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ASSOCIATION OF ORAL CANCER WITH RIGHT HAND DIGIT RATIO (2D:4D) USING RADIOGRAPHIC AND PHOTOGRAPHIC METHOD"- AN OBSERVATIONAL STUDY

Oral Medicine

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ABSTRACT

Background: The second to fourth digit ratio (2D:4D), is a sexually dimorphic trait, with males on the average having lower ratios than females. 2D:4D is established prenatally & also appears to be universal across ethnic groups. Genes like HOX, AR and LIN28b involved in the development of digits have been recently correlated to carcinogenesis. So 2D:4D is a presumed marker for prenatal hormone exposure as well as the action of HOX, AR and LIN28b genes. Hence 2D:4D can be used as a proxy marker to predetermine the susceptibility of tobacco chewers to develop oral cancer.

Objective: This study was undertaken to explore the possible association between digit ratio, oral leukoplakia (OL) and oral cancer (OC) in male tobacco chewers.

Methods: The study included 150 male subjects divided into 3 groups, group I- oral leukoplakia, Group II- oral cancer and Group III- controls with 50 subjects in each group. Digital photographs and radiographs of the right palms were obtained and digits were measured using Adobe Photoshop CS 6. Data was analyzed by ANOVA and Newman-Keuls multiple post hoc procedures.

Result: Risk factor (tobacco consumption) was similar between the study groups. Among the 3 groups, subjects in oral cancer group presented significant higher 2D:4D with p-value-0.00001 in both photograph and radiograph as compared to subjects in Group I and Group III.

Conclusion: The inference of the study is that male tobacco chewers with a higher digit ratio,have higher risk of developing oral cancer. Hence 2D:4D digit ratio can be used as a marker for screening all tobacco users for their susceptibility to develop oral malignancy.

KEYWORDS

Digit ratio, 2D:4D, Oral cancer, Oral leukoplakia, Hoxgenes.

INTRODUCTION

Oral cancer (OC) is one of the most prevalent cancer which ranks sixth in the global perspective of cancer burden with the highest mortality rate. OC is often preceded by oral potentially malignant diseases (PMD's) like leukoplakia, oral submucous fibrosis with a malignant transformation rate of 0.13% to 17.5%.[1,2,3]

In India, oral cancer ranks first among all cancers in men and as number three, among cancers in women.[4] The reason for high prevalence of OC in India is primarily attributed to tobacco consumption in the smokeless form.[5]Tobacco is the main etiological factor of oral cancer but it has been correlated to nutrition, oral hygiene, p53, HOX (homeobox) and AR (androgen receptor) genes as only 10-15% tobacco users develop OC[6-10]. Hence exploring new techniques for early prediction of OC is the need of the hour. Most of the screening methods and markers to predetermine tobacco users for their susceptibility to develop OC are invasive, expensive and not easily accessible. One such presumed marker that has generated considerable interest among medical and dental fraternity is the digit ratio or 2D:4D.[11]The digit ratio or 2D:4D is the ratio between the length of the second finger to the length of the fourth finger. Considerable evidence suggest that 2D:4D may be predictive of susceptibility to some types of cancer and this is predominantly true for cancers which show sex differences in their occurrence, progression and/ or prognosis.[12]

The second to fourth digit ratio (2D:4D), is a sexually diamorphic trait, with males on the average having lower ratios than females. 2D:4D is established in the uterus and unaffected by puberty. It also appears to be universal across ethnic groups, and it exists in mammals and other primates. 2D:4D is positively associated with prenatal estrogen and negatively associated with prenatal testosterone. 2D:4D could be influenced by many genes like HOX, AR, and a variant of the LIN28b genes as well as prenatal hormone exposure. These genes have been correlated to carcinogenesis.[13-19]HOX genes are involved in morphogenesis and cell differentiation of digits.[13]During normal development, HOX genes stimulate the proliferation of progenitor cells and when overexpressed promote tumorigenesis. [20,21,22,24,25,26]. Studies have shown overexpression of HOX genes in head and neck cancer.[14,23,24,25] As HOX function is reflected in 2D:4D, it could be used as a presumed marker for susceptibility to diseases influenced by these genes such as oral cancer. Thus 2D:4D could help identify patients with predisposition to oral cancer.

