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Full Length Research Paper

Oral cancer: The Nigerian experience

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Oral cancer is one of the ten most common cancers worldwide and the five years survival rate is still disappointingly low. The incidence of oral cancer varies from different regions of the world with highest rates reported in the South-east Asia especially in India where oral cancer accounts for 15 - 40% of cancers and is the most common cancer in men. Although, tobacco and alcohol use are the most important risk factors in the development of oral cancer, some reports from Nigeria suggests otherwise. Tobacco and chronic alcohol use have been found to be low in cancer patients in various studies from Nigeria, whereas most of these patients are from the lower income, poorly educated class in the society. More so, oral cancer patients from a study in Nigeria were found to consume less fruits than controls and had statistically significant lower serum antioxidant vitamins levels when compared with a non-cancer group. We suggest that poverty, illiteracy, malnutrition and possibly a yet to be determined chronic infection may be more important risk factors than the well-established risk factors (tobacco and alcohol use) in the development of oral cancer in Nigerian cases.

Key words: Oral cancer, tobacco, alcohol, risk factors.

INTRODUCTION

Cancers of the oral cavity, pharynx and salivary glands are responsible for an estimated 390,000 (3.9% of total) new cases of cancer worldwide in 2000 and is still a major health challenge because the five years survival rate remains disappointingly low at about 50% (Macfarlane et al., 1994; Otoh et al., 2004). The highest rates of oral cancer have been reported in countries such as India, Sri-Lanka, South Vietnam, Papua New Guinea, the Philippines, Hong Kong and Taiwan and mainly attributable to use of tobacco in various forms (Garewal, 1991). Oral malignant neoplasms represent 2 - 4% of all malignant lesions in the United States of America (Krutchkoff et al., 1990), 2% of cancers in Britain (Binnie, 1976) and 1% in Australia (Sugerman and Savage, 1999). Oral cancers are the commonest cancers amongst men in India and the number three amongst women after breast and cervix uteri tumours (Nair et al., 1988; Rudolph and Atvis, 2003) accounting for between 15 - 50% of all cancer cases in India.

Oral cancer is believed to be relatively rare amongst Africans (Davies and Wilson, 1954). Arotiba et al. (1999) in a review of 246 oral squamous cell carcinoma patients in University College Hospital Ibadan reported that 1.2% of all malignant lesions are oral squamous cell carcinoma. Oji et al. (2007) in Eastern Nigeria reported that oral cancer accounted for 2.7% of all cancer cases seen at the University of Nigeria Teaching Hospital (UNTH) Enugu over a six-year period while Otoh et al. (2005) in Maiduguri, North-eastern Nigeria, reported an average rate of 20 cases per annum over a six-year period Though, it has been suggested that these rates may be under reported in Nigeria because of the low dentist: population ratio, poor and inadequate hospital services and a poor (and almost non-existent) cancer registry in

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Nigeria (Otoh et al., 2004).

Age distribution

Though oral cancer may occur at any age, it is essentially a disease of the elderly; and it has been reported that more than 95% of oral cancers occur in persons older than 40 years of age in most regions of the world (Johnson, 1991). The increased incidence of cancer with advancing age may be partly due to the increasing level of free radical reactions with age. Also, there is said to be a diminishing ability of the immune system to eliminate altered cells because of immune tolerance, thus the effectiveness of cancer surveillance by immune cells is reduced with advancing age (Enwonwu and Meeks, 1995).

However, some reports from Africa found less proportion of oral cancer cases occurring in persons older than 40 years with Chidzonga in Zimbabwe and Ajayi in Lagos reporting 70.8 and 75% of oral carncinomas occurring above 40 years of age respectively (Chidzonga, 2006; Ajayi et al., 2007). The lower percentage of oral cancer occurring above 40 years of age in African studies compared to Caucasian studies, may be due to the lower life expectancy and or early exposure to risk factors in Africans. It is known that the percentage of people under 40 years is much higher and life expectancy (47 years) is much lower in the Nigerian population than in the developed nations (Ajayi et al., 2007). A trend towards increased incidence of oral cancers in relatively younger age groups has been reported in United Kingdom and United States. Though the reason(s) for this trend is uncertain (Effiom et al., 2008), infection by human papilloma virus (HPV) is thought to be more plausible than the more established aetiologic factors such as tobacco and alcohol, mainly because HPV positivity was found chiefly in young oral cancer patients who consume less alcohol and tobacco (Monsjou et al., 2012). Other researchers are of the opinion that inherited inability to metabolize pro-carcinogens and carcinogens or defects in a patient's ability to repair DNA damage may be important in the aetiogenesis of squamous cell carcinoma in patients below 40 years of age (Adeyemi et al., 2008).

