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REVIEW ARTICLE

Oral Sex and HPV: Population Based Indications

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Abstract Human pappilloma virus (HPV) is well established in etiology of uterine cervical cancers, but its role in head and neck cancer is strongly suggested through many epidemiological and laboratory studies. Although HPV-16 induced oropharyngeal cancer is a distinct molecular entity, its role at other sub-sites (oral cavity, larynx, nasopharynx, hypopharynx) is less well established. Oral sex is supposedly the most commonly practiced unnatural sex across the globe and may prove to be a potential transmitting link between cancers of the uterine cervix and the oropharynx in males particularly in those 10–15% non-smokers. In India with the second largest population (higher population density than China) the oral sex is likely to be a common 'recreation-tool' amongst the majority (poor) and with the concurrent highly prevalent bad cervical/oral hygiene the HPV is likely to synergize other carcinogens. Hence in accordance (or coincidently), in India the cervical cancer happens to be the commonest cancer amongst females while oral/oropharyngeal cancer amongst males. Oral sex as a link between these two cancer types, can largely be argued considering a poor level of evidence in the existing literature. The modern world has even commercialized oral sex in the form of flavored condoms. The inadequate world literature currently is of a low level of evidence to conclude such a relationship because no such specific prospective study has been carried out and also due to wide (and unpredictable) variety of sexual practices, such a relationship can only be speculated. This article briefly reviews the existing literature on various modes and population based indications for HPV to be implicated in head and neck cancer with reference to oral sexual practice.

Keywords Oral sex · HPV

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Human pappilloma viruses (HPV) are well-established etiological factors for development of cervical cancer (specially types 16 & 18) and also highly likely to be involved in the cancer of head and neck. Although a clear cut evidence for causation of head and neck cancer as established for the uterine cervix is not yet available [1], the trends for increased risk of cancer of oral cavity, larynx and pharynx subsequent to the occurrence of cancer of cervix have been found, suggesting common etiological factors besides smoking. It may not be absolutely irrelevant to think oral sex as a vector for transmission of HPV from uterine cervix to oral cavity/oropharynx. We did a PubMed search with words like 'cancer', 'HPV', 'HSV', 'Uterine cervi*', 'cervi*', 'oral sex', 'unnatural sex', 'homosex*', 'oral cavity', oropharynx*', 'laryn*', 'nasopharyn*', 'head & neck' in different combinations. The relevant literature was reviewed for the prevalence/characteristics of HPV infection in uterine cervical cancer and at different sites in head and neck. The current literature on oral sexual practices was also reviewed to find indications for a possible relationship with oral sexual mode of transmission. The other irrelevant and unauthentic literature was not considered in the study. Furthermore our population data to see some preliminary trends was adapted from an authentic IARC-WHO publication as will be discussed later.

Although a relatively less knowledge exists about the prevalence, determinants and the natural history of HPV infection in the epithelium of oral cavity and pharynx; the accumulating epidemiologic and laboratory data constantly

supports the etiologic role of HPV (especially type 16) in a fraction of oropharyngeal/tonsillar cancer and also in smaller fraction of oral cavity cancer. HPV has been found in substantial proportion of benign upper aero-digestive tract lesions. For example the oral cavity lesions include oral papillomas (associated with HPV-6 and HPV-11), focal epithelial hyperplasia (HPV-13 & HPV-32), and erythoplakia (HPV-16) and laryngeal lesions include recurrent papillomatosis (types 6 or 11). Hence the high risk HPVs (16 & 18) are tumorogenic in human epithelial tumors while the others that include low risk ones (especially 6 & 11) cause benign lesions. In a PCR based HPV detection study on 98 squamous cell cancer of head and neck [2], only 26% were found to be HPV positive. Stratified according to tumor location, the frequency of HPV positive lesions was 18% in oral cavity, 45% in oropharynx, 25% in hypopharynx, 8% in nasopharynx and 7% in larynx. The role of HPV in oral cavity is not fully clear but strong laboratory evidence has been obtained for an active role of HPV in oral cancer from a study showing transcriptionally active, integrated HPV-16 DNA that persisted in oral cancer cell line showing features indistinguishable from those of the primary tumor [3]. Herrero [4] while reporting the HPV predominantly in oropharyngeal/tonsillar cancer, further stressed that there is not yet any compelling evidence to prove the causative role of HPV in laryngeal cancer given that recurrent respiratory papillomatosis is clearly caused by HPV. Clayman et al. [5] found that 46% (30 of 65) of laryngeal and hypopharyngeal tumors had detectable HPV DNA. Venuti et al. [6]. demonstrated the commonest type of HPV DNA isolated from laryngeal cancer specimen to be type 16 followed by type 6. Although HPV types 6 & 11 are predominantly seen with benign papillomatoses, but a different variety is possibly associated with cancer.

