risk of HNC.

Regarding gender status of study population, females were less than male. Female included 132 (41.2%) patients versus 156(48.8%) controls, while male comprised of 188(58.8%) patients and 164(51.2%) controls. Statistical analysis showed no significant difference between the groups ($\chi^2_{(1)} = 3.63$; $p = 0.057$). The Multiple logistic regression analysis showed that Male (OR 1.36; 95% CI; 1.00-1.85; $p = 0.057$) were at increased risk for HNC as compared to females.

Regarding marital status, 264(82.5%) patients were married and 54(17.5%) were unmarried. while 262(81.9%) controls were married and 58(18.1%) were unmarried. Statistical analysis showed significant difference between the groups ($\chi^2_{(1)} = 0.918$; $p = 0.043$). The Multiple logistic regression analysis showed that unmarried to (OR 1.04; 95% CI; 0.69-1.56; 0.043) were significantly at increased risk of HNC than married population.

The study participants were divided into four groups regarding monthly income, (PKR $\leq 20,000$, >20,000-40,000, >40,000-60,000 and > 60,000). Highest number of patients were 254(79.4%) and controls were 151(47.2%) in income group $\leq 20,000.00$, followed by 49(15.3%) patients and 86(26.9%) controls in income group >20,000-40,000, while 04(1.2%) patients and 82(25.6%) controls were in income group >40,000-60,000 but 13(4.1%) patients and 1(0.3%) control was in >60,000 income group.

Statistical analysis showed highly significant difference between the groups ($\chi^2_{(3)} = 1.174$; $p < 0.001$). The multiple logistic regression analysis showed that patients of income groups >20,000-40,000 and >40,000-60,000 (OR 0.339; 95% CI 0.23-0.508; $p < 0.001$) and OR 0.03; 95% CI 0.01-0.81; $p < 0.001$ respectively) were significantly at reduced risk of HNC but income group >60,000 (OR 7.73; 95% CI 1.00-59.67; $p = 0.05$) was significantly at increased risk of HNC compared to income group PKR < 20,000 (Table 1).

The study population was categorized as employed and unemployed regarding occupation. Employed patients 227(70.9%) were less than 262(81.1%) employed controls, while unemployed patients 93(29.1%) were more than unemployed controls 58(18.1%).

The statistical analysis showed significant difference between the groups ($\chi^2_{(1)} = 11.18$; $p < 0.001$). The Multiple logistic analysis showed that unemployed were at two times increased risk to HNC than employed population (OR 1.88; 95% CI 1.29-2.73; $p = 0.001$).

Regarding the types of occupation, the study population was divided into six groups (Labourer, Businessmen, Office worker, Housewife, Retired and students). The highest number of patients and controls were in labourer group 200(88.1%) vs 144(45.0%). In Business group, 17(7.5%) were patients and 82(25.6%) were controls while in office worker group 10(3.1%) were patients and 36(11.2%) were controls but in house-workers group, 42(13.1%) patients and 51(15.9%) controls were present and retired group included 04(2.1%) patients and 0(0%) controls. The students group comprised of 47(14.7%) patients and 7(1.1%) controls. Statistical analysis showed significant difference among the groups ($\chi^2_{(5)} = 1.010$; $p < 0.001$). The multiple logistic regression analysis showed that Businessmen group, Officer, Housewife and retired (OR 0.149; 95% CI 0.085-0.26; $p < 0.001$), OR 0.20; 95% CI 0.96-0.416; $p < 0.001$), (OR 0.593; 95% CI 0.37-0.94; $p = 0.026$) and (OR 6.0314-09) respectively were significantly at reduced risk of HNC but student group (OR 4.83; 95% CI 2.124-11.00; $p < 0.001$) was significantly at increased risk of HNC compared to labourer group (Table 1).

The living area of study population was divided as Urban and Rural area. In urban area 57(17.8%) patients were less than the 245(76.6%) controls of urban area, while in rural area, patients were more 263(82.2%) than controls 75(23.4%). Statistical analysis showed highly significant difference between the groups ($\chi^2_{(1)} = 2.21$; $p < 0.001$). According to the multiple regression analysis the patients belonging to rural area were at significantly increased risk of HNC than those belonging to urban area (OR 15.07; 95% CI 10.25-22.17; $p < 0.001$).