Sex distribution

Oral cancer affects males about twice as often as females in the industrialized world, possibly due to a greater exposure of males to established risk factors like tobacco and alcohol use. Also, most studies from Africa have shown oral cancer to be more prevalent in males than females (Arotiba et al., 1999; Odukoya et al., 1986; Ajayi et al., 2007). However, Otoh et al. (2005) in Maiduguri North-east Nigeria found a male to female ratio of 3:4 and suggested that the relative higher preponderance of females in their study may be attributed to the increasing exposure of females in North-eastern Nigeria to carcinogens such as tobacco and alcohol. Similarly, some other reports from India, Singapore, Hawaii and in Denmark (Johnson, 1991) found no marked difference in incidence of oral cancer in males and females whilst Van Wyk et al. (1993) found a higher female preponderance in South African Indians with male to female ratio of 1 to 1.6. They attributed this to the fact that areca nut chewing was more common in South African Indian women than men.

Site distribution

The lip is the most common site of oral cancer in fair skinned races particularly in men who work out of doors due their exposure to ultra-violet radiation from the sun (Spitzer et al., 1975). Intraoral cancer in western countries most commonly affects the lateral border of tongue and the floor of the mouth; the buccal mucosa is the next most common site of occurrence followed by mandibular alveolus, retro-molar region and soft palate with the hard palate and dorsum of tongue having the lowest risk (Johnson, 1991). In South-east Asia, the buccal, retro-molar, and commissural mucosa are the most prone sites (Johnson, 1991). Some Nigerian studies from Ibadan, however, show that the tongue, palate and the mandibular alveolus are the sites most commonly affected with the floor of mouth and buccal mucosa being the least affected (Daramola et al., 1979; Arotiba et al., 1999). This is in contrast with studies from Lagos which showed the mandibular gingival to be the commonest site of occurrence followed by the maxillary gingiva and tongue with the floor of mouth having the lowest occurrence (Effiom et al., 2008).

AETIOLOGY

Cancers of the head and neck have been associated with known aetiological and predisposing factors such as tobacco and chronic alcohol use, ingestion of smoked fish, infections especially by viruses, dietary deficiencies and industrial pollution. The association of these predisposing factors are important since their control makes the prevention of cancer possible (Otoh et al., 2005).

Tobacco

The use of tobacco in whatever form is associated with increased risk of intra oral cancer worldwide (Johnson, 1991). It is commonly consumed in betel quid or pan consisting of tobacco mixed with chopped areca nut, slaked lime and catechu, wrapped in a leaf of piper betel

vine. In Indians, spices such as cardamom, cloves and aniseed may be added. In North Africa and the Middle East, a mixture of tobacco, ash and lime in water or oil called nass or nasswar, is commonly held in the mouth (Johnson, 1991). Many different forms of snuff are placed in contact with oral mucosa in northern Europe, France, the USA and parts of Africa including Sudan, Southern Egypt and Saudi Arabia (Johnson, 1991). Users of tobacco quid especially if associated with smoking, have a 10 to 20 times greater risk of developing oral cancer than those who neither chew nor smoke (Enwonwu and Meeks, 1995; Davis and Severson, 1987).

All forms of tobacco use have been strongly linked to the development of oral cancer. Cigar and pipe smoking are associated with a greater risk of the development of oral cancer when compared with cigarette smoking, probably because most cigarettes have filters that reduce the load of carcinogen that will come in contact with the oral mucosa (Rudolph and Atvis, 2003). Carcinogens in tobacco (mainly polycyclic aromatic hydrocarbons), can cause an accumulation of genetic mutations in oral epithelial cells including p53 mutation, mutation and loss of heterozygosity (H-RAS) and amplification (K-RAS and N-RAS) of the RAS oncogenes leading to abnormal and uncontrollable cell division and growth (Scully and Bedi, 2000).