The indications for a causative role of HPV is reflected through many studies but not yet been fully understood. The ability of HPV oncoproteins E6 & E7 to disrupt p53 & Rb mechanisms were previously identified as important in genetic progression of head and neck cancer. Hence HPV infection may be an alternate but functionally analogous pathway for head and neck squamous cell carcinogenesis. Although tobacco and alcohol are largely attributed to head and neck cancer, 15–20% of patients have no such exposure history suggesting heterogeneity in carcinogenesis leading to similar phenotype.

Klussmann et al. [2]. showed that the viral loads in tonsillar tumors were comparable to the viral loads seen in cervical carcinomas. Even circulating HPV-16 DNA has been seen in the serum of the subjects with head and neck tumors who had detectable HPV-16 DNA in their primary tumors [7]. This may possibly suggest a hematogenous spread (may be of cancer cells), when it may be possible for the HPV induced primary cervical cancer to secondarily result in oropharyngeal involvement. On the other hand, Kellokoski et al. [8]. found that simultaneous oral HPV infections appear to be uncommon and genital infections do not appear to predispose individuals to oral HPV infections, assuming the acute infection by HPV cannot be cleared by immunosurveillance mechanisms and HPV sequence is retained as a nucleic acid remnant in the cell. Thus it may also be possible that hematogenous spread of HPV-containing-cancer cells rather than the HPV-DNA is likely to result in synchronous oropharyngeal cancer. Contrary to the situation in cervical cancer, relying on the exfoliative cells in oral cancers appear to grossly underestimate the actual prevalence, as HPV as been shown to be undetectable in exfoliative cells of more than 90% of patients harboring HPV DNA in their biopsy specimen [4]. Sun et al. [9]. showed a positive detection of HPV in mucosal swabs from laryngeal papillomatosis site of the patients, but no swabs from other sites (either of the patient or the relatives) were HPV positive despite the presence of adequate DNA in swabbed material for successful amplification of beta-actin sequences. This is consistent with the absence of reported cases of horizontal transmission to siblings or other family members. The findings are also consistent with the conventional view that juvenile respiratory papillomatosis is transmitted vertically from vaginal condylomas in the mother. Laryngeal papillomatosis has a bimodal age distribution, with peaks before 5 years and in between 20 and 30 years of age, suggesting either a vertical transmission or through sexual contact. Based on this conventional view of vertical transmission of virus from vaginal source, it may be possible for HPV to be acquired by oral sex (heterosexual) during active sexual life. As in respiratory papillomatosis, the oncogenic virus strain (e.g. HPV-16) may have a selective predilection for a particular site (viz. lymphoid follicles of the first defense mechanism located in oropharynx). The study conducted by Kellokoski et al. [8] that did not show any correlation between oral and genital HPV infection, may reflect a more orthotopic natural inhabitance of HPV in genitalia. Although more than 50% females practiced oral sex, but the oral prevalence of HPV in their partners was not estimated. It is highly unlikely for these females to orally stimulate their own genitalia and hence the evidence of direct oral transmission from 'viral-loaded' genitalia cannot be commented upon through this study. Contrary to above, the situation may possibly be very different while estimating the likely oral sexual transmission from an early-malignant/pre-malignant female-genital lesion wherein comparable viral loads may be found in oropharynx and cervical carcinomas as discussed earlier [2]. Not many studies have focused on the association of oral sex behavior with HPV prevalence. Maden et al. [10] concluded absence of any etiologic link

