MINI-REVIEW

Emerging and Established Global Life-Style Risk Factors for Cancer of the Upper Aero-Digestive Tract

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Abstract

Introduction: Upper aero-digestive tract cancer is a multidimensional problem, international trends showing complex rises and falls in incidence and mortality across the globe, with variation across different cultural and socio-economic groups. This paper seeks some explanations and identifies some research and policy needs. Methodological Approach: The literature illustrates the multifactorial nature of carcinogenesis. At the cellular level, it is viewed as a multistep process involving multiple mutations and selection for cells with progressively increasing capacity for proliferation, survival, invasion, and metastasis. Established and emerging risk factors, in addition to changes in incidence and prevalence of cancers of the upper aero-digestive tract, were identified. Risk Factors: Exposure to tobacco and alcohol, as well as diets inadequate in fresh fruits and vegetables, remain the major risk factors, with persistent infection by particular so-called "high risk" genotypes of human papillomavirus increasingly recognised as also playing an important role in a subset of cases, particularly for the oropharynx. Chronic trauma to oral mucosa from poor restorations and prostheses, in addition to poor oral hygiene with a consequent heavy microbial load in the mouth, are also emerging as significant risk factors. Conclusions: Understanding and quantifying the impact of individual risk factors for these cancers is vital for health decision-making, planning and prevention. National policies and programmes should be designed and implemented to control exposure to environmental risks, by legislation if necessary, and to raise awareness so that people are provided with the information and support they need to adopt healthy lifestyles.

Keywords: Upper aero-digestive tract cancer - life style risk factors - tobacco - diet - carcinogenesis - epidemiology

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Introduction

Definition of upper aero-digestive tract cancer

We hereby define squamous cell carcinomas of the upper aero-digestive tract (UADT) by the following ICD cancer diagnostic groups: intra-oral sites [ICD-10 C00-C06], oro-pharynx [ICD-10 C09-C10], and other ill-defined sites of the lip, oral cavity and pharynx [ICD-10 C12-C14] (Slootweg et al., 2005), larynx [ICD-10 C32] and oesophagus [ICD-10 C15] (Richiardi et al., 2012) as illustrated in Figure 1.

Global epidemiology of upper aero-digestive tract cancer

Malignant neoplasms of the lip plus oral cavity and pharynx [ICD:10- C00-C14] excluding other pharyngeal sites [C11-13] are often grouped together in epidemiological data (World Health Organization, 2007). Collectively, they are the fourth most common cancer in the world, with over 400,000 cases estimated annually (Warnakulasuriya, 2009).There is a wide variation in global burden, with incidence in India, across South and South East Asia is amongst the highest in world. Incidence is also increasing elsewhere, e.g. parts of Western and Eastern Europe, Latin America, Pacific regions. In many countries like Australia, more than 50% of oral cancers occur on the lip due to exposure to sun (Ariyawardana et al., 2013). Figure 2 illustrates worldwide estimated age standardized incidence rates per 100,000 for top 25 cancers including the UADT cancer for males and females.

Global incidence and prevalence rates

The globally estimated age standardized incidence rates -ASW(R) per 100,000 for all ages and both sexes for malignant neoplasms of lip plus oral cavity are 4.0, for other pharynx are 1.9, for larynx are 2.1 and for

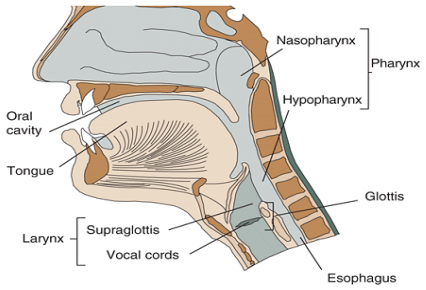

Figure 1. Upper Aero-Digestive Tract Cancer Source: Wikipedia. Available at http://www.springerimages.com/Images/RSS/1-10.1007_978-1-4614-0040-0_3-0

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oesophagus are 5.9 (Ferlay et al., 2012). The five year prevalence rates (proportion per 100,000) for both genders are as follows: for lip plus oral cavity (13.5), other pharynx (6.0), oesophagus (8.9) and larynx (8.5). Two thirds of the global burden of these cancer cases occurs in developing countries, with the Indian subcontinent accounting for one third of the global burden for cancers of lip plus oral cavity (Subramanian et al., 2009). These are largely diseases of the poor (Johnson et al. 2011).