As per location, study population was divided into 3 groups (Southern Punjab, Central Punjab and Northern Punjab). In Southern Punjab patients were 281 (87.8%) and controls were 302 (94.4%), while in Central Punjab patients were 30 (9.4%) and controls 9 (2.8%) were but in Northern Punjab patients were 9 (2.8%) and 9 (2.8%) controls. Highest number of patients and controls belonged to Southern Punjab and lowest number belonged to Northern Punjab. Statistical analysis showed significant difference among the groups ($\chi^2_{(2)} = 12.064$; $p = 0.002$).

The multiple logistic regression analysis showed patients belonging to Central Punjab (OR 3.58; 95% CI 1.67-6.67; $p < 0.001$) were significantly at increased risk of HNC than patients belonging to Northern Punjab (OR 1.075; 95% CI 0.42-2.75; $p = 0.880$).

Regarding the family history, the study population was divided into two group's i.e having family history of cancer and having no family history of cancer. The patients 290(90.6%) with no family history of cancer were less than controls 302(94.4%) but patients 30(9.4%) with family history were more than controls 18(5.6%). Statistically non-significant difference was observed between the groups ($\chi^2_{(1)}=3.243$; $p=0.072$). The multiple logistic regression analysis indicated that patients with family history of cancer were at increased risk of HNC (OR 1.74; 95% CI 0.95-3.18; 0.075) (Table 1).

Table 1: Analysis of demographic risk factors in patients and controls

Parameters	Patients (n=320) n (%)	Controls (n=320) n (%)	Chi -sq Test		Multiple Regression Analysis	
			P-value	Chi -sq value	OR (95% CI)	P-value
Age						
12-37 years	59(18.4)	178(55.6)			Ref	Ref
>37-62 years	187(58.4)	127(39.7)			4.44((3.06-6.44)	<0.001***
>62-87 years	74(23.1)	15(4.7)	<0.001***	1.103	14.88(7.94-27.90)	<0.001***
Gender						
Females	132(41.2)	156(48.8)			Ref	Ref
Males	188(58.8)	164(51.2)	0.057	3.63	1.36(1.00-1.85)	0.057
Marital status						
Married	264(82.5)	262(81.9)			Ref	Ref
Unmarried	56(17.5)	58(18.1)	0.043*	0.918	1.044(0.696-1.565)	0.043*
Monthly income of family (PKR)						
< 20,000	254(79.4)	151(47.2)			Ref	Ref
>20,000-40,000	49(15.3)	86(26.9)			0.339(0.23-0.508)	<0.001***
>40,000-60,000	04(1.2)	82(25.6)			0.029(0.01-0.81)	<0.001***
> 60,000	13(4.1)	1(0.3)	<0.001***	1.174	7.73(1.00-59.67)	0.050*
Occupation						
Employed	227(70.9)	262(81.1)			Ref	Ref
Unemployed	93(29.1)	58(18.1)	0.001***	11.18	1.88(1.29-2.73)	0.001***
Type of occupation						
Labourer	200(62.5)	144(45.0)			Ref	Ref
Business	17(5.3)	82(25.6)			0.149(0.085-0.263)	<0.001***
Office worker	10(3.1)	36(11.2)			0.200(0.096-0.416)	<0.001***
House wife	42(13.1)	51(15.9)			0.59(0.37-0.94)	0.026*
Retired	4(1.2)	0(0)			6.0314E-09
Student	47(14.7)	7(1.1)	<0.001***	1.010	4.83(2.12-11.00)	0.001***
Living Area						
Urban	57(17.8)	245(76.6)			Ref	Ref
Rural	263(82.2)	75(23.4)	<0.001***	2.21	15.07(10.25-22.17)	<0.001***
Location						
Southern Punjab	281(87.8)	302(94.4)			Ref	Ref
Central Punjab	30(9.4)	09(2.8)			3.58(1.67-7.67)	0.001***
Northern Punjab	09(2.8)	09(2.8)	0.002**	12.064	1.075(0.42-2.75)	0.880
Family history of cancer						
No	290(90.6)	302(94.4)			Ref	Ref
Yes	30(9.4%)	18(5.6%)	0.072	3.243	1.74(0.95-3.18)	0.075

