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Research Article

Arsenic in HPV Related Oral Carcinoma- A New Threat of the Decade

Mrs. Pritha Pal[1], Dr. Ajanta Halder[2]

[1]Senior Research Fellow, Department of Genetics, Vivekananda Institute of Medical Sciences, Ramakrishna Mission Seva Pratishthan, 99 Sarat Bose Road, Kolkata- 700026.
[2]Associate Professor, Department of Genetics, Vivekananda Institute of Medical Sciences, Ramakrishna Mission Seva Pratishthan, 99 Sarat Bose Road, Kolkata- 700026.

Abstract:
Oral/oropharyngeal carcinoma is one of the most common cancers worldwide, ranking 3rd in developing countries. In India (West Bengal), it ranks first among all other cancers. Its association with different addictions has already been well established worldwide. Another alarming correlation between human papilloma virus (HPV) infection and oral carcinoma has become a new headache of the clinicians all over the world. In India, few studies are showing this relation of HPV in oral carcinoma. Moreover, a new emerging risk factor is metal toxicity. Various metals have been associated with the development of different cancers. Among these, arsenic is a proven carcinogen. Its toxicity is associated with various cancers worldwide, mainly skin, lung and bladder cancer. But, its relation with oral carcinoma is only being stated in a few studies. In India, only one study in West Bengal has shown this correlation so far, because West Bengal is the most arsenic affected area in this country. However, no study has been done correlating metal (arsenic) toxicity, HPV infection in the development of oral carcinoma worldwide; except one in India, stating the correlation among these two factors with oral carcinoma. So, we have tried to carry out the literature survey from all relevant articles in various newspapers and published research papers in Pubmed, Pubmed Central and Google, in order to bring out a review in this field. To our best knowledge, this is the first ever review work involving arsenic toxicity, human papilloma virus infection and oral carcinoma.

Keywords- Oral carcinoma, risk factors, addictions, arsenic toxicity, HPV infection

Introduction

Oral squamous cell carcinoma (OSCC) is the 6th most common cancers worldwide (Kadashetti et al. 2015, Coelho 2012) and 3rd most common cancers in developing countries (Fazeli et al. 2011). It ranks among the most common carcinomas, contributing to one third of all body cancers in most of the South Asian countries like India, Bangladesh, Pakistan and Sri Lanka (Atkinson et al. 1964). Since drinking water is directly connected with the oral cavity affecting the human body system henceforth, its source should be considered as an important factor in such malignancies, apart from the involvement of the main addictions like intake of oral/smoking tobacco, alcohol, betel quid etc. Moreover, it is reported that West Bengal, India and Bangladesh are the most arsenic affected areas in the world (Ratnaike 2003). The relation of this metal toxicity with skin, lung and bladder carcinoma is well established fact, but its link with the development of oral/oropharyngeal carcinoma is not yet studied well. Another factor namely human papilloma virus infection is well correlated with the oral and oropharyngeal carcinoma in western countries, accounting to the occurrence of this malignancy in young ages more than the late ages. However, its association with this malignancy is not yet well known in developing countries like India. So, our aim of this review is to find out any possible correlation between the arsenic toxicity, human papilloma virus infection and the development of oral/oropharyngeal carcinoma.

Methodology

Research publications on prevalence of oral and oropharyngeal carcinoma worldwide, arsenic toxicity, its association with the development of different cancers and other diseases, human papilloma virus infection, its association with oral carcinoma worldwide, of the past 10 years were searched for in Pubmed, Pubmed Central and Google. Only published data on human subjects was considered and imprecise descriptions of exposure or diagnosis were rejected. Toxicological studies, especially biochemical pathways were not included. Languages other than English were also inclusion criteria.

Discussion

Oral Carcinoma

Oral cancer or mouth cancer (Lozano et al. 2012) is characterized as the presence of any cancerous tissue growth located in the oral or buccal cavity (Werning 2007). It is also known as head and neck cancer in many contexts. Oral carcinoma presents approximately 13% of all cancers (Kadashetti et al. 2015). It may originate as a small primary ulcer or lesion in any of the mouth tissues by metastasis from a distant site of origin or a as a result of the extension from a nearby anatomic structure, such as nasal cavity. It can occur in many histologic types like teratoma, adenocarcinoma originated from a salivary gland, lymphoma from tonsillar or any other lymphoid tissue, or even melanoma from the pigment producing cells of the buccal cavity. There are several types of oral carcinomas, but 90% of these accounts to oral

squamous cell carcinoma (OSCC) (Oral Cancer Facts), while a less occurring type is Kaposi's sarcoma. The sites of malignancy include tongue, floor of the mouth, cheek lining, gums, lips, palate, with the early stage symptoms like persistent red or white patches, non healing ulcers, progressive swelling, unusual surface changes, sudden tooth mobility, oral bleeding or epitaxis or prolonged hoarseness (Ongole et al. 2014). The late stage symptoms include an indurated area, paresthesia or dysesthesia, airway passage obstruction, chronic serious otitis media, otalgia, trismus, dysphagia, cervical lymphadenopathy, persistent pain or referred pain and altered vision (Ongole et al. 2014). The premalignant oral lesions or conditions are characterized by the presence of white patches (leukoplakia), red patches (erythroplakia), mixed red and white patches (erythroleukoplakia), proliferative veruccous leukoplakia (aggressive form of leukoplakia), oral lichen planus, oral submucous fibrosis (OSMF) and actinic cheilitis (Neville et al. 2002). The distribution of oral premalignant lesions or conditions is highly variable globally because of the role of various behavioral, demographic and environmental risk factors and the pattern of risk factors to which people are exposed (Juntanong et al. 2016, Yardimci et al. 2014, Kumar et al. 2015). The overall prevalence of oral premalignant disorders in the Middle East was 2.8%. lichen planus were the most common lesions (1.8%) followed by leukoplakias (0.48%), chronic hyperplastic candidiosis (0.38%) and erythroplakia (0.096%). A study from South India shows the prevalence of OSMF being 3.5%, leukoplakia 3%, erythroplakia 0.3% (Kumar et al. 2015), which was similar to the previous studies (Reichart et al. 2005, Villa et al. 2011, Ikeda et al. 1991).

Prevalence of Oral Carcinoma (International Scenario):

OSCC ranks 15th most common cancer in males and 11th most common cancer in females (Alhazzazi et al. 2016). Around 3,00,000 patients are annually estimated to have oral cancer worldwide (Babshet et al. 2011) and it accounts for 3% of all malignancies in United States (US) (Siegel 2014). The death rate for oral cancer is higher than cervical cancer, Hodgkin's lymphoma, laryngeal cancer, cancer of the testes, thyroid cancer or skin cancer. If the definition of oral carcinoma is extended to include up to larynx, which bears the same risk factors, the numbers of diagnosed cases grow to approximately 50,000 individuals and 13,500 deaths per year in US. An estimate of 6,40,000 new cases have been found each year worldwide, making the problem even more bigger (The Oral Cancer Foundation). In 2013, oral cancer resulted in 1,35,000 deaths up from 84,000 deaths in 1990 (GBD 2013 Mortality Causes of Death Collaborators 2015). Five year survival rates in US are 63% (SEER Stat Fact Sheets 2014). The projected five year relative survival for oral cancer patients in Germany is about 55% (Listl et al. 2013). In US, oral cancer accounts for about 8% of all malignant growths. Men are affected twice as often as women, particularly men older than 40/60. Oral cancer is sixteenth most common cancer in United Kingdom (UK) and it is the nineteenth most common cause of cancer deaths (Oral cancer statistics 2014).

Prevalence of Oral Carcinoma (National Scenario):

In India, the male to female ratio is reported 3:1, which is consistent with many North Indian studies (Singh et al. 2016) due to easy availability of tobacco products to males. The high incidence (54.48%) of orpharyngeal carcinoma (OPC) and oral cavity carcinoma (OCC) in North-Eastern India has been reported by several studies (Sharma et al. 2016, Sharma et al. 2014, Ihsan et al. 2011, Bhattacharjee et al. 2006). This accounts to the dietary habits and high tobacco use by the concerned population. Among men, there has been marked increase in OPC incidence during 1983 to 2002, predominantly in economically developed countries like Japan, Australia, Denmark, Netherlands, Slovakia, UK, Canada, US and Brazil. No significant increase was observed in developing countries like Colombia, Costa Rica, Ecuador, India, Philippines and Thailand. However, there has been a significant increase in OCC incidence in Denmark, Netherlands, UK, Brazil and India. Among women, there has been a significant increase in OPC incidence in European countries like Denmark, Estonia, France, Netherlands, Poland, Slovakia, Switzerland, UK and OCC incidence significantly increased in European countries like Denmark, Estonia, France, Netherlands, Slovakia, UK, Italy, Spain (Chaturvedi et al. 2013). Oral cancer is known to be disease of middle age and most of the males and female cases are in 4th and 5th decade of life at the time of diagnosis of carcinoma (Singh et al. 2016). The age incidence is consistent with other studies (Sharma et al. 2010, Addala et al. 2012). However, the age group bearing potentially malignant oral disorders was found out between 21-30 years (Kadashetti et al. 2015). This is fully agreed by many studies where various parts of India like Gujarat (Patel et al. 2004), Maharashtra (Madani et al. 2012, Chaturvedi et al. 2013), Karnataka and Uttar Pradesh showed young individuals ($\leq$ 45 years) with the development of oral cancer. The occurrence of such disorders at an earlier age as compared to oral cancer cases may point to the time lag apparently present when these disorders may convert into malignancy or the increased use of predisposing habits by the young individuals (Gupta 1997), as a result of urbanization and development. The most affected site of carcinoma is buccal mucosa and gingivobuccal sulcus, both in male and females (Singh et al. 2016). Tongue and floor of mouth carcinoma are more common in western countries due to alcohol consumption and smoking. The extent of cell differentiation also depends on the site of carcinoma. A study in Karnataka reported cases showing poorly differentiating OSCC in tongue, floor of the mouth and palate whereas, well differentiating OSCC in buccal mucosa, the latter being the most common site due to tobacco consumption habits and the next being tongue (Rai et al. 2016). However, another study reported the larynx (36%) being the most affected site of head and neck cancer and the next being the pharynx (28.5%) (Fazeli et al. 2011). This difference in the observation may account to geographical differences and exposure to different risk factors and lifestyles in different places all over the world (Fazeli et al. 2011). The occurrence of OSCC is recently associated with new emerging risk factors like arsenic toxicity, HPV infection (Pal et al. 2014, Pal et al. 2016, Pal et al. 2017, Pal et al. 2018) apart from the patent factors like addictions, poor oral hygiene, poor nutrition.