Survival rates from malignant neoplasm of upper aero-digestive tract

UADT cancer, on average around the world, has one of the lowest figures for five-year survival of all cancers, ranging from 10% to 65%. Survival for each cancer site (all clinical stages combined) is described in terms of 5-year age-standardized relative survival (Sankaranarayanan et al., 2010). Mean overall five year survival rates for cancer

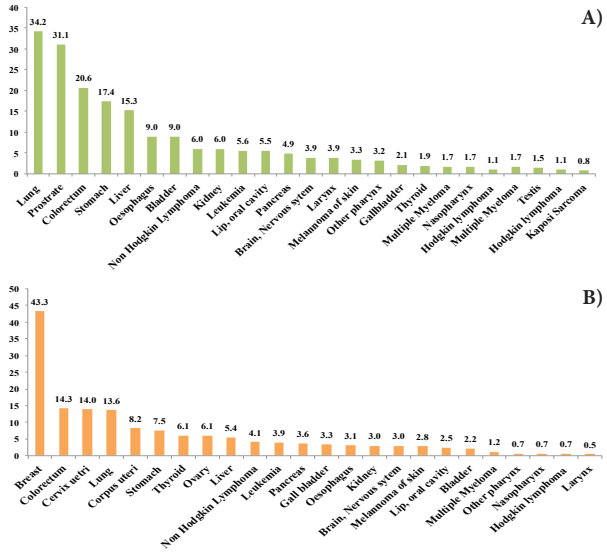

Figure 2. Age Standardized Incidence Rates per 100,000 for the Twenty Five Most Common Cancers among A) Males and B) Females

of lip plus oral cavity are still hovering around 50% (Yeole et al., 2000). Significantly, 10% to 30% of patients with cancer of lip, oral cavity subsequently develop second primary tumours of the upper aero-digestive tract (Furness et al., 2010). Poor survival rates can also be attributed to the fact that half of the oral cancer cases in the nation are diagnosed at advanced Stage III and IV because of delay in seeking medical care and lower acceptance of treatment (Warnakulasuriya, 2009).

Most UADT cancers are limited to the primary site and the regional lymph nodes at the time of diagnosis, and local treatment with surgery and/or radiotherapy may be curative (Sloan et al., 1991). However, when local control is not achieved, these cancers usually progress rapidly, resulting in death within a few years of diagnosis (Hoffman et al., 1998). Most UADT cancers and their management are associated with tremendous physical, emotional and psychosocial disruption (Rogers, 2010). Though, in the management of cancer, primary surgery gives excellent disease specific cure rates. Significantly, worse health related quality of life is experienced in patients who require both surgery and radiotherapy or chemotherapy (Nordgren et al., 2008). There are quite large cultural and ethnic differences in the nature of the psychosocial impacts (Kularatna et al., 2013).

The Process of Development of Cancer

Cancer is a chronic and complex process in which multiple items act together and possibly are capable of causing a malignant neoplasm (Cooper and Hausman, 2013). Current evidence suggests that many alterations in the host immunity and metabolism are involved in addition to neoangiogenesis and exposure to chronic inflammation in a genetically susceptible individual. The carcinogenic changes may be initiated or influenced by chemicals (polycyclic hydrocarbons, aromatic amines, diet and hormones) genes (transgenesis by enhancer-