* $p \leq 0.05$ =significant; ** $p \leq 0.01$ =highly significant; *** $p \leq 0.001$ =very highly significant

The behavioral risk factors included smoking, smoking frequency, chewing habits, poor oral hygiene, sun exposure and gum bleeding. The non-smoker patients 189(59.1%) were

less frequent than controls 261(81.4%) but smoker patients 131(40.9%) were more frequent than controls 59(18.4%). highly significant difference was observed between the groups ($\chi^2_{(1)}=38.80$; $p<0.001$). The logistic regression analysis indicated significantly increased risk to HNC was smoker patients (OR 3.06; 95% CI 2.14-4.40; $p<0.001$). HNC patients showed high frequency of smoking habit than that of controls (40.9%vs 18.4%). Statistically high significant difference was observed between the groups ($\chi^2_{(1)}=38.80$; $p<0.001$). The multiple logistic regression analysis indicated significantly increased risk of HNC in smoker patients (OR 3.06; 95% CI 2.14-4.40). The multiple logistic regression analysis showed that patients of category 1-20 cig/d (OR 2.90; 95% CI 1.90-4.41; $p<0.001$) and patients of category 21-40 cig/d (OR 3.42; 95% CI 1.94-6.00) significantly at increased risk of HNC.

Chewing habits were found to be more frequent in patients than controls (44.1% vs 6.9%). Statistical analysis found highly significant difference between the groups ($\chi^2_{(1)}=1.16$; $p<0.001$). The logistic regression analysis indicated patients in chewing group (OR 10.67; 95% CI 6.56-17.34; $p<0.001$) were significantly at increased risk of HNC. For poor oral hygiene condition in patients and controls (27.2% vs 18.1%), Statistically significant difference was observed between the groups ($\chi^2_{(1)}=7.50$; $p=0.004$). The multiple logistic regression analysis showed that patients with poor oral hygiene (OR 1.69; 95% CI 1.07-2.02; $p=0.006$) were significantly at increased risk of HNC. Regarding exposure to sun in patients and controls (63.4% vs 54.1%), statistical analysis found significant difference between the groups ($\chi^2_{(1)}=5.803$; $p=0.010$). The multiple logistic regression analysis found significantly increased risk of patients (OR 1.48; 95% CI 1.07-2.02; $p=0.016$). Patients 71(22.2%) with gum bleeding were more than controls 61(19.1%). Statistically non-significant difference was observed between the groups ($\chi^2_{(1)}=0.954$; $p=0.329$). The multiple logistic regression analysis showed increased risk of patients with gum bleeding to HNC (OR 1.21; 95% CI 0.825-1.78; $p=0.329$)

Table 2: Analysis of behavioural risk factors in patients and controls

Parameters	Patients (n =320) n(%)	Controls (n=320) n(%)	Chi-sq. Test		Multiple Regression Analysis	
			p-value	Chi-sq. value	OR (95% CI)	p-value
Smoking habits						
No	189(59.1)	261(81.4)			Ref	Ref
Yes	131(40.9)	59(18.4)	<0.001***	38.80	3.06(2.14-4.40)	<0.001***
Smoking frequency						
Never smoked	189(59.1)	261(81.6)			Ref	Ref
1-20 cig/d	84(26.2)	40(12.5)			2.90(1.90-4.41)	<0.001***
21-40 cig/d	47(14.7)	19(5.9)	<0.001***	39.02	3.42(1.94-6.00)	<0.001***
Chewing habits						
No	179(55.9)	298(93.1)			Ref	Ref
Yes	141(44.1)	22(6.9)	<0.001***	1.16	10.67(6.56-17.34)	<0.001***
Poor oral hygiene						
No	233(72.8)	262(81.9)		7.50	Ref	Ref
Yes	87(27.2)	58(18.1)	0.004**		1.69(1.16-2.46)	0.006**
Sun exposure						
No	117(36.6)	147(45.9)			Ref	Ref
Yes	203(63.4)	173(54.1)	0.010**	5.803	1.48(1.07-2.02)	0.016*
Gums bleeding						
No	249(77.8)	259(80.9)			Ref	Ref
Yes	71(22.2)	61(19.1)	0.329	0.954	1.21(0.825-1.78)	0.329

For statistical details and abbreviations see Table 1.