Causes:

The main cause of oral carcinoma is the interplay of the oncogenes, which are activated as a result of DNA mutation. These mutations take place due to the effect of certain carcinogens, which reside the predisposing risk factors like tobacco in the form of chewing and smoking (Kadashetti et al. 2015). Often this contain more than one kind of hazardous content mixed in them, which may result in the exposure to several different toxic substances at the same time, making it most dangerous form of habit (Gupta et al. 2014). In a study of Europeans, smoking and other tobacco use was associated with about 75% of oral cancer cases (Rodriguez et al. 2004). In developing countries like India, where chewing practices are more common, oral cancer represents up to 40% of all cancer compared to just 4% in UK. A study from South India stated that 74.8% of all the OSCC cases had at least one

predisposing habit, mainly chewing areca nut (Ranganathan et al. 2015, Gupta et al. 2014). The study also projects on the shift of common etiology of OSCC from tobacco to areca nut, particularly in South East Asian countries, where the chewing practice is common (Juntanong et al. 2016). This accounts to the ability of the betel nut to produce mutagenic and genotoxic effects on tissues of body which may lead to various malignant and premalignant lesions (Trivedy et al. 2002, Shah et al. 2012). The association of various addictions with OSCC is also ascertained by Pal et al. 2016, Pal et al. 2017 in study population of West Bengal. Besides having at least one risk factor, another study from Karnataka reported a significantly high number of industrial workers with single (11.4%) or combined habits (60.4%), having oral potentially malignant lesions, while non users did not have any oral lesion (Kumar et al. 2015). Many studies point out the combination of more than one habits as the cause of oral malignancy, the fact being explained as the presence of one risk factor (smoking) enhancing the effects of the second risk factor (chewing) and showing synergism in development of oral cancer or potentially malignant oral disorders (Kadashetti et al. 2015, Ho et al. 2007). In a North Indian study, a strong correlation has been found out between the presence of chewing habit and the occurrence of both oral premalignant and malignant lesions (Gupta et al. 2014). The duration, number of times and intensity of the chewing habit is also important. The habit of chewing tobacco or betel quid for hours also affects the extent of oral carcinogenesis. In western countries, the use of smoking tobacco is more prevalent than in India and Indian subcontinent countries, where smokeless tobacco are more consumed (Singh et al. 2016). This is also consistent with another study in Kerala, where the use of smokeless tobacco has been found out potent in creating oral mucosal lesions (Aslesh et al. 2015). Studies also project the use of smoking tobacco in urban areas and chewing tobacco in rural population in developing countries like India (Agrawal et al. 2015). 30% of oral cancer cases have been attributed to chewing (betel quid with tobacco) without smoking, 50% to chewing with smoking (WHO). About 52% of OCC cases in both the genders accounts to the use of smokeless tobacco along with smoking tobacco (Boffetta et al. 2008). Even the occurrence of oral premalignant conditions like OSMF, leukoplakia, lichen planus gets enhanced by the use of the predisposing habits (Pratik et al. 2015, Pal et al. 2016, Pal et al. 2017), and also bear the same trend of males having a higher risk over females, whereas, a different trend of alcohol duration was found, which proved to be related negatively with oral cancer and leukoplakia in a study (Gupta et al. 2014), decreasing it by 0.01 for the two conditions with every extra month of alcohol habit. This study also approaches towards another contradictory aspect of illiteracy and lower income group, being at a lesser risk of developing OSMF and people belonging to the rural locality were also found at a decreasing risk of oral and leukoplakia. This shows that education and urbanization have not significantly reduced the use of these habits and the risk associated, which totally contradicts another study stating a negative link between use of risk factors leading to the development of the malignancy or premalignancy and education, income and urbanization (Epstein et al. 2002, Hashibe et al. 2003, Agrawal et al. 2015).

Other factors include poor oral hygiene, irritation caused by ill-fitting dentures and rough surfaces of teeth, poor nutrition, dietary habits like low consumption of fruits and vegetables (Epstein et al. 2002, Hashibe et al. 2003), life style habits (Fazeli et al. 2011), wood dust exposures, consumption of certain slated fish and others (NCI Factsheet 2013), some chronic infections by fungi, bacteria, viruses etc. (Srinivasprasad et al. 2015). A viral factor also plays an important role in this malignancy, which is Ebstein Barr Virus infection, which has been specifically associated with nasopharyngeal cancer. A new and rapidly growing sub population between 30 and 50 years old (Martin-Hernan et al. 2013) is predominantly none exposed to these risk factors, yet turning out into a new population of oral cancer victims. This indicates the role of another potent risk factor, namely human papilloma virus infection (Pal et al. 2016, Pal et al. 2018). Oral cancer in this group tends to favour the tonsil and tonsillar pillars, base of tongue and the oropharynx, turning into oropharyngeal cancer. Recent data suggests that HPV positive oral cancer individuals have a survival advantage over HPV negative oral cancer individuals, since the former responds better to radiation treatment than latter (MD Anderson News Release). They have better prognosis, especially for nonsmokers as compared to HPV negative cancers. The five year disease free survival rate for HPV positive cancer is significantly higher when appropriately treated with surgery, radiation and chemotherapy, substantiated by multiple studies including research conducted by Gillison et al. 2008.

Patients with hematopoietic stem cell transplantation (HSCT) are also at a higher risk for oral squamous cell carcinoma, which may have more aggressive behaviour with poorer diagnosis, when compared to oral cancer in non-HSCT patients (Elad et al. 2010). This may account for continuous lifelong immune suppression and chronic oral graft-versus-host disease (Elad et al. 2010).

Recently, metal toxicity through drinking water intake has also emerged as a potent risk factor (Su et al. 2010, Arain et al. 2015, Pal et al. 2017, Pal et al. 2018). The relation between these risk factors and the occurrence of this malignancy is well stated in developing countries like India, related to the arrangement of different summits and meets, especially in North Eastern India, the recent one in Agartala, Tripura.

Diagnosis:

There are a variety of screening devices that may assist the clinicians in detecting the stages of oral cancer. A non invasive brush biopsy (Brush Test) can be performed to rule out the presence of dysplasia (pre-cancer) and cancer on areas of the mouth that exhibit an unexplained color variation or lesion. The only definitive method for determining whether cancerous or not is through biopsy and further microscopic evaluation of the cells in the removed sample. A tissue biopsy confirms the diagnosis of oral cancer or precancer. Early diagnosis of oral cancer patients would help in decreasing mortality rates and improving treatment.

Treatment:

In terms of treatment and management, surgical excision of the tumor is usually recommended if the tumor is small enough. Radiation therapy, with or without chemotherapy is often used in conjunction with surgery, or as the definitive radical treatment, especially if the tumor is inoperable. Surgeries include maxillectomy, mandibulectomy, glossectomy, radical neck dissection or combinational i.e. glossectomy and laryngectomy. Chemotherapy is useful in oral cancers when used in combination with radiation therapy. Chemotherapeutic agents like Cisplatin, 5-Fluorouracil etc. have shown effective in the treatment of squamous cell head and neck cancers. Molecularly targeted therapies are developed since the discovery of the role of epidermal growth factor receptor signaling OSCC development, progression and prognosis. These targeted therapies include monoclonal antibodies (such as Cetuximab, Panitumumab etc.) and tyrosine kinase inhibitors (such as Erlotinib, Gefitinib etc.).

The therapeutic after effects include fatigue, speech problems, trouble maintaining weight, thyroid issues, swallowing problems, memory loss, dizziness, hearing loss and sinus damage. Survival rates for oral cancer depend on the precise site and the stage of cancer at diagnosis. 2011 data from SEER database shows that survival is around 57% at five years when all stages of initial diagnosis, all genders, all ethnicities, all age groups and all treatment modalities are considered. Survival rates for stage 1 cancers are approximately 90%, hence the emphasis on early detection to increase survival outcome for patients.This is confirmed by a study in Brazil, which says that the survival rate at 5 years stage was 33.3% while at 10 years stage was 26.9%, meaning that advanced stage was an independent risk factor for death due to this carcinoma (Schneider et al. 2014).

Prognosis:

Prognosis depends on stage and overall health, which includes post operative disfigurement of face, head and neck, complications of radiotherapy, other metastasis (spread) and significant weight loss. Grading of invasive front of tumor is a very important prognostic parameter (Sawair Faleh et al. 2003).