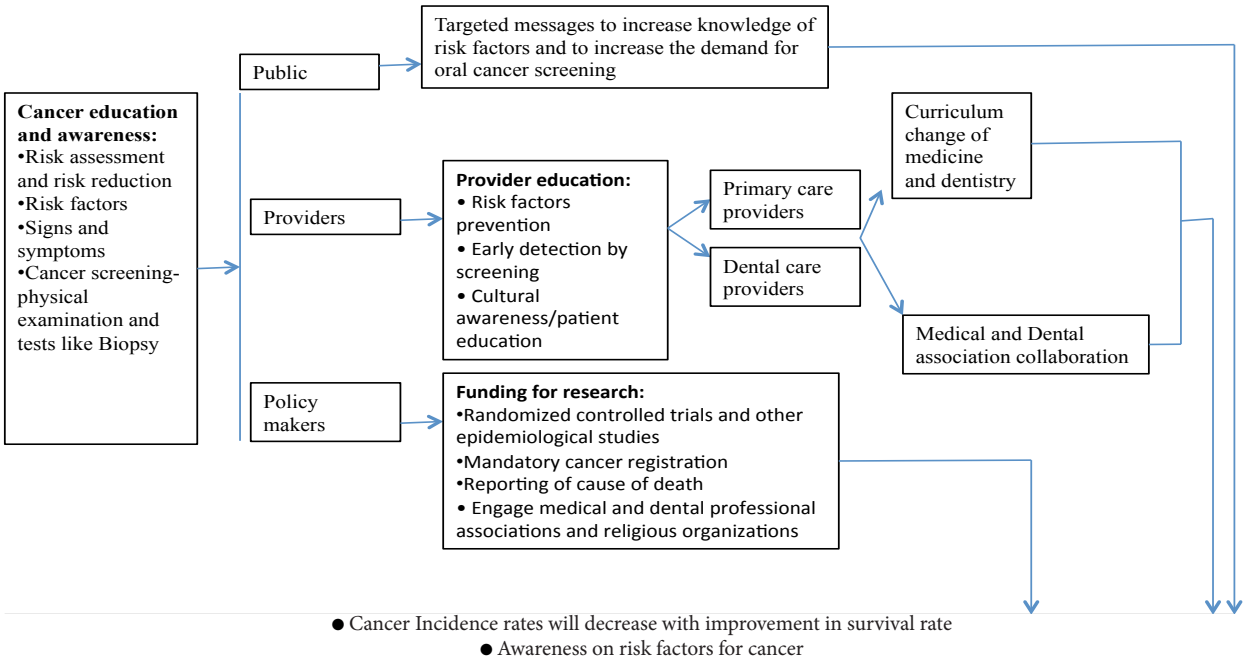

Figure 3. Conceptual Framework for Cancer Prevention and Control

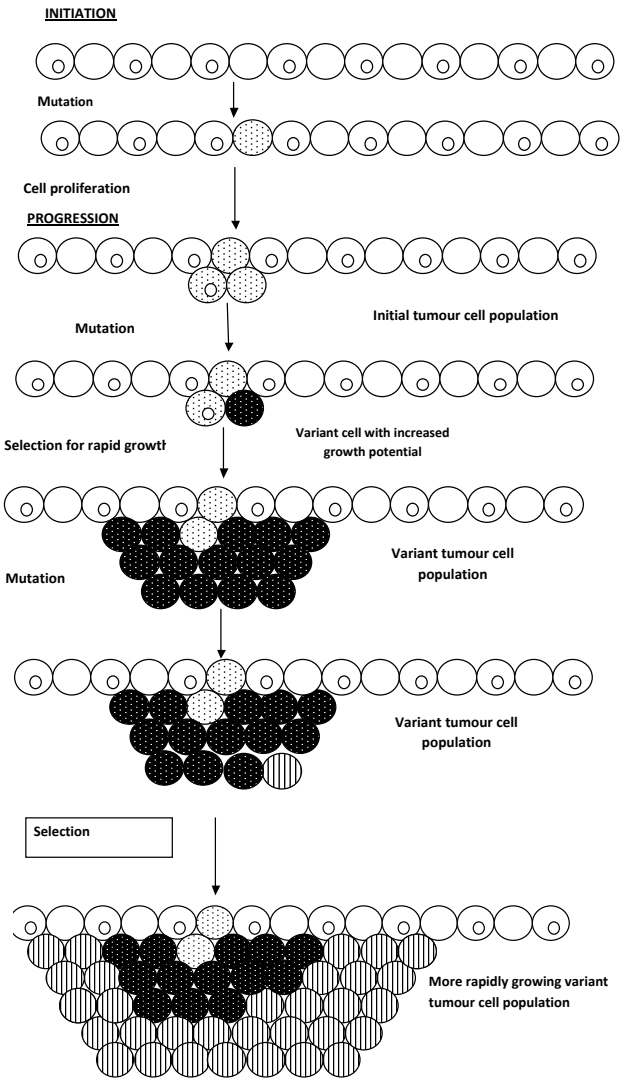

Figure 4. Development of Cancer at the Cellular Level
Modified from: Cooper GM, Hausman RE (2013) The Cell: A Molecular Approach: Sinauer Associates.

promoter-oncogene constructs; selctive),viruses (human papilloma, herpes simplex, retro and hepadna), radiation (ultra violet and ionizing radiation), drugs, tobacco and alcohol consumption, or physical irritants (Khalili, 2008).

At the cellular level as illustrated in Figure 4, the development of cancer is viewed as a multistep process involving mutation and selection for cells with progressively increasing capacity for proliferation, survival, invasion, and metastasis. Tumor initiation is the first stage, which is a result of alteration, change or mutation in the genetic structure and DNA sequences of the initiated cell by a carcinogen leading to abnormal proliferation of a single cell.

Promotion is the second stage which results due to chronic exposure to the carcinogen. The cellular damage at this stage is irreversible. This stage does not involve molecular changes in the structure of DNA but rather in the expression of the genome mediated through promoter-receptor interactions. The immune response is suppressed which enhances the cell division and benign tumor cell is formed (Warshawsky et al., 2006).