between oral cancer, HPV-16 infection and oral sex, but their study was based upon the study of the exfoliative oral cells only (not from oropharyngeal segment or tissue). However they found HPV-6 infection as a risk factor but still no sexual transmission of such was documented. Many contradictory studies have observed positive [11] or negative [12–14] associations of increased sexual behavior (high number of sexual partners, younger age at first intercourse, history of genital warts) with oral cancer risk in men. Although oro-genital contact has not been associated with oral cancer risk in case control studies, but in case-comparison, the odds of a tumor being HPV-positive increased in individuals who reported a history of oral-genital sex or >6 lifetime sex partners [15]. No association between incident oral HPV infection and oral-penile contact during the preceding 12 months was reported in college-aged women [16]. Same gender oral sex was shown to be significantly associated with HPV seroprevalence among men and possibly an exposure at oral-mucosal site is more likely to result in HPV seroconversion when compared with non-mucosal sites (genital region) in men [17]. It is unclear as to why the tonsil appears to be infected preferentially. Notably tonsillar HPV infection was strongly associated with HIV infection, immunosuppression, and several measurements of sexual behavior in univariate analysis [17]. Recent personal communication of Sturgis EM [18] at MD Anderson cancer center (unpublished) reveals more or less an equal incidence of HPV in palatine tonsils and base of tongue. Since both the sites (palatine tonsils and lingual tonsils) have more or less similar type of lymphoid tissues, the epithelium of the deep tonsillar crypts in close contact with lymphoid tissue may be more susceptible to HPV infection or transformation.

At least one study [19] has indicated that oral sex may be involved in the transmission of HPV to the oral cavity but other mechanisms such as vertical (from mother) or through fomites are also possible. Similar to the situation in anogenital sites, HIV carriers appear to have more frequent infections and a wide variety of HPV types, in addition to an increased frequency of HPV associated oral lesions [20]. The strongly positive association of orogenital contact with an HPV infection in HIV-seropositive but not in HIV-seronegative would reflect the different consequence of the same behavior in different settings of immune-suppression. HIV-seropositive individuals were more likely to have an oral HPV infection, even though they reported fewer recent oral sex partners [21]. This could possibly be explained by reactivation of a latent infection, infection persistence or high titer infection more likely to be detected in the setting of immunosuppression. The prevalence of oral infection by genital-mucosal HPV has been shown to be significantly higher [21, 22]. Moreover with severe immunosuppression, oral prevalence was higher than previously reported in the cervical and anal lesions [23, 24]. Similarly, high risk and concurrent multiple-type oral, cervical [25, 26] and anal HPV infections [24, 27] are increased in HIV seropositive individuals.

Oral HPV infection has been shown to be associated with HSV-2 seropositivity, and is an accepted surrogate measurement of several sexual behavior [28]. Moscicki et al. [29]. have demonstrated HSV-2 infection to increase the risk of an incident HPV infection. Also it has been suggested that HSV-2 may act to promote cervical disease progression [30–32], but HSV-2 sequences have not always been found in tumors [33]. Hence an association of oral HPV infection with HSV-2 is a likely evidence of an association with sexual behavior.

HPV seroreactivity is a result of HPV exposure and the following immune response. HPV-16 serologic assays have a limited sensitivity of approximately 50% for the current cervical HPV (DNA) infection [34, 35]. The low sensitivity in cross-sectional studies can possibly be due to a prolonged median time to seroconversion following incident HPV infection [36]. However about 40% of heavily exposed females do not seroconvert [37], and females have a consistently higher seroprevalence than males, despite a higher prevalence of risky sexual behaviors reported by males [21]. This discrepancy in seroprevalence by gender remains an unexplained paradox.

US survey and other data [38] suggest that in terms of absolute numbers, approximately seven times more women than homosexual men engage in unprotected receptive anal intercourse. There are suggestions that anal sex, amongst males who have sex with males as well as heterosexual anal intercourse is prevalent in parts of India [39–43]. Hence it is possible that the incidence of oral sex may also be more common amongst females. In the evolution of animal kingdom however, the oral manipulation of female genitalia by a male under the effect of pheromones is well known. The oral sex act may vary in the extent of duration, and manipulation of the procedure as well as 'exchange of secretions'. Depending upon the degree of 'exchange of secretions', the 'donor-secretions' may just paint the part of the recipient's oral cavity, or may trickle down the entire length of oropharynx, or may even flow down along the entire throat (intra-oral ejaculation). Mostly it is just the painting of oral cavity/oropharynx by foreign secretions that occurs during sexual fore-play. This is sufficient to expose the local mucosa, particularly the lymphoid tissue at the entrance of the gastrointestinal tract to the sexual secretions. Also in case of a unidirectional (practiced by a single partner) oral sex, a subsequent lip-to-lip wet kissing amongst multiple partners (same or the opposite gender) may cause a wide dissemination. There exists throughout Central America the notion of "three dishes" *(los tres platos)*: vaginal, oral and anal sex [44]. Some do not

