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Prevalence of abnormal oral cytology and impact of sexual behavior in women with abnormal cervical cytology

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Summary

Purpose of investigation: To assess the frequency of oral cytological abnormalities in women who have cervical intraepithelial lesions, and transmission of infection depending on their sexual behavior. The authors also aimed to investigate the oral cytological changes in male partners. *Material and Methods:* Thirty patients with abnormal cervical cytological results via punch biopsy formed the case group, and 68 patients constituted the control group with normal cervical smear results. The Bethesda system was used for classification of the cytological alterations. *Results:* Oral dysplasia was significantly higher in the squamous intraepithelial lesion (SIL) group. Oral sex percentage was 43.3% in SIL group, whereas it was 19.1% in the control group. History of genital warts in women with SIL was also significantly higher in the case group. Three patients were diagnosed with abnormal oral cytology in the SIL group (10%), however abnormal oral cytology was not detected in the control group. No oral dysplastic changes was identified in the male partners of women with oral lesions. *Conclusion:* The authors detected oral dysplastic changes in the SIL group, especially in the (low grade squamous intraepithelial lesion (LGSIL) patients. Interestingly they could not find any oral dysplastic changes in the male partners of the study population.

Key words: Oral intraepithelial lesion; Cervical intraepithelial lesion; Human papilloma virus.

Introduction

Intraepithelial lesions caused by human papilloma virus (HPV) infection are important precancerous alterations in the cervical and the oropharyngeal cancers [1-3]. Although cervicovaginal smear screening is an important tool for the early detection of the cytological alterations, still there is an increased incidence of cervical cancer and HPV infection among young women [4, 5]. At least 50% of women are infected by cervical HPV during their lifetime [6, 7]. Genital, oral, and anal mucosa are important anatomical reservoirs for HPV virus [8].

Oral cancers arise from the precancerous lesions of the squamous epithelium, similar to that of the cervical region [9, 10]. HPV has been linked to 99.7% of cervical and 36% of oropharyngeal cancers [11, 12]. Grun *et al.*, reported an incidence of presence of oral and cervical HPV infection that was 9.3% and 74%, respectively, in women in the age group of 15–23 years [13]. The frequency of oral HPV infection varies in the literature (0.6%– 27%) [14, 15]. HPV 16, 6, and 51 were the most commonly seen serotypes in oral infections [16-18].

Both in men and women, HPV infection is the most commonly transmitted sexual disease [19, 20]. HPV infection is highly contagious and it frequently peaks after active sexual life. The risk factors for oral HPV transmission is similar to the cervical cases [21-26], and furthermore it has been shown to be transmitted via fingers, during sexual foreplay [26, 27]. Transmission routes are oral, anal, genital sexual contact or vertically by auto-infection, depending on the sexual behavior [28,29].

Latent infections can only be diagnosed by the molecular biology techniques and not by cytological analyses because there is no cytological abnormalities found in these kind of infections [28-32]. Cancer development due to HPV follows cytological alterations. Hence cytopathologic evaluation is enough for screening [32]. Most of the time, HPV infection is usually detected after the first sexual intercourse, mainly in the adolescents and young adults [33]. It has been shown that HPV infections are eradicated most of the time, and this eradication increases with age [34]. Immune response and repetitive infections might affect the eradication process [34]. In the cytological analysis of the cervix, rectum, and oral cavity, cytological alterations were identified, related to HPV infection [35, 36].

Therefore, the authors aimed to study the frequency of oral cytological abnormalities in women who have cervical intraepithelial lesions, and transmission of infection, depending on their sexual behavior. They also aimed to investigate the oral cytological changes in male partners.

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Table 1. — *Abnormal cervical cytology and their colposcopy-cervical punch biopsy results.*

Abnormal cervical cytology (n=30)	Cervical smear results	Colposcopy (cervical punch biopsy results)	Endocervical curettage
LGSIL	15 (50%)	19 (63.3%)	5 (16.7%)
HGSIL	8 (26.9%)	11 (36.7%)	1 (3.3%)
ASGUS	7 (23.3%)		

ASCUS: atypical squamous cells of undetermined significance;
LGSIL: low grade squamous intraepithelial lesion;
HGSIL: high grade squamous intraepithelial lesion.

Materials and Methods

This case–control study was conducted at the Department of Obstetrics and Gynaecology, Sisli Etfal Research and Training Hospital, in Istanbul, Turkey, between October 2010 and November 2011. The study was approved by the Institutional Human Ethics Committee.

Inclusion criteria: sexually active heterosexual patients, older than 18 years, and their partners. Cervical punch biopsy resulted low grade squamous intraepithelial lesion (LGSIL) and high grade squamous intraepithelial lesion (HGSIL), were included to case group, and normal cervical smear results created control group. Multipartners were defined as those with more than three partners and were included in the study. Exclusion criteria: immunosuppressed patients and pregnant women.