Progression is the third stage which is characterised by its karyotypic instability and evolution, and the development of irreversible, aneuploid malignant neoplasms with metastatic capability, which distinguishes progression from both initiation and promotion. Furthermore, progression stage is characterized by a continuing evolution of chromosomal abnormalities within the cell- mutation, potentially leading to multiple "stages" or changes, which were first described by Foulds as "independent characteristic (Foulds, 1954; Pitot, 1989).

Risk Factors for Upper Aero-digestive Tract Cancer

UADT squamous cell carcinomas are an important global health problem (Ferlay et al., 2012) and a devastating chronic disease of multi factorial origin (Gupta et al., 2012). The large variation in worldwide incidence and mortality from cancers of UADT are mainly attributed to variations in exposure to the major environmental and behavioural risk factors as illustrated in Table 1 (Brunner et al., 2006) and are namely: tobacco, alcohol, inadequate intake of fruits and vegetables, and infection with human papilloma virus in high cancer incidence areas like India (Dal Maso et al., 2002; Boeing et al., 2006; Pelucchi et al., 2006; Polesel et al., 2008; Ansary-Moghaddam et al., 2009; Gupta et al., 2012; Anantharaman et al., 2013). Further, some epidemiological studies show that employment in industries with occupational exposures to wood dust, asbestos, acid mists or solvents and manufacturing of textiles and leather are associated with an increased risk of UADT cancer (Maier et al., 1997; Jayaprakash et al., 2008; Schmeisser et al., 2010; Richiardi