Although, tobacco use is regarded as the most significant factor in aetiology of oral cancer, some studies from Nigeria seem to dispute this notion. Oji and Chukwuneke (2007) in Enugu, found that patients with oral cancer in their tertiary health centre gave no history of tobacco or alcohol misuse. They postulated that poverty, malnutrition, lack of education, poor oral hygiene and chronic malaria may be more important in the aetiology and severity of oral cancer in their series (Oji and Chukwuneke, 2007). A report by Lawoyin et al. (2003) from Ibadan, South-west Nigeria also reported low prevalence of recognised risk factors (tobacco and alcohol use) for oral cancer in their patients.

Furthermore, we previously reported in a study in South-west Nigeria that only 26.1% of oral cancer patients in our study gave history of tobacco use (Lawal et al., 2011). Most other studies have shown higher percentages of tobacco use. Blot et al. (1988) in a study in the United States found 75% of oral cancer cases are associated with tobacco smoking and heavy alcohol use (1988). Lissowaka et al. (2003) reported that 82% of oral cancer cases in Poland reported that they use tobacco compared to 65% of those in their control group. Other studies in Denmark and Brazil reported 86 and 63.9% of oral cancer cases in their studies use alcohol and tobacco (Gervasio et al., 2001; Pinhort et al., 1997).

Alcohol

Alcohol as a risk factor in development of cancer was previously thought to act indirectly and through its synergistic effect with tobacco. The effect of alcohol has been thought to occur through its ability to irritate the oral mucosa and to act as a solvent for carcinogens (especially in tobacco). Contaminants and additives with carcinogenic potentials that are found in alcoholic drinks have also been thought to have a role in oral cancer development (Rudolph and Atvis, 2003). Also, acetyl aldehyde a metabolite of alcohol is known to be a direct carcinogen by causing alteration of the p53 gene and Ras oncogenes (Rudolph and Atvis, 2003). Acetaldehyde is also known to be cytotoxic and causes production of free radicals (Harty et al., 1997). Garro et al., 1992; Mufti et al., 1993 also demonstrated that chronic alcohol con-sumption interferes with repair of alkylated DNA (Ogden and Wight, 1998). Alcohol consumption has consistently being found to be low amongst oral cancer patients in Nigeria (Lawoyin et al., 2003; Oji and Chukwuneke, 2007; Adeyemi et al., 2008) and may not be an important factor in the aetiology of oral cancer in Nigerians. Lawal et al. (2011) had recently shown that only 25.8% of oral cancer patients seen in our study were exposed to alcohol use.

Human Papilloma Virus (HPV) infection

The increasing incidence of oral squamous cell carcinoma in young people and especially in those who do not smoke or use alcohol has indicated a possible aetiologic role for infections such as HPV. High-risk types of HPV include HPV16 and HPV18, both of which are well-established initiators of cervical and anogenital carcinogenesis (Kreimer et al., 2005; Monsjou et al., 2012). The oncogenic potential of HPV is attributable to its ability to insert specific viral DNA fragments (early genes E5, E6 and E7) into the host cellular genome. As a result of this integration, some key functions of tumour suppressor factors are abrogated (p21, p53 and pRb pathways, respectively), leading to defects in apoptosis, DNA repair mechanisms, cell cycle regulation and, finally, to cellular immortalization (Ragin et al., 2007). High-risk HPV DNA was found in nearly 100% of cervical carcinomas and 84% of anal carcinomas, 70% of lower vaginal carcinoma and 40% in vulvar carcinomas. Although, HPV genomic sequences have been identified in head and neck squamous cell carcinoma, a wide range of viral detection rate of between 0 - 100% have been reported. This great disparity in prevalence rate has been attributed to ethno-geographical differences, site of lesions studied (oral, pharyngeal or tonsillar), the differences in specimen type (blood, paraffin embedded tissue, frozen sections) and HPV detection methods.