consider a sexual experience complete unless all the 'three dishes' have been indulged [38]. According to Richard Parker [45], Brazilianist anthropologist (and also as per personal communication June 1999) the practice of anal sex has much more positive value for men than for women who in turn agree to it as a way of pleasing their partners rather than enjoying it themselves. It becomes part of a complex negotiation around sexual practices that involves gendered understandings of pleasure as well as power. Hence considering the complexity of accepting (and practicing) unnatural 'painful' anal-sexual behavior, the likelihood of practicing 'more pleasurable' oral sex seems to be higher and may be an integral part of the foreplay before natural sex. Not much work has been done on this part of 'unnatural' sex but it stands out to be a major potential 'culprit' of orogenital disease transmission. Even oral sex has been commercialized by availability of various flavored condoms. Hence it seems that oral sex is more wide prevalent amongst the population than expected and is possibly the most common unnatural sex act practiced. To the best of our knowledge, no authentic scientific data for oral sex have been published across a large set of population. Hence our assumption is more speculative.

The predisposing factors in this context are multiple sexual partners, tobacco use, a high-risk male sexual partner (who has multiple sexual partners, history of sexually transmitted diseases specially HPV or a personal history of penile cancer) and harboring HPV types 16 & 18. This sexual habitus not only being a well accepted predisposing factor for cervical cancer also seems to be important for oropharyngeal malignancy through oral sex. In India the cervical cancer is the commonest cancer amongst the females and most rural females are known to have a bad cervical hygiene. On the other hand, oral/oropharyngeal cancer is the most common cancer amongst the males (in India), which has been attributed to tobacco though. The majority of rural males similarly have bad oral hygiene. It is essential to examine this aspect of disease transmission as it may possibly prove to be an independent risk factor. Also it may be possible that it stands out to be a stronger risk factor amongst the clinically/sub-clinically immunocompromised. Since HPV (type 16) related oropharyngeal cancer is a distinct molecular pathologic entity, it may be related to that 15–20% of head and neck cancers that occur in nonsmokers and nondrinkers. The independent risk factors may act synergistically to enhance the carcinogenesis. Schwartz et al. [19]. pointed out that HPV-16 seropositive nonsmokers had a 2 fold risk, HPV seronegative current smokers had a 5.8 fold increased risk and HPV seropositive current smokers had an approximately 15 fold increase in risk of developing squamous cell cancer of head and neck. Hence a bad oral hygiene along with a bad cervical hygiene may further enhance the HPV transmission through oral sex.

We found an interesting population based indication where HPV transmission through oral sex may play an important role. Our observations may not be conclusive but since not much work of a high level of evidence, has been reported in this area, a large lacuna still exists. We compared the incidence (ASR) of cancer of tonsil in males with the cancer of uterine cervix of a single registry from the latest publication of IARC entitled 'Cancer incidence in five continents'; vol. VIII [46] (an authentic source of the latest IARC world records). Thirteen representative countries from all the continents across the globe were selected at random. For each country the cancer registry with the highest incidence of cancer cervix was selected. Similar data from all cancer registries of USA and India was also obtained (Table 1). A regression analysis was performed with both cancer of tonsil and cervix as independent variables, through STATISTICA software. However such a comparison is scientifically incorrect considering the other confounding factors, and unknown latency period for cancer causation etc., but we intended to see a relation if any. We assumed that a practice of oral sex would vary amongst different registries, but a higher incidence of cervical cancer reflecting the higher prevalence of HPV may more predispose the respective males for tonsillar cancer due to oral sex. The scatter plots as per the regression analysis are depicted in Figs. 1, 2, and 3. A wide variation of ASR of cancers at the two sites can be appreciated at different registries depicting the respective cancer-related practices prevalent in those regions. Although we expected the trends of oropharyngeal cancer (rates) would parallel that of the uterine cervical cancer, but a comparison through regression analysis, of the world population did not reveal such trends (Fig. 1; adjusted $R^2 = 0.07$, $p = 0.16$), and even a high degree of dissimilarity was encountered in Indian population (Fig. 2; adjusted $R^2 = -0.13$, $p = 0.84$). On the contrary the US population showed some positive link (Fig. 3; adjusted $R^2 = 0.42$, $p = 0.0007$). Again, we do not know, how a HPV infection (that one day would cause cervical cancer or already has caused cervical cancer) is transmitted to another person who many get oropharyngeal cancer many years later. Hence our observations are in no way conclusive but just reveal a weak level of evidence suggesting such a possibility.