Table 1. Identified Risk Factors for Upper Aero Digestive Tract Cancer

Socioeconomic, cultural, political & environmental factors	Common Modifiable Risk Factors	Non- Modifiable Risk Factors	Intermediate risk factors
Globalization	Smoking tobacco	Age	Raised blood glucose
Urbanization	Smokeless tobacco	Gender	Abnormal blood lipids
Population ageing	Alcohol	Hereditary	Overweight/obesity
Westernization	Diet poor in fruits & vegetables		
	Inadequate physical activity		
	Air pollution		
	Occupational hazards		
	Dental risk factors		
	Unsafe sexual practices		
	Non steroidal anti-inflammatory drugs		

*Source: Brunner, E., & Marmot, M. G. (2006). 'Social Organization, Stress, and Health.' In M. G. Marmot & R. G. Wilkinson (Eds.), Social Determinants of Health. Oxford: Oxford University Press

et al., 2012). Furthermore, there are very few studies which have suggested a positive relationship between UADT cancer risk and family history of head and neck cancer along with other cancers (Goldstein et al., 1994; Negri et al., 2009). Associations between socioeconomic status (SES) and UADT cancer have been observed and low SES has been independently linked to an increased incidence and poorer survival (Conway et al., 2010; Sharpe et al., 2012).

It is important to note that risk factors to health do not occur in isolation (Johnson, 2003a). The chain of events within the risk factors leading to an adverse health outcome includes both proximal and distal causes -- proximal factors act directly or almost directly to cause disease, and distal causes are further back in the causal chain and act via a number of intermediary causes. The factors that lead to someone developing disease on a particular day are likely to have their roots in a complex chain of environmental events that may have begun years previously, which in turn were shaped by broader socioeconomic determinants. Most of the risks cannot be disentangled in order to be considered in isolation, as they act at different levels, which vary over time (Kuh et al., 2003).

Aetiology

Oral potentially malignant disorders

Particularly, in South Asia, the majority of oral cancers arise from pre-existing long-standing lesions, now termed oral potentially malignant disorders (Warnakulasuriya et al., 2007) in recognition of the fact that systemic, cellular and molecular changes are much wider than any particular macroscopically visible oral lesion.

Age distribution

Traditionally, cancer of UADT is a disease mainly affecting the older age group. This has generally been attributed to indiscriminate substance abuse, particularly tobacco and related products (smoked and smokeless),, over a considerable period of time (Sherin et al., 2008).

The most prominent factor determining susceptibility to cancer is age which could be attributed to the time needed for the cellular events involved in the development of a neoplasm to take place. Immune competence and the immune cell surveillance diminishes with age which further contributes to the direct relation between age and the malignancy (Derhovanessian et al., 2008). In high incidence countries of the world like India, many cases are diagnosed under the age of 40 years which is attributed to high tobacco consumption starting at relatively young age (Sherin et al., 2008; Warnakulasuriya, 2009).

Gender differences

Worldwide, for cancer of lip plus oral cavity the highest age standardized incidence rates per 100,000 among males (22.9) and females (16.0) are seen in Melanesia. For cancer of other pharynx, both males (7.5) and females (1.6) from Western Europe show the highest ASR(W). For cancer of larynx among males the highest incidence rates are seen in the Caribbean (7.9) and similarly females (0.9) from Caribbean, Eastern and Western Asia, South Africa and North America share the same statistics for highest rates. For cancer of oesophagus the highest ASR(W) among males (16.9) are seen in Eastern Asia and in Western Europe for females (1.6).

Socioeconomic position

The relationship between UADT cancer incidence and socioeconomic inequalities, while recognised, remains relatively under-described and unexplored by age, tumour subtype, and sex (Conway et al., 2008; Johnson et al., 2011; Sharpe et al., 2012) in low and middle income countries. Associations between socioeconomic status and UADT cancer have been observed in several studies, and low SES has been independently linked to an increased incidence and poorer survival (Egger et al., 1997; Menvielle et al., 2004). Social status is usually measured by education, income and occupation.