Diet & Supplementation:

High consumption of green leafy vegetables, fruits, fish, pulses, milk, nuts is considered to be protective against any form of carcinoma. Based on the evidence criteria of the WHO, risk reduction by a high intake of fruit is assessed as possible, while a lowered risk by a high vegetable intake is probable (Ströhle et al. 2007). Especially raw vegetables and fruits seem to exert anticancer properties. A study carried in European Prospective Investigation into Cancer and Nutrition stated that high consumption of fruits can reduce the risk of prostate cancer (Perez-Cornago et al. 2017). This is consistent with another study which indicates that high fruit and vegetable consumption has inverse association with the risk of oral pharyngeal carcinoma (Garavello et al. 2009). Nanri et al. 2017 also reported that high intake of vegetables, fruit, soy products, potatoes, seaweed, mushrooms, and fish may act as a protective measure against major cardiovascular diseases and different carcinomas in Japanese adults. Another study from Germany points out to null association of poultry consumption with the incidence of colorectal carcinoma (Carr et al. 2017). However, a study depicts a positive association of high egg consumption and the increased risk of nasopharyngeal carcinoma, which is in turn reduced by high intake of fresh vegetables (Polesel et al. 2013). This is consistent with another study which states high consumption of eggs and poultry with skin was associated higher risk of prostate carcinoma (Richman et al. 2010). Moreover, another study in China suggests that high consumption of total vegetables, certain fruits, milk, and eggs may reduce the risk of breast cancer to a large extent whereas, high intake of animal source foods may in turn increase the risk (Bao et al. 2012). The study also states a null association of this carcinoma with the intake of cereals, meat, fish, dairy products, and sweets.Another study points out that higher intake of vegetables, fruit, fish, poultry, whole grains, and low-fat dairy may reduce the risk of pancreatic carcinoma among men, but not associated with the same risk among women (Chan et al. 2013). A study from China suggests that low intake of fish, seafood, leafy and other vegetables, fruits, milk and dairy products, eggs are significant risk factors for oral carcinoma (Chen et al. 2017). A Japanese study states that higher intake of vegetables, peanuts, fish, and boiled egg accounts to reduction in the risk of adenocarcinoma while instant noodles, instant food items, and deep-fried foods intake contributed to the increased risk (Takayama et al. 2013). However, a study in Norway states a positive association of high amount of potato consumption and the incidence of colorectal carcinoma (Asli et al. 2017). A study also indicates that piperine is essential in oral squamous cell carcinoma due to its ability to induce apoptosis through cell cycle arrest and mitochondrial oxidative stress (Siddiqui et al. 2017). Instead, intake of high amount of processed meat, red meat over poultry and fish is considered to bear a linear trend with the development of carcinoma. A study from Italy suggests the intake of processed meat being linearly correlated with the risk of proximal colon carcinoma, while this study also reports null association with colorectal cancer (Rosato et al. 2017). However, a study in Germany indicates a positive association between intake of processed meat and development of colorectal cancer (Carr et al. 2017). Another also suggests a positive correlation of intake of processed and red meat with the occurrence of colorectal cancer, rather than the intake of milk and whole grains, the latter which prove to be protective (Vieira et al. 2017). A study from Netherlands also points out the null effect of fish in the risk of oral cancer; rather it focuses on the effect of processed meat on the same (Perloy et al. 2017). Studies also suggest the effect of red and processed meat intake in the development of pancreatic carcinoma, colon carcinoma, colorectal carcinoma and breast carcinoma (Paluszkiewicz et al. 2012, Beaney et al. 2017, Turner et al. 2017, Wada et al. 2017, Zhang et al. 2009). However, the study on breast carcinoma indicates no significant association between consumption of total and red meat, poultry, fish, or egg with breast cancer risk. A study from Netherlands also found no association of fresh meat, other types of meat, fish, eggs, dietary intake of total fat and different types of fat with the risk of pancreatic cancer (Heinen et al. 2009). Studies even reported high correlation between intake of red meat during adolescence and the occurrence of breast carcinoma (Farvid et al. 2015, Farvid et al. 2014) and subsequent replacement of the red meat intake by the intake of legumes, poultry, nuts and fish may reduce the risk to a large extent (Farvid et al. 2014). Studies have also been carried out, which state that substituting the intake of total or processed meat with fish or poultry reduces the progression of prostate carcinoma, independent of stage and grade (Wilson et al. 2016). However, a study states a different aspect in case of oral premalignancy, indicating low consumption of foods from animal origin has proven to be more risky, when compared to low consumption of fruits and green leafy vegetables (Carley et al. 1994). No association was observed between the intake of total fish and total meat and the increased risk of colorectal carcinoma by a study in China, rather eel, shrimp, shellfish consumption and high egg intake was found positively correlated with the risk (Lee et al. 2009). Beverages like tea (green, black) and coffee have also proven

to be protective against the occurrence of carcinoma. A study from Japan has also been consistent with this finding, stating the role of coffee in reducing the risk of colon and rectal carcinoma (Senda Nakagawa et al. 2017). This is consistent with another study where coffee and tea intake has proven beneficial in case of oral and pharyngeal carcinoma (Garavello et al. 2009), while hot maté drinking has been related to increased risk in studies from Argentina and Brazil.

In various countries, natural supplementation procedures have been undertaken in order to avoid the after effects of chemical, radiation therapy or surgery. Black tea as well as green tea has proven anti-carcinogenic by various studies (Gupta et al. 2002, Sur et al. 2016), but this effect is modified by the carcinogenic effects of passive smoking and cooking oil fumes' exposure (Chen et al. 2016). Both the forms of tea supplementation have proven out to be really beneficial in oral cancer prevention due to their anti-carcinogenesis (Chen et al. 2015, Liu et al. 2014, Tao et al. 2015, Zhang et al. 2014, Aghbali et al. 2014). It can be used as an anti cancer agent due to its anti-genotoxic effect (Pal et al. 2012) and remarkable content of anti-oxidants, helping in reduction of cancer progression, the effect of which can be detected through DNA damage assays. This is stated by a study in West Bengal, where there was an observed reduction in chromosomal abnormalities and micronuclei formation (which are considered as important biomarkers (Pal et al. 2016, Pal et al. 2017)) of the concerned individuals after one year of black tea supplementation (Halder et al. 2005). However, another study carried out in China states that increased tea consumption has no significant effect on the risk of common malignancies (Zhang et al. 2015). Moreover, aqueous garlic extract has proven beneficial in treating arsenic induced carcinogenesis on account of its antioxidant activity, chelating efficacy, and/or oxidizing capability of trivalent arsenic to its less toxic pentavalent form (Chowdhury et al. 2008).

Human Papilloma Virus and Oral Carcinoma

Human papilloma virus is an epitheliotropic DNA virus of the family Papillomaviridae (de Villiers et al. 2004), which contains a small, double stranded, non-enveloped circular DNA bound to cellular histones. Its diameter ranges from 52 to 55 nm. The viral DNA genome encodes eight open reading frames (ORFs), which is divided into three functional parts: early (E) region, late (L) region and long control region (LCR). The early region constitutes 45% and the late region comprises of 40% of the whole genome. Early ORFs encode for E1, E2, E3, E4, E5, E6, E7 proteins necessary for replication, cellular transformation and control of viral transcription. E1 and E2 maintain viral DNA and facilitate the segregation of the viral genome during cell division. These two proteins, along with E4 and E5 are expressed during the viral DNA amplification which occurs in differentiated cells in upper epithelial layers. During productive infection, E6 and E7 stimulate cell cycle progression. Late regions (L1 ORF & L2 ORF) encode for major and minor capsid proteins respectively, taking part in the virion assembly. LCR is essential for the viral DNA replication and transcription. Noncoding upstream regulatory region encompassing the origin of replication, the E6/E7 gene promoter, and the enhancers and silencers, is located between early and late regions (Syrjänen et al. 2011, Prabhu et al. 2013, de Villiers et al. 2009). The genotypic variations in the viral DNA bases sequences E6 and E7 account to the different HPV types, which finally classifies this virus into high and low risk types, depending on the virus oncogenic phenotype. High risk includes HPV 16, 18, 31, 33, 35, 45, 51, 52, 56, 58, 59 and low risk are HPV 6, 11, 42, 43, 44 (Syrjänen et al. 2011, Prabhu et al. 2013, deVilliers et al. 2009). Low risk HPVs like HPV 6 & 11 are mainly associated with a range of oral benign papillomatous lesions including oral squamous papilloma, oral verruca culgaris, oral condylomaaccuminatum and focal epithelial hyperplasia. High risk HPVs like HPV 16 & 18 are mainly associated with oral potentially malignant disorders (OPMD) and OSCC (Prabhu et al. 2013); HPV 16 &18 with OSCC and only HPV 16 with oral leukoplakia, including proliferative verrucous leukoplakia. HPV is attributed to be one of the important causative agents in cervical carcinoma (zur Hausen et al. 1974, zur Hausen 1976, zur Hausen 1977). Investigators have also shown that HPV may act as an independent factor or as an associated factor along with tobacco and alcohol in the oral carcinogenesis (Smith et al. 2010, Elango et al. 2011). The reported rates of HPV DNA in OPMDs and OSCC range between 0% and 100%, the variation owing to the difference in ethnicity, geographic locations to variations in methods used for HPV detection (Campisi et al. 2007).The specific of role of HPV in cervical cancer is well established but its infection pathway in the development of OSCC is still under debate (Gupta et al. 2015). The relationship between HPV and OSCC was first suggested in 1983, but its presence was only confirmed 2 years later (Lima et al. 2014). HPV positive carcinomas share some resemblance with cervical carcinoma. Most of the HPV positive tumors show p16 over expression (Gupta et al. 2015). The expression of p53 and bcl-2 is not associated with HPV positive OSCC and mutations in p53 are rarely seen in HPV positive tumors if compared to HPV negative tumors (Oliveira et al. 2009). Patients with HPV positive OSCC usually are younger and tending towards the female group (Friedman et al. 2014) and more often at a higher stage with large metastatic lymph nodes (Goldenberg et al. 2008). Many studieshave also confirmed that HPV positive tumors in head and neck regions, especially those who are p16 positive (Lassen et al. 2009), have a better prognosis if compared to HPV negative (Gupta et al. 2015). Especially HPV positive oropharyngeal cases have now being identified as a favourable prognostic subgroup (Ang et al. 2010, Friedman et al. 2014, Dayyani et al. 2010, Benson et al. 2014).However, HPV positive cases with p53 mutation have the worst prognosis (Chakrobarty et al. 2014). Between 1973 and 2003, HPV positive head and neck cancer cases have increased by 0.8% annually (Chaturvedi et al. 2008). This increment is mainly attributed to oropharyngeal cancers (Friedman et al. 2014). A study in West Bengal, India also stated a positive association of HPV infection with the occurrence of OSCC (Pal et al. 2016, Pal et al. 2018). Recent reports suggest that 60-70% of all oropharyngeal cancers are HPV positive (Benson et al. 2014). However, the corresponding figure in case of oral cancers is only around 6-20% (Benson et al. 2014, Lingen et al. 2013, Isayeva et al. 2012). Therefore, HPV 16 & 18 vaccines can reduce the occurrence of cervical carcinoma to a large extent (Kulkarni et al. 2011), so is the attempt to reduce the risk of OSCC.