In literature 2D:4D has been correlated to many gender linked traits and pathologies. In recent years numerous studies have shown possible correlation of 2D:4D with oral cancer[11], prostate cancer risk and severity[13,29,33], cervical dysplasia[34], alcohol dependency[35] and various psychological and behavioural characteristics like aggression, assertiveness, decision making, attention deficit disorder, male dominance, variation in menstrual cycle etc.

There is a paucity of research regarding association of digit ratio with oral cancer. Hence in the present study an attempt was made to investigate the possible correlation of oral leukoplakia and oral cancer to the ratio of second to fourth digit of the right hand in male tobacco chewers. The present study is a simple, inexpensive and non-invasive way of screening high risk individuals i.e. male tobacco chewers for their susceptibility to develop oral cancer.

MATERIALS AND METHOD

SOURCE OF DATA

Study sample included 150 subjects between 25 to 60 years reporting to the Department of Oral Medicine and Radiology, after obtaining an informed consent. The study was approved by the Ethical and Research committee of Institute. The first step included interviewing the subjects regarding their tobacco habits, its duration and frequency.

METHOD OF COLLECTION OF DATA

A total of 150 male tobacco chewers were included in this study, divided into following three groups:

Group I: Clinically and histopathologically confirmed cases of oral leukoplakia (n=50)

GroupII: Clinically and histopathologically confirmed cases of oral squamous cell carcinoma (n=50)

GroupIII: Control group with no precancerous and cancerous

lesions(n=50)

SELECTION CRITERIA

Inclusion criteria

1. Male tobacco chewers with oral leukoplakia.
2. Male tobacco chewers with oral squamous cell carcinoma.
3. Male tobacco chewers without any precancerous and cancerous lesions.

Exclusion criteria

1. Females
2. Subjects with a history of right index or ring finger fracture/ deformities
3. Subjects with a history of hormonal disorders
4. Other concurrent oral lesions and precancerous lesions

PROCEDURE

A detailed case history was followed by clinical examination and histopathological confirmation, photograph of the right palm was taken using Sony cyber-shot DSC-WX150/S digital camera. For standardisation a metallic scale was kept on the radial side of the right palm. Standardised camera configurations were used for all photographs to avoid discrepancies between the images. Individuals kept their wrist, back of right hands and fingers extended and placed on a flat surface through the capturing process. Image analysis was made by Adobe photoshop CS6 measuring tool using 100% zoom. In the photograph length of the index and ring fingers of the right palm was measured in a linear fashion from the middle point of the most proximal crease up to the tip of the finger. Measurements were repeated at three different times. Then index finger length was divided by the ring finger length, originating the 2D:4D ratio. The analysed ratio was the mean of the three measurements performed.

The digital radiograph of the right palm was taken using Kodak 8000C digital panoramic and cephalometric system placing 1cm stainless steel wire on the sensor on the radial side of the right palm. For standardisation 1cm stainless steel wire was used. The length of the second and the fourth finger was measured from the proximal end of the proximal phalanx to the distal tip of the distal phalanx using Adobe photoshop CS6 measuring tool with 100% zoom. 2D:4D measurements were made similar to photographs.

STATISTICALANALYSIS

The statistical significant difference between the three groups with and without precancerous and cancerous lesions was calculated using one-way analysis of variance (ANOVA) test. Pair wise comparison of 2D:4D in the three groups was done by Newman-Keuls multiple post hoc procedures. p-value of less than 0.05 was considered to be statistically significant. Comparison of 2D:4D by photograph and radiograph methods in all the three groups was done by paired t test. Correlation of 2D:4D between photograph and radiograph methods in all the groups was done by Karl Pearson's correlation coefficient.