Behavioural risk factors

Tobacco smoking: tobacco use is the single most important modifiable risk factor for upper aero-digestive tract cancer; a meta-analysis of data available worldwide has determined the relative risk in current smokers to be 2.56 (95% confidence interval, 2.20–2.97) for the latter ($p<0.001$) (Johnson et al., 2003).

Bidi smoking: Bidi is the most popular form of smoked tobacco and an age-old form of indigenous smoking widely practiced more specifically in South-East Asia by the people of lower socioeconomic status (Rahman et al., 2000; Jayalekshmi et al., 2010).

It is also associated with a significantly higher UADT cancer mortality as compared to tobacco chewing (Mathur et al., 2011). Bidi is made of about 0.2-0.5 g raw, dried and crushed tobacco flakes (naturally cured) rolled by hand in tendu leaf (Diospyrus mebunoxylon or Diospyrus ebenum) or white paper (Rahman et al., 2000). Nicotine and tar content are higher in bidi than that of a cigarette (Rahman et al., 2000). Studies that collected covariate information, the risk was persistently increased after adjustment for cigarette smoking or tobacco chewing, diet, alcohol use, and education level (Vineis et al., 2004).

Betel quid chewing: betel quid is a mixture of areca nut, slaked lime (aqueous calcium hydroxide paste), with or without tobacco, condiments and with and without sweeteners wrapped in a betel leaf. It is chewed and held in the mouth like a quid. Gutka is powered mixture of areca nut, tobacco, slacked lime, sandalwood and fragrance. Chewing of areca nut alone is a widely practiced socially accepted addiction predominantly among females in South and South-East Asian populations. Carcinogenic nitrosamines derived from areca nut are formed in the saliva of chewers. These nitrosamines induce the oral pre-neoplastic disorders with high propensity to progress to cancer of oral cavity, pharynx and oesophagus (Secretan et al., 2009).

Alcohol: effects of smoking and alcohol on the risk of upper aero-digestive tract cancer are synergetic and cumulative rather than additive (Hashibe et al., 2009; de Menzes et al., 2013). Individuals who both smoked and consumed alcohol had double the risk of upper aero-

digestive tract cancer in comparison with those who only smoked: the relative risk was 6.93 (95% confidence interval 4.99-9.62) (p<0.001) (Boodhooa et al., 2009). The risk of UADT cancer rises steeply with the intensity of alcohol drinking. In a meta-analysis of 26 studies on oral and pharyngeal cancer, consumption of 25, 50, and100 g/day of alcohol gave pooled relative risks (RRs) of 1.75, 2.85, and 6.01, respectively (Bagnardi et al., 2001). The relation with duration of alcohol consumption is less consistent (Franceschi et al., 2000). Likewise, the pattern of risk after stopping drinking is unclear, and the RR seems to appreciably decrease only after 15-20 years since stopping drinking (Franceschi et al., 2000).

Human papilloma virus: Evidence from case series, case–control and cohort studies suggest that human papilloma virus (HPV) plays a role in a significant subset of UADT cancers, particularly cancer in the tonsil and base of tongue (Cobo et al., 2008; Goot-Heah et al., 2012).

HPV positivity designates a specific subgroup of oropharyngeal squamous cell carcinomas that arise preferentially among individuals with no consumption of tobacco and alcohol and that have a favourable outcome attributable to an increased sensitivity toward radiotherapy (Smith et al., 1998; Furniss et al., 2009). The epidemiological, molecular, and mechanistic association of HPV16 and UADT cancer is strongest for the oropharynx. Conversely, HPV18 appears to be rare in oropharyngeal cancers (Gillison et al., 2008; Anantharaman et al., 2013). The relationship between HPV infection and laryngeal cancer is of particular interest, given that recurrent respiratory papillomatosis is clearly caused by benign proliferative growths induced by HPV 6 or 11 infection of the laryngeal epithelium (Herrero, 2003).