The risk factors for HPV positive head and neck squamous cell carcinoma are mainly related to sexual habits rather than tobacco and alcohol use in HPV negative cancers (Hennessey et al., 2009). The risk for HPV-positive HNSCC increases with increasing numbers

of both oral and vaginal sexual partners, a history of genital warts, and a younger age at first intercourse (Hennessey et al., 2009). Previous studies have consistently shown that HPV infection conferred a higher risk of oropharyngeal cancer when compared with oral cavity cancer (Hennessey et al., 2009). A meta-analysis of 17 studies found that HPV is most strongly associated with tonsillar cancer (OR 15.1, 95% CI 6.8-33.7), is intermediate for oropharyngeal cancer in general (OR 4.3, 95% CI 2.1-8.9), and is weakest for oral cancer (OR 2.0, 95% CI 1.0-4.2) (Hobbs et al., 2006). Similarly, a study found HPV in 3.9% (95% CI, 2.5-5.3) of oral cavity tumours and 18.3% of oropharyngeal squamous cell carcinomas (Herrero et al., 2003).

Additionally, many studies have shown that persons with HPV-positive oropharyngeal cancers are more responsive to treatment and have better rates of disease-specific survival than those with HPV-negative oropharyngeal cancers (Hennessey et al., 2009). Preliminary reports from a study in our centre using PCR to detect HPV (unpublished), showed that all the oral cancer cases studied were HPV negative and HPV may not be important in the aetiogenesis of oral cancer in Nigerians.

Socio-economic factors

Studies on the association of socio-economic status and oral cancer have been somewhat conflicting (Hashibe et al., 2003). Some studies reported no association between oral cancer and education and occupation, while others showed a decreased risk of oral cancer with higher socio economic status based on occupation and higher levels of education (Greenberg et al., 1991; Elwood et al., 1984; Williams and Horm, 1977).

The reports of studies from Nigeria, however, have consistently shown oral cancer to be more prevalent in the low socio-economic groups (Oji and Chukwuneke, 2007; Adeyemi et al., 2008; Lawal et al., 2011). We previously reported that income of less than ₦50,000 a month (approximately $1 a day) and lack of a secondary education were associated with increased risk (odds ratio 5.75 and 1.04 respectively) of developing oral cancer in a South-west Nigerian population (Lawal et al., 2011). These findings have been previously corroborated by studies from India and United States of America. Kerr et al. (2004) in a study in the United States reported that in addition to higher prevalence of alcohol and tobacco use, people of lower socio economic groups were more likely to consume less fruits and vegetables and this was similar to the findings of Hashibe in India (Greenberg et al., 1991).

Furthermore, people in low socio-economic groups were less likely to have access to proper health services and health education that would empower them to make informed decisions that would protect and improve their health (Poul, 2008). A study in Canada found that people in lower socio economic class were less likely to visit their dentist regularly and suggested that increased incidence of oral cancer in this group may also be related to their poor oral hygiene (Johnson et al., 2010).

DIET AND NUTRITION

One of the earliest suggestions that nutrition may play a role in aetiology of oral cancer comes from studies in Sweden that found a link between Iron deficiency anaemia (Plummer- Vinson syndrome) and pharyngeal cancer in women (Winn, 1995). People whose diets are deficient in fruits and vegetables have been found to be at a higher risk of developing oral cancer (Winn, 1995). Winn (1995) in a study in North Carolina USA showed that people who consumed 0 - 1 servings of fruits per week were significantly more likely to have oral cancer than those who consumed 7 or more servings per week. Other studies from India and Brazil have shown that regular consumption of fruits and vegetables are protective against oral cancer (Franco et al., 1989).

Franceschi et al. 1992, suggested that high intake of particular dietary staples may be an indication of poor diet in general and that inadequate nutrition enhances cancer risk. They opined that this may be due to the fact that dietary deficiencies are linked to high consumption of certain foods (for example maize is low in riboflavin) (Winn, 1995). Martinez in Puerto-Rico (Winn, 1995) found that patients with oral, pharyngeal and esophageal can-cers ate less food than did control subjects, were more likely to eat only one meal a day and were more likely to eat irregularly. However, it was reported that subjects with head and neck cancer were not more likely than control subjects to take inadequate diet (Winn, 1995).