Transmission:

The prevalence sites of HPV are mainly the epithelium of vagina, vulva, penis, anal canal, cervix, perianal region, cryptis of tonsil and oropharynx. The normal buccal mucosa may also as a site for recurrent HPV associated lesions, the

prevalence percentage ranging between 0.6% and 81% (D'Souza et al. 2009, Ragin et al. 2011). HPV may get transmitted to the oral cavity by means of multiple pathways like sexual transmission, autoinfection, and rarely through perinatal transmission of the neonate during its passage through an infected birth canal of the concerned mother (D'Souza et al. 2009, Kreimer et al. 2004).

Pathogenesis:

HPV infection bears affinity towards squamous epithelial cells, keratinocytes. The viral DNA and the viral gene expression are linked to the keratinocyte level of differentiation (Campisi et al. 2007, Femiano 2007). The viral genome undergoes episomal replication during the initial phase of infection, after which few copies of the viral DNA per host cell are present. This episomal form acts as a reservoir of infected cells and is later responsible for the latent state of infection (Campisi et al. 2007). The viral genes are expressed sequentially from early to late genes, when the infection becomes productive, which is followed by the epithelial squamous differentiation, starting from basal and parabasal cells, where early portions of the viral genome are more active and progressing towards the higher epithelial layers along with the formation of complete virion (Campisi et al. 2007, Santoro et al. 1997). In HPV infected basal cells, E1 and E2 proteins are expressed for regulating the early viral DNA transcription. When E2 expression is more pronounced, it represses the viral replication by blocking the required transcription factors, by means of a negative feedback (Feller et al. 2009, Longworth et al. 2004). In case of high risk HPVs, E6 and E7 may also get expressed along with E1 and E2 in the basal cells, leading to a proliferative phase characterized by an increasing number of HPV infected basal cells, transforming into intraepithelial or invasive neoplasm (Feller et al. 2009, Doorbar 2005). E2 mediated the viral DNA copy distribution to the daughter cells along with the basal cell division, leaving behind some of the copies in the progenitor cells, as episomes, in both high and low risk types (Feller et al. 2009, von Knebel Doeberitz 2002). As the epithelial cells mature, HPV cycle progresses to productive replication (Feller et al. 2009, Doorbar 2005). The matured epithelial cells express E6 and E7 proteins in the suprabasal layers, where E6 prevents apoptosis and E7 activates the cellular DNA replication allowing matured cells to re-enter the S-phase of the cell cycle, thus making the cellular replication machinery available for viral DNA replication (Feller et al. 2009, Longworth et al. 2004, von Knebel Doeberitz 2002, Elgui de Oliveira 2007). Along with the epithelial cell maturation, many cellular factors facilitate late viral gene expression by activating late viral promoter located within the E7 ORF. Eventually, the virus escapes from the shedding epithelial cells, mediated by L1 and L2 proteins (Feller et al. 2009, von Knebel Doeberitz 2002).

Molecular Mechanism:

The viral genome is integrated into the host genome, which is the necessary event for the keratinocytes immortality (Prabhu et al. 2013). The circular form of the viral genome breaks at the level of E1 and E2 regions, during the process of integration (Syrjänen et al. 2011, Prabhu et al. 2013, de Villiers et al. 2009). This causes the loss of E6 and E7 control, making these ultimately involved in the cellular cycle by inhibiting the normal functions of p53 and pRb, respectively. The most important function of E6 is to promote p53 degradation, through its interaction with a cellular protein, E6 associated protein (E6AP). The most important gene involved in carcinogenesis is the tumor suppressor gene p53, which tends to get mutated in case of carcinogenesis, with an approximate value of 50% of cases (Kashima et al. 1990). It is a 393 amino acid protein located in the short arm of chromosome 17 (Ibrahim et al. 1998), protects cells from DNA damage caused by radiation, chemical carcinogens or other mechanism. p53 does it by apoptosis or by arresting the cell cycle so that DNA repair can take place (Whyte et al. 2002). Moreover, E6 protein also interferes with other pro-apoptotic proteins, BAK and procaspase 8, leading to the ceasation of apoptosis (Narisawa Saito et al. 2007, Thomas et al. 1999, Garnett et al. 2006). Other proteins may also target E6, which might contribute in cellular transformation, with telomerase as one probable important example (Narisawa Saito et al. 2007). E7 binds to the retinoblastoma tumor suppressor gene product, pRb and its family members, p107 and p130. pRb, in its hypophosphorylated state, can bind to the transcriptions factors E2F family members and suppress the regular transcription of the genes involved in DNA synthesis and cell cycle progression (Narisawa Saito et al. 2007, Dyson 1998). Since E7 can bind to unphosphorylated pRb, it may induce premature entry of cells into S-phase by disrupting pRb-E2F complexes. E7 mainly enables the viral replication in the upper layers of the epithelium, where uninfected and new daughter cells normally differentiate and exit the cell cycle. p16 (INK4A, which prevents the phosphorylation of pRb family members) is overexpressed when pRb is activated by HPV E7. So, this p16 overexpression is used as a useful biomarker for detecting HPV infection in affected cells (Narisawa Saito et al. 2007, Ishikawa et al. 2006). However, this is contradicted in a study from North India (Singh et al. 2015), stating that HPV is not significantly associated with p16 over expression while all p16 positive cases are associated with a history of tobacco consumption. This may be due to the tobacco related oncogenic pathway co-existing with HPV related events in these cases. E6 and E7 can cooperate with cellular oncoproteins Ras, Myc, thus enabling the virus to act at the level of growth factors and cellular and nuclear metabolism, ultimately leading to the production of oncogenic cells (Narisawa Saito et al. 2007)

Synergistic mechanism between E6 & E7 (zur Hausen 2002):

E6 and E7 act in a synergistic mechanism and exert their oncogenicity. E6 helps in the degradation of p53 and the pro apoptotic protein BAK, which leads to the prevented apoptosis and chromosomal instability. E6 leads to the promotion of the release of SRC family of kinases and telomerase; ultimately generating the HPV transformed phenotype. This process is fully counteracted by INK4A (p16, a kinase inhibitor), which is a kinase inhibitor. In this way, the malignant transformation is inhibited to an extent. On the other hand, E7 interacts with pRb-E2F complex, by binding with the unphosphorylated pRb, releasing high levels of E2F, and leading to unprevented apoptosis and inhibited pRb also promotes high secretion of INK4A. But, E7 rescues E6 from INK4A inhibition by promoting the release of S phase cyclins A & E, and reducing the secretion of other kinase inhibitors, WAF1 (p21/CIP1) and KIP1 (p27), which leads to tumorigenesis. On contrary, E6 prevents the induction of apoptosis (resulting from the release of E2F by E7) by degrading p53 and BAK.

So, it can be stated as follows:

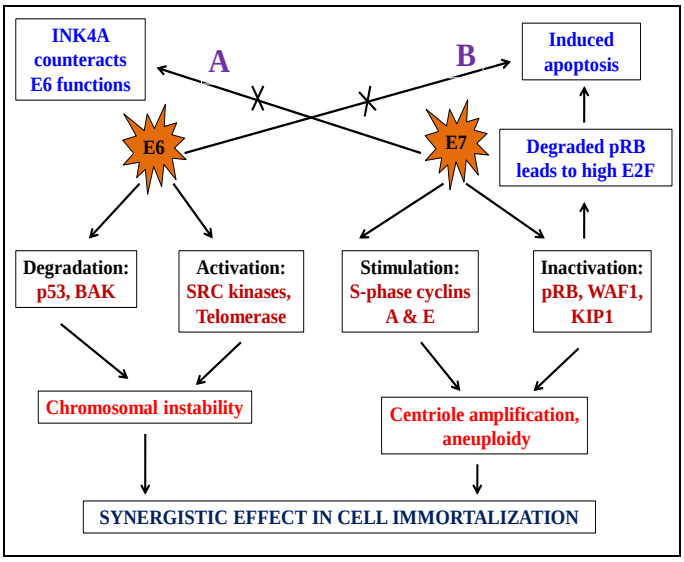

Figure A: Synergistic effect of E6 and E7 in cell immortalization

A: E6 seems to be impaired by INK4A, whereas, E7 bypasses this inhibition by directly activating cyclins A and E.