Diet and nutrition: nutritional factors play a major role in cancer initiation and development (Comba et al., 2010). The most consistent findings support the beneficial role of a dietary pattern based on specifically yellow and orange fruit and green cruciferous vegetables and other selected micronutrients contained in such foods and consumption of olive oil related to reduced risk of UADT neoplasms (Boeing et al., 2006; Pelucchi et al., 2011; Steffen et al., 2012). There is possibly an unfavourable relationship between meats-specially red meat, animal products and UADT cancer (O'Doherty et al., 2011; Steffen et al., 2012). Furthermore, inverse association between caffeinated coffee drinking and risk of cancer of the oral cavity and pharynx have been suggested (Galeone et al., 2010; Al-Dakkak, 2011). There has been very inconsistent findings from previous studies for nil effect/ protective or as positive risk factor concerning the consumption of dairy products like milk and cheese and risk of UADT cancer (Sapkota et al., 2008).

Occupational risk factors

Globally, some epidemiological studies (Patel et al., 2003; Conway et al., 2008) show that employment in industries with occupational exposures to asbestos, coal dust, acid mists or solvents, textile and leather manufacturing and construction workers are associated with an increased risk of pharyngeal, laryngeal and oesophageal cancer (Blane, 1996; Berney et al., 2003; Schmeisser et al., 2010).

Globally re-emerging risk factors

Occupational characteristics may not only have an effect on cancer outcome via exposures but also by influencing opportunities for social and economic participation. In addition, occupation may be a surrogate variable for lifestyle and psychosocial determinants of health-related behaviours. Some of the other emerging risk factors which have been proposed, are chronic irritation from dental factors (poor dentition, trauma due to ill-fitted partial/complete dentures or from sharp/broken tooth), chronic ulcers, chronic oral infection like periodontitis and low frequency of oral hygiene (Wynder et al., 1957; Graham et al., 1977; Thumfart et al., 1978; Franco et al., 1989; Zheng et al., 1990; Marshall et al., 1992; Maier et al., 1993; Velly et al., 1998; Warnakulasuriya, 2009). However, the causative role of chronic trauma of oral mucosa on oral carcinogenesis remains controversial. Some authors proposed it as a cause, on the other hand, some suggest it is a result of increase in volume of tumour (Thumfart et al., 1978). In contrast to Lockhart, several case control studies exhibit a positive relationship between dental status and cancer of oral cavity (Zheng et al., 1990; Bundgaard et al., 1995; Velly et al., 1998; Talamini et al., 2000; Rosenquist et al., 2005). However, the nature of association with dental variation is difficult to pinpoint, because of confounding effect of lifestyle determinants in addition to the socioeconomic and cultural characteristics.

Chronic trauma of the oral mucosa

Chronic trauma of the oral mucosa (CTOM) is the result of repeated mechanical irritative action of an intraoral injury agent. Defective teeth (malpositioned or with sharp or rough surfaces because of decay or fractures), ill-fitting dentures (sharp or rough surfaces, lack of retention, stability or overextended flanges) and/or parafunctional habits (e.g. oral mucosa biting or sucking, tongue interposition or thrusting), acting individually or together, could all be responsible of this mechanical irritation (Piemonte et al., 2010; Turker et al., 2010).

CTOM could generate lesions on a healthy mucosa or intensify previous oral diseases in addition to its role as promoter or progressor factor of oral neoplasms. Epidemiological (Lockhart et al., 1998; Velly et al., 1998; Dayal et al., 2000; Rosenquist et al., 2005) as well as laboratory studies (Konstantinidis et al., 1982; Jones et al., 1993) describe a possible causal relationship between CTOM and cancer of lip plus oral cavity. The mechanism by which CTOM is thought to contribute to carcinogenesis is yet not clearly identified.