Cervical cytologic samples were collected from the women, who were admitted to the outpatient clinics. LGSIL and HGSIL reported cases were evaluated with colposcopy and biopsy. Atypical squamous cells of undetermined significance (ASCUS) cases received antibiotics, and smear test was repeated after the treatment. If the ASCUS persisted in the smear test after the antibiotic treatment, then the cervical biopsy and colposcopy were performed. HGSIL and LGSIL cases were included in the study. Ten days after the cervical smear test, oral mucosal smear samples were obtained from both the patients and their partners. Sexual behaviors were assessed in both the genders and history of the genital warts were investigated in both the genders. Patients and their partners were examined orally for lesions. During the study period, 30 patients showed abnormal cervical cytological results via punch biopsy and formed the case group and 68 patients constituted the control group with normal cervical smear results.

Cervical cytologic samples were obtained by Papanicolaou (PAP)–smear conventional method, which was examined by one pathologist at the present Pathology Department. The Bethesda system was used for classification of the cytological alterations. Oral samples were obtained from the buccal mucosa with dacron cotton swabs, smeared on a glass slide, and fixation was done with alcohol, and were examined by the same pathologist. Oral lesions related to HPV, were regarded as oral intraepithelial lesions, and were referred to the ear, nose and throat (ENT) specialist.

The normality of the distribution of continuous variables was assessed by the Kolmogorov–Smirnov test. The chi-square test was used for the categorical variables. Student's *t*-test was used for normally distributed continuous variables, and the Mann–Whitney *U*-test was used for non-normally distributed variables. A p-value < 0.05 was considered as indicating the statistical significance.

Results

During the study period, 30 samples were diagnosed with squamous intraepithelial lesion (SIL). Among the SIL cases, seven (23.3%) were diagnosed with ASCUS, 15 (50%) were diagnosed with LGSIL, and 11 (36.7%) were diagnosed with HGSIL. After colposcopic biopsy, 19 (63.3%) patients had LGSIL, and 11 (36.7%) had HGSIL. After biopsy, four patients with ASCUS were diagnosed with LGSIL, and three with HGSIL (Table 1).

Table 2. — *Demographic data and sexual behavior of the case (cervical dysplasia) and control groups.*

	SIL (n=30)	Control group (n=68)	*p value*
Age (years)	37.9 ± 8.2	33.2 ± 7.4	0.006
Age distribution			0.01
18-25	3 (10%)	13 (19.1%)	
26-30	3 (10%)	10 (14.7%)	
31-40	10 (33.3%)	34 (50%)	
≥40	14 (46.7%)	11 (16.2%)	
Parity	2.2 ± 1.5	1.1 ± 1.2	0.001
Smoking	13 (43.3%)	16 (23.5%)	0.049
Alcohol consumption	9 (30%)	20 (29.4%)	0.95
Oral dysplasia	3 (10%)	0	0.008
Oral dysplasia in partner	0	0	
Anal intercourse	5 (16.7%)	2 (2.9%)	0.016
Oral intercourse	13 (43.3%)	13 (19.1%)	0.01
History of genital warts	15 (50%)	7 (10.3%)	0.000
History of genital warts in male partner	1 (3.3%)	0	
Multiple sex partner history in females	6 (20%)	13 (19.1%)	0.92
Multiple sex partner history in males	30 (100%)	35 (51.5%)	0.000

SIL: squamous intraepithelial lesion.

Demographic data of the case group (cervical dysplasia, n=30) and control group (n=68) are shown in Table 2. SIL cases were detected in older age, with significant parity. Oral and anal intercourse (oral dysplasia), was significantly higher in the SIL group. Oral sex percentage was 43.3% in SIL group, whereas it was 19.1% in the control group. History of genital warts in women with SIL was also significantly higher in the case group. Fifteen (50%) of the patients who had SIL had a history of genital warts. Multiple sex partner history was significant in male partners of SIL group, compared to the control group. However multiple sex partners among female patients were not significant between the two groups (Table 2). Three patients were diagnosed with abnormal oral cytology in the SIL group (10%), however abnormal oral cytology was not detected in the control group. When sexual behaviour was evaluated, 13 (43.3%) of the patients had a history of oral sex and five (50%) had a history of anal sex. Also, six (20%) of the SIL group had multipartners.