As depicted in the scatter plot (Fig. 1) the dissimilarities in the relationship between the two types of cancer across the countries may be due to multi-factorial etiologies of oropharyngeal and cervical cancers of which HPV is only one. Also the representative countries included in the current world data on cancer incidence are not likely to reflect the entire globe. For example the cancer registries from the underdeveloped world may not show the same validity as that of the affluent countries in terms of the

Table 1 Incidence (ASR) of cancer of oropharynx (tonsil) and uterine cervix: a wide variation in ASR reflect diverse cancer-related-practices in respective regions

S. no.	Country/registry	Oropharynx (male)	Uterine cervix
Across population based registries of 13 countries of the world			
1	USA (whites): Detroit	1.6	6.9
	USA (Blacks): Detroit	3.9	11.3
2	Canada: Manitoba	1	8.1
3	Brazil: Goiania	0.8	38.2
4	France: Somme	6.4	9.7
5	Italy: North east	1.4	7.3
6	U.K.: North western England	0.9	11.7
7	China: Taiwan	1.2	24.9
8	India: Delhi	2.1	25.8
9	Japan: Nagasaki Prefecture	0.4	10.9
10	Australia: Northern territory	4.4	16.3
11	New Zealand	0.7	9.6
12	Uganda	0.7	41.4
13	Zimbabwe	0.1	55
Across population based cancer registries of India			
1	Ahemedabad	2.8	13.4
2	Bangalore	1.1	23.5
3	Madras	1.3	30.1
4	Delhi	2.1	25.8
5	Karunagappally	0.5	15
6	Bombay	1.7	17.1
7	Nagpur	2	23.2
8	Poona	1.1	22.5
9	Trivandrum	0.8	10.9
Across population based registries of USA			
1	LA California		
	White	1.5	7.3
	Black	1.8	10.4
2	San Francesco		
	White	1.7	6
	Black	1.7	8
3	Connecticut		
	White	1.5	6.3
	Black	3.5	11
4	Georgia		
	White	1.7	7.6
	Black	2.2	9.6
5	Iowa	1.3	7
6	Louisiana Central		
	White	1.4	7.9
	Black	2.5	16.9
7	New Orleans		
	White	1.7	5.5
	Black	3.1	17.5
8	New Jersey		
	White	1.2	8.6
	Black	2.1	14.5
9	NY state		
	White	1.1	8.6
	Black	2	13.2
10	Utah	0.6	6.4
11	Washington	1.3	6.8
12	SEER		
	White	1.4	6.8
	Black	2.9	10.2

Adapted from 'Cancer Incidence in Five Continents; Volume VIII; IARC-WHO publication 2002

reliability of accurately representing the true population burden. India is a typical example of such a situation (Fig. 2) because with half the number of population based registries and thrice the population of United States, Indian registries are unlikely to show the same accuracy in depicting the incidence across the country. Ironically, India has only a single rural population based registry despite the fact that 80% of Indian population lives in rural areas. Moreover the southern part of India is better represented than the northern part in terms of number of cancer registries. Hence the rural (majority) population particularly that of northern part of the country is grossly under-represented. The sexual practices too vary widely across the globe contributing to a wide variation in this mode of transmission of cancer. Most important factor for such dissimilarity (figure) in India can be accounted for by the confounding effect of widely prevalent tobacco related chewing (e.g. pan, betel nut etc.) practices. Also it may be possible that the higher prevalence of sex (and thus oral sex) may be more prevalent in underdeveloped nations with high population densities, since the increased sexual activity (possibly contributing to increased population burden) may be the cheapest available source of recreation amongst poor population. Therefore as expected, if the effect of the confounding factor (tobacco chewing) is eliminated and the population is relatively better represented such as in USA, a positive trend can be appreciated (Fig. 3) between these 2 types of cancer, which otherwise is not evident due to aforementioned reasons. Hence the relationship of both these cancers to oral sexual practices, unless specifically sought for, (the contribution of the later as a connecting link of cancer transmission) can only be strongly suspected. However ongoing cancer control measures based upon the existing association does need to