Chronic periodontitis

Chronic periodontitis is a multi-factorial, opportunistic inflammation of the periodontium mostly caused by gram-negative, anaerobic bacteria. Microbial toxins, proteases and endotoxins are secreted, inducing an inflammation through stimulation of monocytes with further excretion of mediators like prostaglandin E2, thromboxane B2, interleukin-1, -6, -8, -17, tumor necrosis factor and collagenases (Champagne et al., 2003; Sharma et al.,

2011). An induction of oral squamous cell carcinoma by such chronic bacterial inflammation appears possible since the involved inflammatory mediators, cytokines and bacterial toxins have shown to have a potential for malignant transformation *in vitro* (Coussens et al., 2002; Sharma et al., 2011).

Use of non steroidal anti-inflammatory drugs

Long term use of non steroidal anti-inflammatory drugs (NSAD) like aspirin has a protective effect on incidence of cancer of oesophagus. However, there are limited number of epidemiological studies which support its beneficial effect on cancer of lip plus oral cavity (Thun et al., 2002). NSAID, acts on the arachidonic acid metabolism, blocking the synthesis of thromboxane, prostacyclin and prostaglandins, which in turn can influence cell proliferation, and hence cancer growth (Marnett, 1992). A specific target of the protection against UADT cancers by aspirin and other NSAID is the inhibition of cyclooxygenase-2, which is important for apoptosis,and therefore for control of the mechanisms of carcinogenesis (Morgan et al., 1998; Zimmermann et al., 1999).

Family history of cancer

There is an evidence of family history of head and neck cancer as a marker of an increased risk of oral cavity (Garavello et al., 2008). However, no clear pattern emerges from epidemiological studies: some of them found a stronger association in younger subjects compared to older subjects (Garavello et al., 2008) others found a contrary result (Negri et al., 2009).

Prevention of UADT Cancer

Prevention of upper aero-digestive tract cancer can be targeted at primary, secondary and tertiary stages forming an integral part of cancer control policy (Moore et al., 2010; Mendis, 2010; Gupta et al., 2013) as illustrated in Figure 4. The most cost effective approach is the primary prevention by life style risk factor modification where the primary target is established risk factors like tobacco in its all forms, alcohol and diet inadequate in fruits and vegetables. The methods to prevent smoked and smokeless tobacco and alcohol consumption initiation can be classified into three phases, population-based interventions, such as mass media campaigns and increased taxes on alcohol and tobacco products, community-based interventions, such as school-based prevention programs, smoke-free places, provider-based interventions, such as counselling, including telephone counselling, telephone quit-lines or oral examination, education about nicotine replacement therapy may be more effective. Advocating healthy lifestyles with focus on diets rich in vegetables, fruits, fibre, milk (to some extent), less quantity of red meat, antioxidants and appropriate physical activity should also be a part of primary prevention (Gupta et al., 2013).

Secondary prevention includes the screening of cancer cases of upper aero-digestive tract where the primary care providers including the dental surgeons, head and neck cancer surgeons should also focus on identification and diagnosis of oral potentially malignant disorders which have a very high malignant rate for cancer of lip plus oral cavity (Saleh et al., 2014). Primary care providers should refer the patients with positive findings to health professionals experts for their clinical opinion, support with habit cessation, biopsy if indicated in the judgement of the professional, and further management (Khalili, 2008).

Tertiary prevention should target better access to medical and health care services especially in low middle income countries. The curriculum of dental and medical care should incorporate population and community based health care services. The health policy makers should enforce mandatory cancer registration and reporting of cause of death in all the countries. Sufficient funding should be allocated for research into new and innovative methods for cancer prevention at all stages at population level (Mendis, 2010; Johnson et al., 2011).

Conclusion

Cancer is a multidimensional problem with immense impact on individuals and their families, on all health services; and on wider society. Carcinogenicity is dose-dependent and magnified by multiple exposures. Conversely, low and single exposures do not significantly increase cancer risk. By quantifying the impact of risk factors on diseases, evidence-based choices can be made about the most effective interventions to improve global health. We need to re-orient oral health research, practice, and policy toward a 'social determinants' model: a closer collaboration between, and integration with, dental and general health research.

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