Regarding diet status, the subjects were divided into three categories including vegetarian, having mixed diet and meat fonder. Mixed diet users were frequent in patients than controls (44.7% vs 29.4%). However vegetarians were more in control group 211(65.9%) than patients 119(37.2%).

Meat fonder were more in patients 58(18.1%) vs controls 15(4.7%). Logistic regression analysis showed that meat fonder and mixed diet were had significantly high risk of HNC than vegetarian diet (OR 6.86; 95% CI= 3.72-12.63; $p < 0.001$) and (OR 2.10; 95% CI= 1.97-3.80; $p < 0.001$) respectively (Table 3).

Consumption of fruit and vegetables showed highly significant difference between groups ($\chi^2_{(2)} 51.70$; $p < 0.001$) and low consumption had 1.76 fold increased risk of HNC (OR; 1.76 95% CI= 1.97-3.80). Moderate usage of fruit and vegetables had reduced risk of HNC (OR; 0.34 95% CI= 0.20-0.57, $p = 0.002$). (Table 3)

Table 3: Diet pattern in HNC patients and controls

Parameters	Patients (n=320) n(%)	Controls (n=320) n (%)	Chi –sq test		Multiple Regression Analysis	
			Chi –sq value	P-value	OR (95% CI)	P-value
<i>Diet</i>						
Vegetarian	119(37.2)	211(65.9)			Ref	Ref
Mixed diet	143(44.7)	94(29.4)			2.70 (1.91-3.80)	<0.001***
Meat fonder	58(18.1)	15(4.7)	<0.001***	121.75	6.86 (3.72-12.63)	<0.001***
Consumption of fruit and vegetables						
High	83(25.9)	94(29.4)			Ref	Ref
Moderate	27(8.4)	91(28.4)			0.34 (0.20-0.57)	0.002**
Low	210(65.6)	135(42.2)	<0.001***	51.70	1.76 (1.22-2.54)	<0.001***

For statistical details and abbreviations see Table 1.

The study population related to anaemic status was divided into two groups (anaemic and non-anaemic). The non anaemic patients (50%) were less than controls (96%) but anaemic patients (50%) were more than controls (4%) (Figure 1).

Statistically significantly high difference was observed between the groups ($\chi^2_{(1)} = 1.70$; $p < 0.001$). The multiple logistic regression analysis indicated significantly increased risk of HNC in anaemic patients (OR 22.132; 95%CI 12.41-39.48).