According to the oral sex habit of the study population, they were divided into two groups. Three cases of oral dysplasia were detected in oral sex group, whereas oral dys-

Table 3. — *Comparison of the data according to their oral sex habit.*

	Presence of oral sex habit (n=26)	No oral sex habit (n=72)	*p value*
Age distribution (years)			0.003
18-25	9 (34.6%)	7 (9.7%)	
26-30	6 (23.1%)	7 (9.7%)	
31-40	8 (30.8%)	36 (50%)	
≥ 40	3 (11.5%)	22 (30.6%)	
Smoking	14 (53.8%)	15 (20.8%)	0.002
Alcohol consumption	14 (58.3%)	15 (20.8%)	0.002
Oral dysplasia	3 (11.5%)	0	0.003
Anal intercourse	6 (23.1%)	1 (1.4%)	0.000
History of genital warts	12 (26.5%)	10 (13.9%)	0.001
History of genital warts in male partner	1	0	
History of female polygamy	11 (42.3%)	8 (11.1%)	0.001
History of male polygamy	23 (88.4%)	42 (58.3%)	0.005

plasia was not identified in the control group. The percentage of oral and anal sex, genital warts in females, smoking, alcohol consumption, multiple partner history, in both genders, were all significantly more common in the oral sex group (Table 3). All were discovered with LGSIL (20%, 3/15 cases). No oral lesions were detected in the patients with HGSIL. The mean age of patients was 42.3 ± 12.2 years. Two of them were above 40 years of age. One patients had engaged in anal intercourse and two in oral sex. Interestingly no oral dysplastic changes was identified in the male partners of women with oral lesions. Furthermore no oral lesion was detected in the male partners of the study population.

Thirteen (43.3%) patients diagnosed with SIL were smokers and nine (30%) had a history of alcohol consumption. Out of 13 smokers, one (7.6%) patient was diagnosed with oral dysplasia. Out of 17 patients who were non-smokers in the SIL group, two of them (11.7%) were diagnosed with oral dysplasia. Out of nine patients who consumed alcohol in SIL group, one had oral dysplasia (11.1%), and out of 21 patients who were non-alcoholics, two (9.52%) had oral dysplasia. The relationship between smoking and alcohol consumption with oral dysplasia were not significant in SIL group ($p = 0.71$, $p = 0.89$, respectively).

Discussion

In the present study the authors detected oral dysplastic changes (10%) in the SIL group, especially in the LGSIL patients. Interestingly they could not find any oral dysplastic changes in the male partners of the study population.

Currently, oral cytological examination is not performed routinely in the patients with SIL. Cervical cytological abnormality is important in the risk groups, in terms of cytological screening. Since it is a cheap method and it is easy to perform, the patients with SIL could be included in to the screening program, in terms of oral dysplastic changes. According to the previous studies, oral cytological evaluation seems to be sufficient in detection of the oral cytological abnormalities [37, 38].

The incidence of oral HPV infection was 6.1% in the female sex workers [26,39]. In the study by Kurose *et al.* [40], the incidence of oral HPV infection was 0.8% in the general population. Zonta *et al.* [35], detected oral dysplasia in 11.1% of the patients with SIL. In the present study, the incidence of oral dysplasia in the patients with SIL was 10%. Abnormal findings in the cervical cytology is an important risk factor for oral HPV infection [28, 35, 39, 41]. In the previous studies, it has been demonstrated that, although there was no oral and cervical concordance in HPV types, the high incidence of oral infections in the patients with SIL demonstrated that cervix was an important reservoir for HPV infection, and oral genital interaction has an important role in the contamination of HPV infection [35, 39, 41].

Zonta *et al.* [35] observed that oral HPV infections were most frequently seen between the age group of 20–30 years. However, in the study conducted by Ragin *et al.* [41], the mean age was 51.8 years. In the current study, the oral cytological changes related to HPV infections were seen in the individuals with the mean age of 42 years.

Polygamy plays an important role in the contamination of HPV infection. The more frequent an individual encounters HPV infection, the higher the risk of being infected by this infection, and the higher the risk of encountering with different types of HPV, due to polygamy. It has been demonstrated that in addition to the sexual behavioral pattern, polygamy and the rate of indirect meeting with the infection, are important in the contamination of HPV infection. In the study by Zonta *et al.* [35], HPV positivity was observed to be higher in the heterosexual women, compared to the homosexual women. In the study by Ragin *et al.* [41], the frequency of oral HPV was found to be same in the heterosexual and the bisexual women. The male partner is an important risk factor in the contamination of the infection. In the current study, the incidence of SIL and oral dysplastic lesions were significantly correlated with the male polygamy, yet uncorrelated with the female polygamy. It was also reported that polygamy is an important risk factor in oral infections [41]. In the current study, male polygamy was considered significant for the development of oral dysplasia, rather than in female polygamy. Also male polygamy was important in the patients with SIL. Moreover it is assumed that sexual intercourse with a male partner could cause more oral HPV infection, compared to sexual intercourse with a female partner [14,41]. When the incidence of oral HPV infection was compared between oral and vaginal sexual intercourse, it was observed more frequently in the patients who had vaginal intercourse, however further studies are still needed [20]. The present authors found that the incidence of cigarette smoking, history of oral and rectal sexual intercourse, male polygamy, and history of papil-

loma were significantly higher in the patients with SIL, as compared to the control group.