RESULTS

In the present study an association of 2D:4D or digit ratio between oral leukoplakia, oral cancer and controls was determined. Study population included 150 subjects divided into three groups consisting of 50 tobacco chewers with leukoplakia designated as Group I, 50 tobacco chewers with oral cancer as Group II and 50 tobacco chewers with no precancerous or cancerous lesion as Group III. When photographic 2D:4D was compared between the groups, the results were statistically significant between group I and group III (p value=0.00001) and between group II and group III (p value=0.00002) as illustrated in figure 1. When radiographic 2D:4D was compared between the groups, the mean 2D:4D was high in Group II(cancer group) followed by Group I (leukoplakia group) and the results were statistically significant as illustrated in figure 2. In this study comparison of photographic and radiographic 2D:4D between the groups showed statistically significant results as shown in table 1.Correlation between photographic and radiographic 2D:4D among the groups was statistically significant as shown in table 2.

DISCUSSION

In India smokeless tobacco use is the major risk factor for potentially malignant lesion and malignancy.[6]Oral cancer is usually preceded by potentially malignant lesions like oral leukoplakia, erythroplakia and erythroleukoplakia.[1,2,3]Early recognition is crucial to improve oral cancer survival rates, quality of life, preserve function and enhance aesthetic and psychological outcomes.[27]

Various factors have been implicated in the etiology of oral cancer which include tobacco, alcohol, viruses, diet, family history, immune deficiency, genetic factors. Tobacco is the main etiological factor but it has been correlated to nutrition, oral hygiene, p53, HOX (homeobox) and AR (androgen receptor) genes as only 10-15% tobacco users develop Oral Cancer.[6-10]Significant data also suggests that the carcinogenic process is driven by an interaction between exposure to exogenous carcinogens and inherent genetic susceptibility. Consequently individuals with genetic instability may be at a greater risk for developing cancer.[5,26,28]

Identifying individuals at high risk of developing oral cancer could be of great value to decrease the incidence of OC. There are various markers to determine the individuals' susceptibility to OC. Most of the screening methods available are invasive, expensive and not feasible. It has been suggested that many genes which take part in the control of finger development can also give an indication to the development of premalignancy and malignancy.[7,13,14] One such possible marker is 2D:4D. The 2D:4D being an inexpensive and non invasive method is rather a unique approach for identifying high risk individuals.

2D: 4D has been studied extensively in cancers like prostate and cervix but only limited data is available on oral cancer.[11] A study was conducted by Jung et al, in 2010 to investigate the relationship between digit length pattern and prostate cancer in the Korean population found that those with lower digit ratio had higher mean prostate specific antigen level and higher risk of prostate biopsy and prostate cancer.[13] Another study was carried out by Rahman AA et al in 2011 to observe the protective effect of a high 2D:4D hand pattern on prostate cancer risk. The study concluded that high 2D:4D hand pattern might represent a simple marker for prostate cancer risk, particularly in men under 60 years of age.[29]

Only male subjects were included in our study as 2D:4D is sexually dimorphicbiometric marker.[30,31]i.e normally males have lower 2D:4D when compared to females which is related to prenatal testosterone and estrogen levels in utero and determined genetically by HOX and AR gene expression. This sexual dimorphism of 2D:4D is stronger in right hand than left hand.[32]

There was no significant difference in the mean duration of tobacco use among the three groups. This data is consistent with the findings of Renato Hopp et al[11] in 2011, who observed that duration of tobacco consumption was similar among subjects with oral leukoplakia, oral cancer and tobacco consuming males.