B: E6, in turn, prevents E7 induced apoptosis by degrading the apoptosis-inducing proteins p53 and BAK.

Association of HPV and Oral Carcinoma (International Scenario):

The reduction in OCC incidence in developed countries due to the decrease in the prevalence of the habits is observed along with the increase in OPC in the young agers and also in female group. This accounts to the HPV infection in oropharynx, tongue, tonsil, periodontal pockets and oral cancer in young adults (Elango et al. 2011). HPV prevalence in oral and oropharyngeal cancers range between 0% and 100% (Blot et al. 1988). Due to current trends in the spread of HPV 16, as of early 2011 the virus is now considered the primary causative factor in 63% of newly diagnosed patients. Majority (>50%) of oral cancers are HPV positive in US. It is widely prevalent in younger patients and is associated with multiple sexual partners and oral sexual practices. Recent studies show that about 25% of mouth and 35% of throat cancers are associated with HPV. The shift of pattern, particularly from oral cavity carcinoma (OCC) to oropharyngeal carcinoma (OPC) in developed countries and mainly prevalent in younger population mainly accounts to the cause of this viral infection (Koo et al. 2013). The OCC incidence has declined in recent years in many parts of the world, whereas, OPC incidence has increased over the last two decades in several countries (Marur et al. 2010, Ramqvist et al. 2010, Chaturvedi 2012, Gillison et al. 2012) like Australia (Hong et al. 2010), Canada (Auluck et al. 2010), Denmark (Blomberg et al. 2010), Netherlands (Braakhuis et al. 2009), Norway (Mork et al. 2010), Sweden (Hammarstedt et al. 2006), US (Chaturvedi et al. 2008) and UK (Reddy et al. 2010). This is confirmed by another study, stating the incidence of OPC to have significantly increased during 1983 to 2002 predominantly in the developed countries and younger ages (Chaturvedi et al. 2013). Consistent with this hypothesis, subsequent molecular studies carried out in Australia (Hong et al. 2010), Sweden (Hammarstedt et al. 2006) and US (Reddy et al. 2010) have reported significant increases in the proportion of HPV positive OPCs since 1980s, particularly among young ages (Chaturvedi et al. 2013). Studies have also confirmed HPV as an established cause of OPC (D'Souza et al. 2007, Gillison et al. 2000), whereas it's etiologic role in OCC is unclear (Gillison et al. 2000, de Martel et al. 2012, Lingen et al. 2013).

Association of HPV and Oral Carcinoma (National Scenario):

There is a wide variation of HPV incidence in India, indicating the role of HPV infection in need to get verified more in this developing country. A study from Northern India indicates a low prevalence of HPV and oral carcinoma (Singh et al. 2015), which is in contradiction with another study in Southern India, indicating a high prevalence (Elango et al. 2011). A study in southern India reported the prevalence being 40.4% (Bijina et al. 2016), while another study from Southern India shows HPV prevalence of 80-90% (Kulkarni et al. 2011). A study from West Bengal indicates HPV positivity in HNSCC tumors being 69% (Mitra et al. 2007). However, another study from Southern India has stated no role of HPV in oral carcinogenesis (Laprise et al. 2016). Moreover studies in West Bengal have pointed 22.5% and 35% of HPV association with OSCC (Pal et al. 2016, Pal et al. 2018 respectively). This has been depicted in Table 1 and Figure 1.

Published articles on HPV infection and oral carcinoma	Part of India	Year	Association rate (in %)
Mitra et al.	East	2007	69
Kulkarni et al.	South	2011	96.7
Elango et al.	South	2011	48
Singh et al.	North	2015	9.2
Bijina et al.	South	2016	40.4
Laprise et al.	South	2016	0
Pal et al.	East	2016	22.5
Pal et al.	East	2018	35

Table 1: Tabular representation of various published studies on HPV infection associated with OSCC in a negative or a positive way, in different parts of India

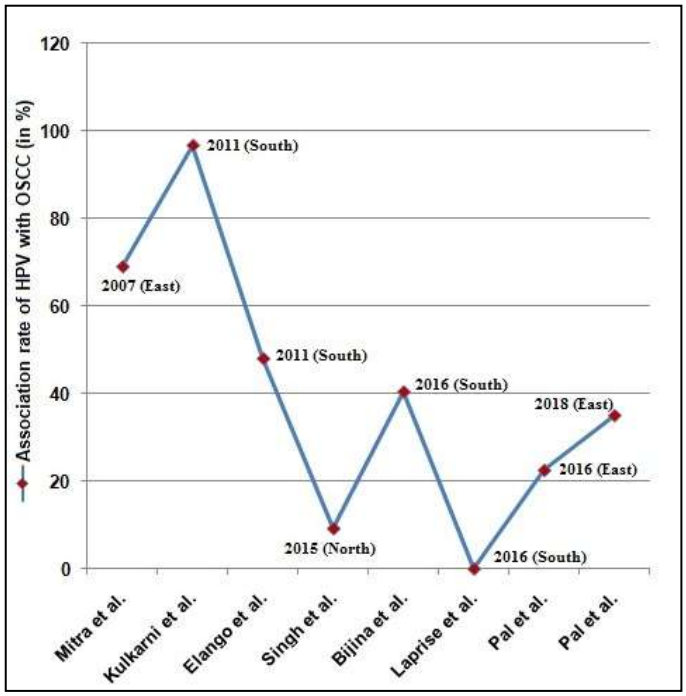

Figure 1. The figure shows the variable association rates of HPV infection with oral carcinoma in different parts of India; studied from 2007 to 2016

In India, HPV DNA has been detected less frequently in tumor specimens from individuals having habits of predisposing risk factors than the non users (Gupta et al. 2015). This is also consistent with another in Kerala which says that negative history of tobacco usage has shown a trend towards HPV positivity in OSCC patients (Kane et al. 2015). This study also suggests that the combined effect of oral tobacco and HPV is also a potent factor in oral carcinogenesis, especially in case of infection by high risk strains. Another study also reported high incidence of HPV infection in tobacco chewers (Balaram et al. 1995). Numerous studies have suggested additive effect of tobacco and alcohol consumption and HPV (Schwartz et al. 1998, Smith et al. 2004). However, a study from North India suggests an inclination towards tobacco habit in the oral carcinoma (Singh et al. 2015). This also states that the use of tobacco may act as an inhibiting effect for the viral infection. The etiological factors for oral precancerous lesions in Indian population are different from those of the western countries. While HPV 16, 18 have been found as a significant risk factor for oral cancerous lesions in western studies, in India, this role needs to be verified more, especially in case of premalignant oral lesions like leukoplakia (Bhargava et al. 2016). The stage of differentiation in carcinoma is also important in HPV infection. A study in Karnataka states that HPV was found to be more predominantly observed in the specimens of well differentiated and moderately differentiated oral carcinomas, as compared to poorly differentiated oral carcinoma (Bijina et al. 2016). This can be the reason for increased response to chemoradiotherapy, targeted therapy and immunotherapy for HPV associated carcinomas compared to HPV negative ones. The study also suggests that although HPV is associated with a number of proliferative epithelial lesions, its point of entry and site of replication in the oral cavity are not clearly known. Since the gingival pocket is the only site exposed to the outer environment and there, the basal cell are known to be the target cells of HPV infection, it may be assumed to be the point of entry as well as reservoir of HPV (Hormia et al. 2005).

Arsenic Toxicity And Oral Carcinoma

Arsenic is a ubiquitous naturally occurring metalloid (Sekhon 2013), which exists in both organic and inorganic form. The latter is more toxic than the former. This metalloid is termed as heavy metal since it shares its chemical properties with the heavy metals like- mercury, lead, cadmium, zinc etc. (Duruibe et al. 2007). Some studies categorize arsenic as a non-essential metal since it falls in the classification of metals which do not exert any gross beneficial physiological and biochemical functions (Tchounwou et al. 2012). It exists in its two oxidation states, arsenite (As^{3+}) and arsenate (As^{5+}), the former being more toxic.