The oral and the rectal regions are important as being reservoirs for the recontamination of the infection [8]. Oral-genital contaminations could prevent the recovery from the infection. On the other hand, in the present study, oral sexual intercourse affected the frequency of oral dysplasia. It is thought that there is different affinity and clearance of HPV infection, according to the different mucosal regions. In the current study, oral mucosal region was less affected that the cervical region. Oral mucosa was the least affected region in terms of autoinfection and horizontal infection.

There are studies related to the clearance and persistence of cervical HPV and its relationship with smoking and alcohol consumption. In a previous study, it has been demonstrated that the clearance of cervical HPV infections was 67% within 12 months, followed by the diagnosis [34, 42]. It has also been demonstrated that the recurrence of cervical viral infection was related to the age and the chronic alcoholic consumption. However, it was not related to cigarette smoking [8]. Moreover, the viral recurrence was high in the immunosuppressive patients [20]. Nevertheless, in some studies, it was observed that cigarette smoking was a high risk factor for the development of new cervical infections [41]. In the current study, while there was no correlation between SIL and alcohol consumption, a correlation was found between SIL and cigarette smoking; however the incidence of oral dysplasia was not significant in cigarette smoking and alcohol consumption.

Autoinfections could develop through the anatomical reserves in oral, rectal, vulvar, vaginal, and cervical regions. These regions could cause recurrent infections and lead to long-term infections [1]. In the current study, when the incidence of oral dysplasia and SIL in the patients with history of genital warts were examined, it was found to be higher in the patients with genital warts. This supports the finding that cervical lesions and macroscopic lesions are important reservoir regions for HPV. Thus, there would be more frequent recurrent oral and cervical infections, and development of more frequent cytological abnormalities. The present authors found oral dysplasia lesions more frequently in the patients who had history of genital papilloma and cervical dysplasia. However all oral dysplasia cases were observed in LGSIL patients, in contrast they did not identify oral mucosal lesions in HGSIL patients. A similar study was also conducted by Zonta *et al.* [35].

The prevalence of HPV types causing oral, anal, and cervical infections is different [2, 3, 12]. In the previous studies, a correlation was observed between cervical and oral infections, however, no correlation was observed with the same serotype of HPV infection, and this results showed that the autoinfection was not frequent [35]. In addition, it has been demonstrated that oral infection develops with different types of HPV [41]. In another study, by Hippeläinen *et al*. [43], no correlation was found between high-risk HPV serotypes in women, and with high-risk HPV serotypes in their male partners. In the present study the authors could not identify any oral lesions in male partners of the cervical dysplasia group. This demonstrated that the oral-oral contamination between the partners was not frequent in this study population, however more detailed information is needed. However oral dysplastic changes was only present in the females who had oral sex behavior. Although the correlation of HPV serotypes in cervical and oral infections were not found to be concordant, it has been demonstrated that the most frequent HPV types observed in the patients with oropharyngeal and cervical cancers, were similar [18, 39, 41, 44]. As the present authors found that oral dysplasia was more frequently seen in the patients with SIL, the immunization program used in the prevention of cervical cancers might also be important in the prevention of oropharyngeal cancers.

Limitations of the present study: (a) the small sample size, (b) the absence of HPV typing, and (c) the absence of typing of the infections of the male genital region.

The current study demonstrated that oral intraepithelial lesions (OILs) was seen in the patients, with SIL, at a higher rate. This high rate was more noticeable, especially in the patients who have LGSIL, genital papillomas, oral sexual intercourse, and male polygamous partners [30, 35, 39, 41]. These results demonstrated that the genital region is an important reserve and cause of recurrent infections. The diagnosis of cervical HPV infections with cytological screening and determination of the prevalence of oral infection is also epidemiologically important. Since OIL has not been observed in the male patients, it demonstrates that there is a need for further studies with higher number of patients to investigate the oral-oral contamination, as a risk factor between the partners.

In conclusion, the prevalence of SIL and OIL was found to be significantly correlated with male polygamy, yet not significantly correlated with female polygamy. Moreover, the incidence of OIL and SIL was higher in the patients who had oral sexual intercourse. Further broader studies are needed to understand the link between the epidemiology of the sexual behaviors and HPV infections.

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