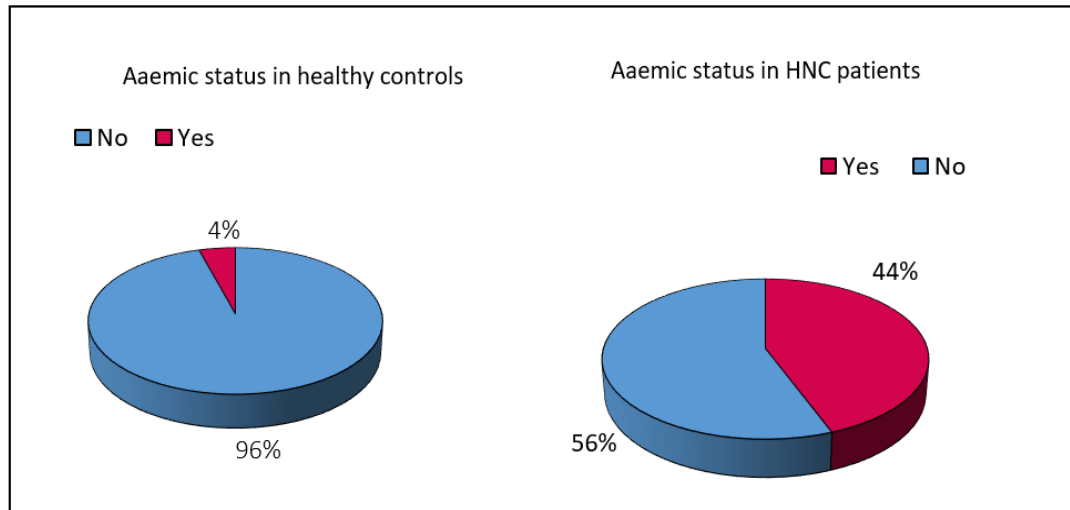


Figure 1: Association of anaemic status in HNC patients and control

4. DISCUSSION

The objective of current study was to observe the prevalence of risk factors of HNC in Punjab province of Pakistan. The results of study showed highly significant difference in patients and controls for age, smoking, chewing habits, diet pattern, consumption of fruit and vegetables, anaemic status of body, socioeconomic status, occupational status, monthly income and type of occupation ($p < 0.001$). Poor oral hygiene ($p = 0.006$), sun exposure ($p = 0.016$), location in Punjab ($p = 0.002$) and gender ($p = 0.057$) were also found significantly different.

High frequency of patients was observed in age group <38-62 years. This result supported by variety of studies signify higher frequency of HNC patients were seen in old age usually above 60 years in both genders [12], [13], [14]. Contradictory result was seen by Khawar et al. where high percentage of patients were from age 41-55 years group [15].

In another study oral cancer ranks as the most prevalent cancer in indian men [16]. High frequency (86%) of male patients of HNC was observed by Alvarenga et al. [12]. Male to female ratio observed was 8.43: 1, where 89.4% male were observed in HNC patients which differs from recent study where ratio of male to female was 1.2:1 [6].

Environmental and second hand tobacco smoke exposure was also high significantly associated with HNC with p-value < 0.001 (OR 3.21 and 5.32). These results are similar to some recent studies [18], [19]. In another study, 74.6% of Canadian OSCC patients and 46.0% of Indians were smokers [20]. Highest frequency of smoker were observed 84.40% in any form of smoked and smokeless by Chauhan et al. 2022 in both gender [6].

Chewing tobacco was associated with increased risk to oral cancer with OR 1.81 (95% CI 1.04-3.17) [21]. Betel quid use had 13 fold more risk to develop oropharyngeal cancer in Taiwan and china as compared to Indian population with 3 fold risk [22]. In one of another study , 72.3% of Squamous cell carcinoma of Indian patients were betel quid chewer [20]. In Myanmar betel quid with tobacco is chewed by huge population [23]. In Nepal adolescent used to chew areca nut more as compared to smokeless tobacco [24].

According to Hashim et al. 2016, oral hygiene and periodontal disease had contributed in the expansion of head and neck cancer mainly in oral carcinoma with odd ratio 0.83 and 95% of CI 0.79-0.88 [25]. In another study, it had been clearly mentioned that extensive use of mouth wash was responsible for HNC [26].

Low socioeconomic status people were associated with high risk factors of HNC like tobacco [27]. Similar results were observed by another study of oral cancer (OR= 3.89, 95% CI 1.28- 11.82) [28]. These results support current study.

In another study, an increased risk of SCC in head and neck area was observed associated with sunlight exposure [29]. Similar results were found in the current study.

However high risk value was observed by Negri et al, in cross sectional study of HNC with 7.2 fold increased risk with (95%; CI 5.5–9.5) in patients with had family history of cancer as well as smokers and drinkers [30]. Afterwards, in another case-control study, 2.27fold high risk was found with a high association (95% CI: 1.26–4.10) in Family History of Cancer and patients of HNC which were under 45 years [31]. According to Xiao 2022 history of cancer in family might be a risk of oral squamous cell carcinoma with p-value 0.007 (OR=1.540 95%CI 1.128-2.102) in patients with no restriction of age [32].

A number of studies had shown a defensive consequence association with elevated consumption of fruits and vegetables [33], [34]. A study in India explored that HNC patients who were habitual to eat fruits and green leafy vegetables exposed decreases risk by 2 folds as contrast to butter and pulses users [35]. The same tendency was described by Clarence et a.[36] that is similar to current study results.

5. CONCLUSION

Current study results elaborated that demographic and behavioural factors as well as diet play a critical role in HNC development among the population of Punjab, Pakistan. Among demographic factors late age, unmarried status, low income, unemployment, rural dwelling and belonging to central Punjab were the key factors contributing in HNC development. Among behavioural factors smoking habit and its high frequency, chewing habits, poor oral hygiene and sun exposure proved to be the major contributing factors. Diet pattern also found to be involved in HNC development as meat fonder habit and low consumption of fruit and vegetables were the significant contributing factors towards HNC.

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