In a study conducted in South-west Nigeria, we discovered that not consuming fruits and vegetables regularly was associated with an increased risk of developing oral cancer (OR 3.0 and 1.32) (Lawal et al., 2011). Also, we found that the serum levels of antioxidant vitamins A, C and E were significantly lower in oral cancer patient compared with those of normal patients ($p=0.001$, $p=0.013$ and $p=0.015$ respectively). In the same vein, we reported that the risk of developing oral cancer was much higher in people with lower serum vitamins A, C and E (OR= 10.89, 11.35 and 5.6) when compared with the risk in people who took tobacco or alcohol (OR= 4.05 and 1.09) (Lawal et al., 2012).

It is suggested that protective effects of the antioxidant vitamins against cancers may be attributable to their free radical mopping effects and their ability to boost immune response. Free radicals are highly unstable and if unchecked by antioxidants, are capable of damaging cell constituents, including DNA, as well as other opportune targets, particularly those containing polyunsaturated fatty acids (Lippman et al., 1994).

Kola nut

Smoking cigarette and habitually chewing kola nut with it may be a social habit that is peculiar to some Nigerian smokers. Some people, however, chew kola nut to induce sleeplessness, prolong their capacity for work and increase their mental efficiency probably because of its caffeine content (Odukoya et al., 1990). *Cola acuminata* and *Cola nitida rubra* are two types of kola nut commonly eaten by Nigerians but *C. acuminata* is preferred because of its perceived greater stimulating effect as confirmed by Somorin who reported higher caffeine content for *C. acuminata* (Odukoya et al., 1990). Although, studies linking the use of kola nut with oral cancer are rare, Odukoya et al. (1990) in a study in South-west Nigeria, observed that smoking and kola nut chewing had a statistically significant ($p<0.005$) influence on the karyopyknotic index scores of palatal mucosa of volunteers with people that smoke and chew kola nut having a higher karyopyknotic index score than those that smoke alone and in non-smokers (Odukoya et al., 1990).

Furthermore, people who chew kola nut without smoking had a higher karyopyknotic index score than in the non-kolanut, non-smoking group. They suggested a potentiation of the cigarette smoking-induced palatal keratinization by kola nut (Odukoya et al., 1990). The carcinogenic potential of kola nut has been linked with the fact that it contains up to 5 - 10% of tanins which previously has been listed among compounds with known and suspected carcinogenic potentials (Odukoya et al., 1990).

FUTURE RESEARCH OPPORTUNITIES

The investigation of the molecular events associated with oral cancer in Nigeria is desirable, since it has previously been shown that there are racial differences in molecular events that lead to oral cancer. The molecular changes found to be associated with oral carcinomas in western countries (UK, USA and Australia) are mainly p53 mutations but these are rare in the east (India and South east Asia) where more of RAS oncogenes abnormalities are common (Scully and Bedi, 2000). Also, the concept of the role of tumour microenvironment in the pathogene-sis and prognosis of cancers have generated keen in-terest amongst many researchers, and studies of tumour microenvironment in Nigerian oral cancer cases will add to the knowledge in this novel area of cancer research which might in future be a potential target for more effective cancer treatment.

Conclusion

Though considered to be the most important aetiologic factors, the experiences from Nigeria suggests that tobacco and alcohol play a less important role in the aetiology of oral cancer compared to reports from other parts of the world. We opine that oral cancer in Nigeria may be an interplay of poverty, malnutrition, immune suppression and possibly a yet to be determined infective agent which act as modifiers to genetic predisposition. The efforts by the Nigerian government to alleviate poverty and improve both adult and general education needs to be strengthened as we believe these will go a long way in reducing the burden of oral cancers in the Nigerian population. In addition, concerted efforts is needed by both government and non-governmental organisations (NGOs) in improving oral health education and advocacy, and the importance of proper diet and nutrition in preventing oral cancer should be emphasised in cancer awareness campaigns.

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