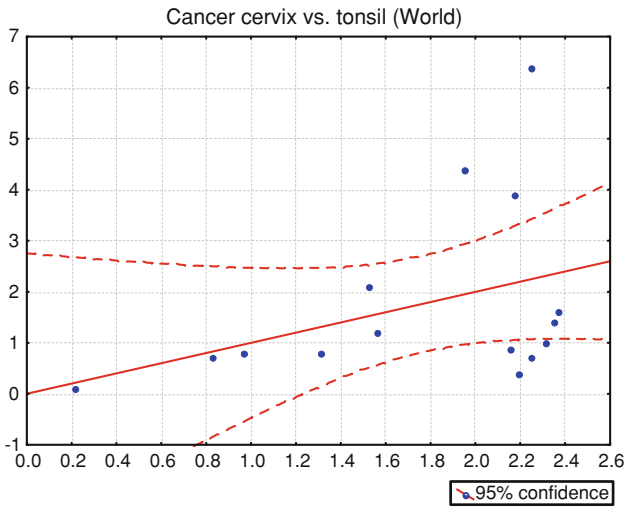

Fig. 1 Regression analysis scatter plot (cervix vs. tonsil) for world ($R^2 = 0.07$, $p = 0.16$)

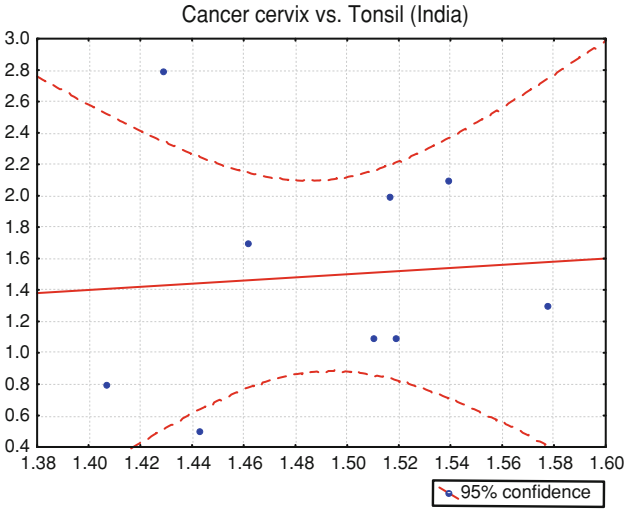

Fig. 2 Regression analysis scatter plot (cervix vs. tonsil) for India ($R^2 = 0.13$, $p = 0.84$) that does not reveal any positive link, probably due to many confounding factors and skewed data distribution

incorporate the importance of this mode of transmission for a better chemoprevention.

Conclusion

Although tobacco and alcohol have largely been attributed to the causation of head and neck cancer, 15–20% of patients have no such exposure history suggesting the role of HPV in these subsets of patients. Consistent results have shown that HPV-16 is associated with significant increased risk for oropharyngeal cancer particularly the Waldeyer's ring including the palatine tonsil. Whether oral sex is a causative vector for linking cervical (uterine) and tonsillar

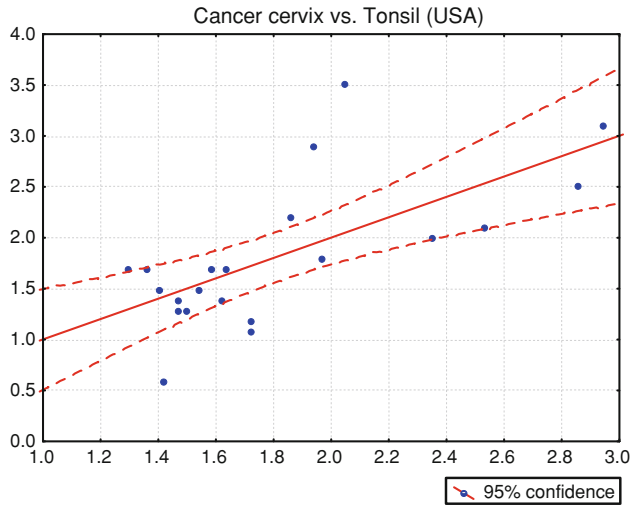

Fig. 3 Regression analysis scatter plot (cervix vs. tonsil) for USA that show a positive evidence ($R^2 = 0.42$, $p = 0.0007$)

malignancy has yet to be established. To date we do not have any hard epidemiological facts to answer this question, but the existing literature does not overrule this possibility. The oral sex is supposedly the most widely practiced unnatural sex worldwide that may further synergize the effects of other carcinogens. Our population based comparison may be scientifically incorrect, yet suggests some preliminary trends to be further investigated more scientifically. However ongoing cancer control measures need to incorporate the importance of this mode of transmission for a better chemoprevention.

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