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Head and Neck Squamous Cell Carcinoma in the Young: A Spectrum or a Distinct Group? Part 1

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Abstract While most head and neck squamous carcinoma (HNSCC) occurs in older people, an increasing number of young patients are being affected worldwide, with up to 5.5% <40. These are predominantly oral and oropharyngeal cancers. Some patients have heavy exposure to the usual risk factors, but an increasing number do not. Part of this trend appears to be due to rising numbers of HPV associated tonsil carcinoma, particularly in males (smokers and non-smokers). A subset of young patients, however, is non-smoking females usually with tongue cancers, not related to HPV, the aetiology of which is unclear. Various mechanisms may be at work here: the variation in ability to detoxify the products of smoke and alcohol varies in individuals, which may explain why environmental exposure to smoke seems to play a role in some non-smokers with HNSCC. The role of marijuana remains possible but uncertain, and it may be that anaemia is a co-factor. There is an increased risk of HNSCC in first degree relatives of HNSCC patients, and while inherited syndromes associated with HNSCC are rare, elucidation of their genetics may help to develop our understanding the disease in these young patients without recognised risk factors.

Keywords Head and neck cancer · Young patients · Squamous cell carcinoma · Malignancy · Etiology

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Most head and neck squamous cell carcinomas (HNSCC) occur in the 60+ age group but a there has been a trend for an increasing percentage of younger patients in the US, various European countries and China, since the 1970s [1]. In the Indian sub-continent, where there is a much higher overall rate of HNSCC, a similar trend is occurring [2]. In addition, there appear to be changes in the site of primary, with a relative increase in oral and oropharyngeal cancers. Shiboski noted carcinoma of tonsil, tongue and base of tongue increasing in young white patients from 1973–2001 in the US [3], and a Scandinavian study noted an increase of X 5–6 in tongue carcinoma in the under 40s, compared with an increase of X 2 in the over 40s.

What percentage of HNSCC patients are young varies depending greatly on the chosen age cut off, with 6.7% <45 years, compared with a rate of 0.4–3.6% in the <40 year age group [1]. The sex distribution in younger patients shows a decrease in the male:female ratio. The ratio may also be site dependent [4, 5]. In an Irish study of patients aged <40 [4], just over half were aged <35, and the percentage <40 from 1993 to 2008 was 4.6%. The psychological impact and quality of life issues in patients at such a young age (range 17–39) are challenging.

This trend is probably is due to multiple factors. In the UK, Llewellyn indicates many young patients are heavy smokers and drinkers and although the exposure time still seems short, some have had 20+ years of smoking by their early forties [6]. It appears that many in the 40–45 age group have traditional risk factor exposure and represent the tail end of the more usual patient group, whereas patients <40 are more likely to be non-smokers. An increase in younger patients without exposure to tobacco or betel nut has also been reported in India. In the West, smokeless tobacco has not emerged as a significant factor in young patients. There has been a documented of a rise in

oropharyngeal cancer, particularly in the US, usually in males with tonsillar cancer, many of whom are non-smokers. This group who are strongly associated with HPV, are younger than usual and, although many are in the 50–60s age group [7], El Mofty demonstrated a strong association with HPV16 and tonsillar cancer in males <40 [8]. HPV oncogenes E6 and E7 act through inactivation of p53 and Rb tumour suppressor genes, inducing cell cycle deregulation and genomic instability (see also part 2). Although tonsillectomy rates have also dropped dramatically over the last 40 years, the differing racial and sex distributions suggest that there is an effect independent of the tonsillectomy trend, probably due to HPV [9].