Arsenic is a major environmental contaminant, which is a potent paradoxical human carcinogen. Its effect in various cancers has been reported, specially skin, lung, kidney, bladder carcinomas, whereas, now a days, its association with OSCC is also well studied (Pal et al. 2016, Pal et al. 2017, Pal et al. 2018). There has been no ideal animal model that can be used to study its toxicity in humans, initiating all the researchers to carry on the study in human cell lines and on affected individuals in exposed areas (Ghosh et al. 2008). Arsenic toxicity is affecting millions of people worldwide causing deleterious health impacts including carcinoma and death. At present, people living in more than 35 countries across the world are affected by drinking arsenic contaminated ground water (Das et al. 2012). An approximate figure of more than 137 million people in 70 countries of the world is affected by drinking heavily contaminated ground water (Mondal et al. 2010). Arsenic contamination in drinking water has become a major concern worldwide especially for developing countries, being considered as a potent risk factor in various countries like Bangladesh, Taiwan, India, Mexico, China, Chile, Argentina and USA (Singh et al. 2011). Arsenic contamination in the ground water has been noticed in West Bengal (Pal et al. 2014), Bihar, Uttar Pradesh, Jharkhand, Assam and Chhattisgarh. This problem is also prevalent in Bangladesh, Argentina, Canada, China, Mongolia, Taiwan and Saudi Arabia (Singh et al. 2013). However, there is reportedly low concentration of inorganic arsenic in US, which do not result in substantial additional cancer risk to the general US population, but there are some areas with higher levels of naturally occurring inorganic arsenic (potentially > 100µg/l), where residents rely on unregulated drinking water wells (Lynch et al. 2017). Arsenic contamination mainly occurs from drinking water from natural geological sources rather than from mining, smelting or agricultural sources (Matschullat 2000). However, in zones of intensive mining activities, arsenic can be equally released in air or water (De Gregori et al. 2003). Due to these geological conditions and anthropogenic activities, high arsenic content is found to get accumulated in soil and water. This type of situation is compounded in extremely arid zones like some areas of Northern Chile, where water sources are scanty and contaminated water serves as the main sources of drinking water and irrigation supply (De Gregori et al. 2003). For lifetime intake of arsenic around 500µg/l from drinking water, it can be estimated that 10% of all deaths would be attributable to ingestion of arsenic, mainly as consequences of lung and bladder cancer. This is in accordance with studies in Chile and Taiwan. The WHO guidelines declared safety limit of arsenic concentration in drinking water being 10µg/l and a maximum permissible limit of arsenic in drinking water is 50µg/l (Steinmaus et al. 2005). According to Bureau of Indian Standard, the arsenic level for drinking water is 0.01 mg/l and according to Rajiv Gandhi national drinking water Mission, it is 0.05mg/l known as the "Maximum Permissible Limit" (Nickson et al. 2007). It is reported that a number over 200 million people in the whole world are at a risk of getting arsenic contamination, out of which more than half resides in Bengal Delta Plain including West Bengal and Bangladesh (Washington 2001). These two areas are the worst affected areas in the world (Ratnaike 2003). The arsenic content in this zone is found to be 800µg/l in drinking water (Kinniburgh et al. 2001). It has been reported that 79.9 million and 42.7 million people are affected with arsenic concentration in ground water above the WHO recommended permissible concentration of 50µg/l in 42 districts of Bangladesh and nine adjacent districts of West Bengal respectively (Chowdhury et al. 2000).The arsenic concentration in ground water of some places in West Bengal is reported to be as high as 3400µg/l (Guha Mazumder et al. 1998). This is regarded as the greatest arsenic calamity in the world (Mandal et al. 1996). More than 26 million people in West Bengal are chronically affected by arsenic contamination in drinking water (Banerjee et al. 2014). In fact, much of the oral cancer effected individuals have been reported with their dwellings in the highly arsenic effected regions of this state (Pal et al. 2014, Pal et al. 2016, Pal et al. 2017, Pal et al. 2018). The age range of cases under arsenic poisoning falls mainly among adults older than 19 years (Bronstein et al. 2011) and also in children younger than 6 years (NPDS 2007 data). Men are more likely to experience industrial arsenic exposure than women. However, the male/female difference in risk estimation of arsenic induced

cancer says that it depends not on the gender, but on the individuals who are exposed to arsenic and who are not. The lower background cancer rates in women indicate that men are more exposed to the metal. But, due to the assumed fact that men are in habit of drinking twice as compared to women, may also depict the reduced carcinogenic potency of arsenic in case of men. Although there is no biological reason to consider females to be at a higher risk, both the genders' risks are considered average in terms of arsenic toxicity.

Exposure:

One plausible mechanism of arsenic accumulation in the Bengal delta Plain can be the deposition of arsenic containing alluvial sediments by rivers like Ganga, Brahmaputra, Meghna and other small rivers flowing across this plain into the Bay of Bengal during the late Quaternary age or Holocene age (Mukherjee et al. 2001). The arsenic accumulated in this plain might have been absorbed as oxyanions onto oxyhydroxides of iron, aluminium and manganese, which were then further dissolved by biogeochemical processes in the reducing environment, thereby releasing arsenic into the ground water (Mukherjee et al. 2001). Arsenic can also be absorbed from various products like cosmetics, pesticides, fungicides, herbicides, insecticides, paints, wood preservatives, cotton desiccants etc., where it has been used as a constituent (Ratnaike 2003). Intoxication by this heavy metal can result from breathing sawdust, workplace air, smoke from arsenic-preserved wood or from ingesting contaminated water, food or soil (Agency for Toxic Substances and Disease Registry 1993). Arsenic is entering the ground water through natural weathering processes of arsenic bearing rocks and minerals and also by effluent discharge processes from various industries like petroleum refining, fertilizer, pesticides, herbicides, glass and ceramics, wood preservatives, alloys, electronics, catalysts and feed additives/veterinary chemicals (Singh et al. 2013). The exposure to arsenic is either caused through the oral route involving contaminated food and water or through inhalation of agricultural pesticides and mining activities (Singh et al. 2011). Arsenic in food occurs as relatively nontoxic organic compounds (arsenobentaine and arsenocholine) found in seafood, fish and algae (Edmonds et al. 1987). These organic compounds cause raised arsenic levels in blood but are quickly excreted unchanged in urine (Buchet et al. 1996, Han et al. 1998). Arsenic intake is higher through solid foods than through liquid foods (Thomas et al. 1999, Tripathi et al. 1997). The average daily intake of arsenic by humans is approximately 300 µg; through food and water (Kwong 1997). Organic and inorganic forms of arsenic may enter the plant food chain through the contaminated ground water needed for irrigation or from the soil and agricultural products (Tamaki et al. 1992). These issues are of serious concern in countries like Bangladesh where 97% of the rural population depends on the ground water for drinking, cooking and irrigation purposes (Ratnaike 2003). A cohort study in West Bengal involved over 400 human subjects not significantly exposed to arsenic through drinking water, yet showing elevated genotoxic effects, as measured by micronuclei assay in urothelial cells, were found to have been associated with staple consumption of cooked rice with >200µg/kg arsenic. So, rice has also been recently identified as a major exposure route (Banerjee et al. 2013).The relatively high proportionof the more toxic inorganic forms of arsenic in rice together with its high bioavailabilities andbioaccessibilities add to the increasing concern that arsenic in rice could be a health threat to millions of people (Banerjee et al. 2013). Another study from West Bengalpointed out on the fact cooked rice typically results in lower magnitude of arsenic exposure, rather individually rice or water or both rice and water acts as the dominant exposure routes (Mondal et al. 2010).

Absorption and metabolism:

The main site of arsenic absorption is the small intestine by means of an electrogenic procedure involving a proton (H+) gradient (Gonzalez et al. 1997). The optimum pH for arsenic absorption is 5.0 (Silver et al. 1984), although the pH of the small intestine is 7.0 due to pancreatic bicarbonate secretion (Ratnaike et al. 2000). On absorption, this is stored in various internal organs of human system like liver, kidney, heart and lungs to a considerable amount capable of causing various disorders. This is less absorbed in muscles and nerve tissues. This accumulation leads to many disorders including cancer, diabetes, neurotoxicity, hepatotoxicity, cardiac dysfunction. The absorbed arsenic undergoes hepatic biomethylation forming monomethylarsonic acid (MMA) and dimethylarsonic acid (DMA) which are less toxic yet harmful (Thompson 1993, Aposhian 1997). About half of the ingested arsenic is excreted through urine in three to five days. DMA is the main urinary metabolite (60-70%) compared to MMA (Hopenhayen-Rich et al. 1993). The highest absorption of arsenic takes place in kidneys and liver in case of acute intake (Benramdane et al. 1999). Small amounts of less than 5 mg arsenic intake can result in vomiting and diarrhea. The lethal dose of arsenic in case of its acute poisoning is between 100 and 300 mg (Schoolmeester et al. 1980). The acute lethal dose of inorganic arsenic in case of humans is found to be 0.6 mg/kg/day (Opresko 1992). In chronic arsenic ingestion, arsenic gathers in liver, kidneys, heart, lungs and small amounts in muscles, nerves, gastro intestinal tract and spleen (Benramdane et al. 1999). Although most of the ingested arsenic is cleared from these sites, yet residual amounts remain stored in keratin rich tissues like nails, hair and skin after a span of two weeks (Ratnaike 2003). Levels of arsenic content between 0.1 and 0.5 mg/kg in hair samples indicates chronic poisoning while 1.0 to 3.0 mg/kg indicates acute poisoning (Ratnaike 2003).

Mechanism of toxicity:

Arsenic exhibits its toxicity by inhibiting around 200 enzymes involved in cellular energy pathways, DNA synthesis and repair, and is substituted for phosphate in high energy compounds such as Adenosine Tri-phosphate (ATP) (Ratnaike 2003). This toxicity is metabolized by reduction and methylation reactions, catalysed by Glutathione-S-transferase omega-1 (GSTO1) and As^{3+}methyl transferase (AS3MT) involving arsenic methylation via one carbon metabolism by S-adenosyl methionine (SAM) as methyl donor and reduced glutathione (GSH) as electron donor in reductase reaction. GSTO1 reduces methylarsonate (MA^{5+}) and arsenate (As^{5+}) to methylarsonite (MA^{3+}) and arsenite (As^{3+}) respectively. These toxic trivalent arsenicals formed during reduction are detoxified by AS3MT to less toxic pentavalent arsenicals, $MA^{5+}$and dimethylarsonate (DMA5+) (Lindberg et al. 2007). The trivalent form of arsenic exerts greater genotoxic effects than the pentavalent form as it can be easily taken up by the cells (Dopp et al. 2004). Unbound arsenic also exerts its toxicity by generating reactive oxygen intermediates during their redox cycling and metabolic activation processes causing lipid peroxidation and DNA damage (Cobo et al. 1997).