This is the first study where combination of two methods has been used. One was photographic method with standard stainless steel for standardisation using digital camera and 2D:4D was measured by using Adobe photoshop CS 6 with 100% zoom. Three independent measurements were taken to rule out intra observer variability Second was digital radiographic method of right palm with 1cm stainless steel wire attached to the x ray sensor for standardisation using panoramic machine. In our study the mean 2D:4D with photographic method was 0.9689±0.0098 in group I (Oral leukoplakia), 0.9720±0.0124 in group II(oral cancer) and 0.9505±0.0175 in group III(controls). In radiographic method the mean 2D:4D was 0.9619±0.0109 in group I (oral cancer), 0.9677±0.0133 in group II (oral leukoplakia) and 0.9424±0.0176 in group III (controls).

Our study showed that 2D:4D in men was greater than 0.95 in group I (leukoplakia) and group II (oral cancer) and p value was statistically significant in all the three groups. These results are comparable to study conducted by Renato Hopp et al[10] in 2011, who observed that mean 2D:4D was 0.9700±0.0098 in oral cancer patients, 0.9625±0.0512 in patients with oral leukoplakia and 0.9643±0.0365 in the controls.

In the present study an attempt has been made to use 2D:4D to identify male tobacco chewers who are susceptible to develop oral cancer. Limitations of the present study was small sample size, only subjects reporting to our institution were included which could lead to possibility of selection bias. Hence further studies with larger sample size need to be carried out within the community to substantiate the results.

CONCLUSION

The present study revealed a statistically significant higher 2D:4D in tobacco chewers with oral cancer and oral leukoplakia as compared to tobacco chewers without any lesions. The findings of this study suggest that though tobacco is the major risk factor for oral cancer, genetic factors may also play a role.

Based on this study future research can be carried out to investigate the relation between oral cancer and genetic and hormonal factors that could be represented by digit ratio (2D:4D). Thus to conclude 2D:4D can be used as an inexpensive and noninvasive method to identify the susceptibility of tobacco chewers to develop oral cancer, which can reduce the burden of oral cancer.

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Graphs and Tables

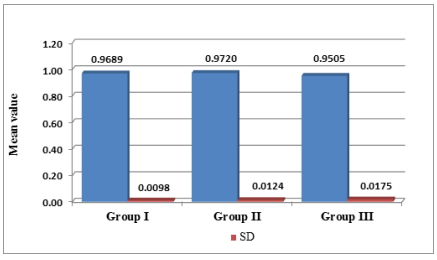

Figure1. Comparison of Photographic 2D:4D between the three groups.

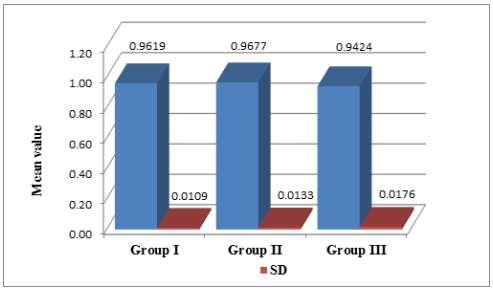

Figure 2. Comparison of Radiographic 2D:4D between the three groups.

Table 1: Comparison of photographic and radiographic 2D:4D between group I, II and III using paired't' test (*p<0.05)

Groups	Methods	Mean	Std.Dv.	Mean Diff.	SD Diff.	Paired t	p-value
Group I	Photograph	0.9689	0.0098				
	Radiograph	0.9619	0.0109	0.0070	0.0069	7.1202	0.00001*
Group II	Photograph	0.9720	0.0124				
	Radiograph	0.9677	0.0133	0.0043	0.0056	5.4499	0.00001*
Group III	Photograph	0.9505	0.0175				
	Radiograph	0.9424	0.0176	0.0081	0.0043	13.2348	0.00001*

Table 2. Correlation between Photographic 2D:4D and Radiographic 2D:4D in groups I, II and III using Karl Pearson's correlation coefficient (*p<0.05)

Groups	Correlation between photographic & radiographic2D:4D	p-value
Group I	Photograph with Radiograph	0.00001*
Group II	Photograph with Radiograph	0.00001*
Group III	Photograph with Radiograph	0.00001*

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