The main possible modes of arsenic carcinogenicity are oxidative stress, direct genotoxic effects, altered expression of growth factors, and altered DNA repairing mechanisms (Singh et al. 2011). Arsenic has been found to possess tumor promoting properties by enhancing intracellular signal transduction, activating transcription factors and altering gene

expression involved in cell growth, proliferation and malignant transformation (Singh et al. 2011). Arsenic is also known to induce senescence and elongation of telomere length (Chatterjee et al. 2015). The induction of arsenic associated carcinogenicity results from MAPK signal transduction, activating transcription factors like AP1, NFkB to alter various gene expressions (Yang et al. 2002). It also causes focal adhesion kinase activation, which mediates many downstream signaling pathways involved in cell adhesion, cell migration, cell survival, cell cycle control, carcinogenesis and tumor cell necrosis (Liu et al. 2005) like integrin, Src, Rho, Grb2, EGFR, ERK, cadherins. Different compounds of arsenate (As^{5+}) generate oxidative stress, resulting in an elevation of 8-hydroxydeoxyguanosine, a marker of oxidative DNA damage, which further stimulates cell proliferation and induces carcinogenicity (Kinoshita et al. 2007, Suzuki et al. 2009). Various risk factors like intake of tobacco (smoking/smokeless) have been shown to synergistically act with arsenic in the induction of carcinogenicity. A case of bladder cancer has been stated by Bates et al. 1995 and Hays et al. 2006. The action of arsenic in skin cancer is in synergism with sunlight, which results in blocking of DNA repair and physiological apoptosis, stimulation of angiogenesis, altering DNA methylation patterns, dysregulation of cell cycle control (Klein et al. 2007).

Prevention and Management:

The measures of prevention from arsenic toxicity and the development of various malignant diseases lie in the search of a threshold for carcinogenic effects to manifest and also to determine the dose and duration of exposure to the metal (Abernathy et al. 1999). More research is required to find out a link between the toxic manifestations and the possible genetic polymorphism, age, gender, nutritional status along with the protective role of vitamins, minerals and antioxidants. One possible way to reduce arsenic consumption from the ground water is to harvest rain water and harness surface water in places like Bangladesh where annual rainfall is quite high, around 1500-2000nm and even 3400nm in its eastern parts. No treatment benefits have been discovered yet to treat and manage chronic arsenic poisoning. Options lie in the vitamin and mineral supplementation and antioxidant therapy. However, such measures before being undertaken in human subjects require proper validation. Presently, chronic arsenic poisoning therapy is limited to supportive measures.

Arsenic & therapy:

Arsenic has been used as a therapeutic agent since 2400 years, on account of its significant medicinal properties (Klaassen 1996). Arsenic has been used as a healing agent in Fowler's solution (containing 1% of arsenic trioxide preparation) in diseases like leukemia, skin conditions (psoriasis, dermatitis herpetiformis, eczema), stomatitis, and gingivitis in infants and Vincent's angina (Ratnaike 2003). This solution was also prescribed as a health tonic. Arsephenamine (neoarsphenamine), containing 30% arsenic was used intravenously in the treatment of syphilis, yaws and some protozoan infections (Ratnaike 2003). The use of arsenical pastes for cancers in skin and breast was in use since 1880s and arsenous acid was used to treat hypertension, bleeding gastric ulcers, heartburn and chronic rheumatism (Aronson 1994). Arsenic's antileukemic activity was first reported in the early 1800s. Arsenic trioxide was first administered as the antileukemic agent being gradually replaced by radiation therapy (Antman 2001). It is still now widely in use for remission in patients with promyelocytic leukemia, on account of its ability in the induction of apoptosis (Shen et al. 1997, Bergstrom et al. 1998, Soignet et al. 1998, Fenaux et al. 2001, Zhu et al. 2002). Until it got supplanted by modern chemotherapy, arsenic trioxide after radiation was used to be considered as the most effective treatment procedure against chronic myelocytic leukemia (CML) and other types of leukemia (Antman 2001). Recently, some studies in China have reported the induction of clinical and hematological responses by arsenic trioxide in patients with relapsed acute promyelocytic leukemia (Sun et al. 1992, Zhang et al. 1996, Shen et al. 1997). Arsenic induces apoptosis by releasing an apoptosis inducing factor (AIF) from the mitochondrial intermembrane space from where it translocates to the nucleus (Lorenzo et al. 1999). AIF then affects apoptosis, resulting in altered nuclear biochemistry, chromatin condensation, DNA fragmentation and cell death. Many Chinese traditional medications contain arsenic sulphate in preparations such as pills, tablets etc. for the treatment of syphilis, psoriasis, asthma, rheumatism, haemorrhoids, cough and pruritus. It is also used as analgesic, anti-inflammatory agent and as a treatment for some malignant tumors (Wong et al. 1998, Ko 1999, Shen et al. 1999). In India, herbal medicines containing arsenic are used in some homeopathic preparations (Kew et al. 1993) and haematologicalmalignancies (Treleaven et al. 1993). In Korea, arsenic has been prescribed as a constituent of herbal medicine for haemarrhoids (Mitchell-Heggs et al. 1990).

Arsenic & other diseases:

Acute arsenic poisoning may result in nausea, vomiting, abdominal pain and severe diarrhea (Ratnaike 2003). In the absence of the first signs of gastrointestinal problems, excessive salivation may occur along with acute psychosis, toxic cardiomyopathy with seizures (Ratnaike 2003). Diarrhea characterized with bloody rice water stool resulting in severe dehydration, reduced circulating blood volume and consequent circulatory collapse are very frequent. Haematological abnormalities may include intravascular coagulation, haemaglobinuria, bone marrow depression, severe pancytopenia, normocytic normochromic anemia and basophilic stippling (Greenberg et al. 1979, Wilkinson et al. 1975, Lerman et al. 1980). Renal failure (Wilkinson et al. 1975) and respiratory failure with pulmonary oedema (Lerman et al. 1980) and peripheral neuropathy (Freeman et al. 1978, Le Quesne 1982) may also be the outcomes of acute poisoning of arsenic in humans. Chronic arsenic ingestion through contaminated drinking water results in the accumulation of arsenite and MA^{3+} in vital organs and tissues, resulting in atherosclerosis, hypertension, ischemic heart diseases, diabetes, hepatotoxicity, nephrotoxicity (Hansen 1990, Chen et al. 1995, Chen et al. 1996, Rahman et al. 1995, Liu et al. 2000, Gurr et al. 2003). Long term exposure to arsenic may lead to multisystem disease, the most fatal one being malignancy (Ratnaike 2003). The clinical symptoms and features of the consequences of the chronic toxicity may vary from individuals to individuals, among different population groups and geographic regions. The onset of chronic toxicity outcomes resides in mainly non-specific symptoms of abdominal pain, diarrhea and sore throat (Ratnaike 2003). On long term exposure, dermatological changes include hyperpigmentation, palmar and solar keratosis. Arsenic associated skin cancer, Bowen's disease is an unusual manifestation found in Asians, due to the high skin melanin content and increased exposure to ultraviolet radiation (Ratnaike 2003). Chronic arsenic toxicity may also lead to gastrointestinal disorders and cardiovascular diseases as well. It has been reported that 74 Taiwanese individuals with ischemic heart disease were found to stay in arseniasishyperendemic villages, thus pointing out towards a

positive link between these two factors (Hsueh et al. 1998, Tsai et al. 1999). Another study in West Bengal has revealed the occurrence of cardiovascular disorders along with liver diseases among the arsenic exposed individuals, indicated by elevated serum levels of liver injury biomarkers and inflammatory cytokines (Das et al. 2012). Studies also suggested the association of chronic arsenic toxicity with the development of peripheral vascular diseases in Chile (Borgono et al. 1977). Guo et al. in 1997 also reported a positive relation between chronic arsenic toxicity and transitional cell carcinomas in bladder, kidney, ureter and urethra in both males and females. A study in Finland showed an occurrence of bladder carcinoma, but not kidney carcinoma, despite the low As concentration in their wells (Kurttio et al. 1999). Arsenic consumed through contaminated drinking water by pregnant mothers has been found to reflect considerable amount of As in cord blood, maternal blood. The placental arsenic count of those individuals was found to be higher when compared to the women unexposed to arsenic in Andes (Concha et al. 1998). Even the fetus, infants and the children are getting exposed to arsenic when they are breast fed from their mothers. Studies from West Bengal, India suggested the occurrence of both restrictive and obstructive lung diseases in the individuals with the characteristic skin lesions of chronic arsenic toxicity (Mazumder et al. 1998, Mazumder et al. 2000). Similar associations have also been found out in Chile (Borgono et al. 1977) and Taiwan (Tsai et al. 1999). The incidence of endocrine and haematological disorders has also been accounted to chronic As toxicity like diabetes mellitus (Rahman et al. 1998) and neutropenia (Poklis et al. 1990).

Association of arsenic and cancers (International Scenario):

Arsenic exposure has been associated with the occurrence of carcinomas of skin, lung, liver, kidney and bladder in Bangladesh and other countries (Rahman et al. 2001, Everall et al. 1978, Axelson et al. 1978, Hopenhayn Rich et al. 1998, Guo et al. 1997, Tsai et al. 1999). The contamination of ground water by arsenic in Bangladesh leading to arsenic intake through drinking water is the largest poisoning of a population in history, with millions of people exposed (Hussain et al. 2013). Chronic poisoning due to high levels of arsenic in ground water has led to public health emergency in Bangladesh (Alam et al. 2002, Chen et al. 2009) showing its impact on mainly skin cancer and also in other organs like bladder, kidney and lung (Smith et al. 2000), also in Taiwan, the latter on a suffering end from Black Foot Disease (Tseng 2002). It has been reported that populations in countries like Taiwan, Mexico, Chile who consumes high levels of arsenic from drinking water had high rates of skin carcinoma (Tseng et al. 1968, Cebrian et al. 1983, Zaldivar 1974). In Taiwan, the prevalence of skin cancer among highly exposed males aged 60 years and older reached 25% (Tseng et al. 1968).Studies in Germany, Taiwan and US reported a positive association between arsenic toxicity and the occurrence of liver carcinoma (Roth 1957, Falk et al. 1981, Chen et al. 1988, Wu et al. 1989). Another study from Chile reported the association of this metal poisoning and skin and liver carcinoma (Zaldivar et al. 1981).Southern Thailand has implemented various measures to reduce arsenic contamination in drinking water since a high correlation has been found out there between the occurrences of changes of severe skin lesions into carcinoma among arsenicosis patients (Oshikawa et al. 2001). Many studies have also indicated the impact of arsenic poisoning in the causation of lung carcinoma (Kasper et al. 1984, Heddle et al.1983, Goldman 1973, Robson et al. 1963). This was in resemblance with another study carried out in Germany (Luchtuath 1983). Several studies in Argentina supported this association, where the levels of arsenic in drinking water are known to be very high (Bergoglio 1964, Tello 1986, Biagini et al. 1978). Arsenic is a confirmed lung carcinogen in Japan. Studies in south western Taiwan also reported cases of liver, bladder and kidney cancer along with lung cancer in arsenic rich areas (Chen et al. 1988). Another study in Chile suggested the association of lung cancer in arsenic exposed individuals who were never smokers, indicating the independent role of the metal in carcinogenesis (Ferreccio et al. 2000). However, a study in Denmark found no significant association between arsenic exposure in drinking water and the development of skin or lung carcinoma (Baastrup et al. 2008). Similarly, a study carried out in Belgium did not find any association with lung cancer mortality (Buchet et al. 1998). Beyond the studies in Taiwan, many studies in Chile, Argentina and even England have pointed out towards the link between arsenic toxicity and the development of bladder cancer. Another study in Taiwan has concluded that besides cigarette smoking and betel quid chewing, arsenic in farm soils may be an important factor for the development of oral carcinoma in this population (Su et al. 2010). This is consistent with another study in Pakistan where positive association has been found out between the arsenic poisoning and the occurrence of oral carcinoma (Arain et al. 2015). In India, studies have been carried out proving a positive association between the arsenic toxicity and OSCC (Pal et al. 2016, Pal et al. 2017, Pal et al. 2018). This has been depicted in Table 2.

Published articles on arsenic toxicity and oral carcinoma	Country	Association
Su et al. 2010	Taiwan	+ve; p value<0.05
Arain et al. 2015	Pakistan	+ve; p value<0.001
Pal et al. 2016	India	+ve; p value<0.001
Pal et al. 2017	India	+ve; p value<0.001
Pal et al. 2018	India	+ve; p value 2.18e-06

Table 2: Tabular representation of various published studies in world on possible association of arsenic toxicity and OSCC

Association of arsenic and cancers (National Scenario):

About 6 million people in West Bengal, India are exposed to arsenic contamination in groundwater and henceforth in the verge of extreme mortality rates. The positive association of arsenic toxicity and the occurrence of skin carcinoma in India is already suggested (Chakraborty et al. 1987). In India, although many cases were reported with liver fibrosis leading to liver cancer from Chandigarh in early 1978 (Datta et al. 1979), yet occurrence of large number of cases of arsenic induced skin cancer have also been registered from West Bengal in 1984 (Garai et al. 1984). In a study of West Bengal, it has been observed that arsenic exposed individuals, who previously presented severe skin lesions, tend towards the decrease and clearance of the same on choosing to drink safe water for the next few years (Guha Mazumder et al. 2003). In India, arsenic is associated with carcinoma of lung, liver, kidney and bladder as well (Rahman et al. 2001). A recent study in West Bengal also stated a positive association of this metal toxicity with the development of oral malignancy (Pal et al. 2017, Pal et al. 2018).

Arsenic & cytogenetic damage:

Arsenic induces the formation of genetic variants of a superfamily of ubiquitous multifunctional enzymes, Glutathione-S-transferases (GSTs), which play an important role in cellular detoxification (Strange et al. 2001), conjugation of xenobiotics and endogenous substances with glutathione (GSH), induction of other enzymes and proteins essential for cellular functions such as DNA repair (Hayes et al. 1995) and maintenance of cellular genomic integrity and cancer susceptibility. Long term exposure to arsenic may be associated with alterations in chromosomes and DNA, gene mutations, gene deletions, alterations of DNA synthesis and repair ability (Zhang et al. 2007). However, another study in Iran observed no such significant effect of arsenic poisoning resulting in chromosomal anomalies, which is in need of more intensive studies (Dastgiri et al. 2010). Arsenic exposure through the use of arsenic trioxide along with radiation therapy is known to have resulted in chromosome breakage rather than missegregation of chromosomes (Nuta et al. 2014). Moreover, arsenic is shown to induce concentration dependent but not time dependent increases in chromosome damage in bronchial fibroblasts (Xie et al. 2014). Genetic variations might play an important role in arsenic susceptibility, toxicity and carcinogenicity (Banerjee et al. 2014, Ghosh et al. 2006). Arsenic is a known clastogen and an aneugen, giving rise to chromosomal mal-segregation leading to micronuclei formation (Pal et al. 2017) in case of lymphocytes, urothelial and buccal cells as well (Ghosh et al. 2008). The inclination of incidence of micronuclei formation towards lymphocytes when compared to oral buccal cells and urothelial cells as a result of chronic ingestion of arsenic through drinking water is reported in a study in West Bengal (Basu et al. 2004).This study also suggests that symptomatic individuals have a higher level of cytogenetic damage compared to asymptomatic individuals and the latter has significantly higher genotoxicity than unexposed individuals (Ghosh et al. 2006). Thus, genotoxic end points can be utilized as important biomarkers in assessment of arsenic toxicity, as these are considered as the main markers of early biological effects of carcinogenic exposure (Liou et al. 1999). Studies in Mexico, Finland, Argentina and Taiwan have suggested higher incidence of micronuclei, chromosomal aberrations, sister chromatid exchanges and aneuploidy in human populations exposed to arsenic through drinking water (Ostrosky-Wegman et al. 1999, Maki-Paakkanen et al. 1998, Dulout et al. 1996, Liou et al. 1999). Studies from West Bengal, India have also stated the enhanced rates of chromosomal aberrations and sister chromatid exchanges as the indicatives of cytogenetic damage incurred by arsenic toxicity through consumption of contaminated water (Mahata et al. 2003, Mahata et al. 2004). So, human buccal micronucleus assay can be the most widely used technique for measuring the genetic damage in human population studies (Bonassi et al. 2011), since a study in West Bengal showed an enhanced frequency of micronuclei as a result of significant cytogenetic damage in the symptomatic individuals exposed to arsenic through drinking water (Basu et al. 2002). However, role of environment and diet are also essential for a better understanding of the arsenic induced genomic instability (Bhattacharjee et al. 2013).

Conclusion

Oral carcinoma is one of the most common cancers worldwide. Its association with different risk factors like addictions, poor oral hygiene and bad oral habits is well known and established in various countries. Moreover, the link between the human papilloma virus infection and the development of oral and oropharyngeal malignancy has been well stated in western countries, which is reported to be more prevalent in young ages. The literature says variable association rates of this viral infection with this malignancy. But, this possible association has not been established in developing countries like India, where its positive as well as negative correlation has been equally stated in different places. Not much study in this field has been carried out in Eastern India, which has made us to choose the population of West Bengal. Furthermore, it is well known that Bangladesh and West Bengal (India) are the worst arsenic affected areas in the world. Since, we have chosen the population of West Bengal in this study, it is quite definite to include the factor namely, metal toxicity, especially arsenic contamination through drinking water, whether contributing to this malignancy in this zone. The literature depicts a few association rates (in places like Taiwan, Pakistan) of this metal toxicity with the occurrence of oral malignancy, whereas a high association has been stated with skin, lung and bladder carcinoma. Even its association with other diseases like Down Syndrome has been well established (Biswas et al. 2016). So, we have chosen arsenic contamination as a possible potent factor contributing to this carcinoma. However, no study has been carried out in the world correlation these two factors with the oral/oropharyngeal malignancy. This work also opens up into a new phase of research where further studies can be carried out to find out any possible correlation between these two factors, may be suggesting their additive role or whether this viral infection gets promoted in such in vivo environment of metal toxicity, contributing to the development of carcinoma on a larger scale.

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