Increased Susceptibility to Risk Factors

The young age begs the question: are some patients poorly equipped to deal with usual risk factor exposure? MacFarlane notes that tobacco alone without excessive alcohol exposure appears to involve a higher than expected risk for females [10]. The ability to metabolise the harmful components resulting from tobacco and alcohol may vary in humans. Glutathione S transferases are a family of enzymes that play a role in the detoxification of hydrocarbons in tobacco smoke. The GST M1 null genotype is associated with an increased risk of lung carcinoma; studies in HNSCC are inconsistent but some suggest an association with loss of both GSTM1 and GSTT1. By a similar mechanism, the slow acetylator phenotype of N acteyltransferase 2 may be associated with oral cancer. It may be that a susceptible person requires minimal or environmental exposure to develop HNSCC. There are reports of increased environmental smoke exposure in non-smoking HNSCC patients, compared with controls [11].

Alcohol consumption is most commonly a cofactor in HNSCC with tobacco but has also been shown to be an independent factor, relating to drinking alcoholic drinks, not pure ethanol. Its role may involve one or more of the following: as a facilitator of passage of carcinogens into cells, via the liver by enhancing metabolising activity, by activating carcinogenic substances, as a local irritant. As with tobacco, there may be variation in the effect on an individual due to metabolism. There are allelic variants of alcohol dehydrogenase (ADH) which metabolises alcohol to acetaldehyde, and mitochondrial aldehyde dehydrogenase (ALDH), which metabolises acetaldehyde. Change in activity due to these variants, which vary with race, may result in acetaldehyde levels being higher and present for longer, acetaldehyde being secreted in saliva [12].

Family History

If some kind of inherited susceptibility is a factor, a family history of HNSCC might be expected. This can be difficult to thoroughly examine since the record of the relatives' tumour is often less than thoroughly documented. Even so, there are several studies indicating an increased risk in first degree relatives. A family history is associated with an earlier onset of HNSCC and cancers occur in family groups with differing risk habits suggesting that this is not just due to families tending to have the same habits. Aggregation by tumour site has been reported in families.

Minor Risk Factors

Apart from tobacco and alcohol risk factors for HNSCC include poor diet, immunosuppression, lichen planus, marijuana exposure, poor dental hygiene, sub-mucous fibrosis, gastrointestinal reflux and various inherited syndromes. A diet rich in vegetables and fruit has been shown to have a protective role in HNSCC in the <45 year olds [6]. The association of anaemia with oesophageal cancer in Patterson Kelly/Plummer Vinson syndrome is well known, usually occurring in elderly females. In O'Regan's group <40 years, 10% had anaemia, a similar rate to an older HNSCC control group, but higher than the norm (approximately 6%) [4]. Immunosuppression, especially post transplant, is associated with development of dysplastic lesions, although oral cancer is rare. Smoking of marijuana has been proposed as a reason for increasing numbers of young patients and while it may play a role, studies are not conclusive [12]. As regards younger patients, Llewellyn [6] noted a slight but not significant risk for female cannabis smokers. Malignant transformation in lichen planus occurs mainly in association with the atrophic and erosive forms that typically occur in older rather than younger patients [13]. Poor dental hygiene has long been associated with oral cancer. It has been shown that there may be a role for infection as a co-factor in carcinogenesis e.g. inflammation, probably due to Chlamydia, may contribute to of cervical cancer [14]. Recently, demonstration of an exaggerated response to inflammation due to polymorphisms of IL6 and TNF alpha has been noted in some HNSCC patients that may result in a carcinogenic effect at a site of inflammation [15]. Thus, there may be an unexpected effect from minor inflammation in certain patients with marginally poor oral hygiene or lichen planus.

Syndromes Associated with HNSCC

Several well characterised but rare inherited syndromes have been to some extent associated with HNSCC e.g.

laryngeal cancer in Bloom and Li Fraumeni syndromes, and oral cancer in Bloom syndrome, ataxia telangiectasia and xeroderma pigmentosa. Familial HNSCC with germline mutations of p16INK4a has been described [12]. Interesting developments have emerged in the genetics of dyskeratosis congenita, in which the various mutations all involve components of the telomerase complex [16]. The primary defect appears to be dysfunction in telomere maintenance. Similar mutations in Fanconi anaemia, aplastic anaemia and myelodysplastic syndrome indicate that these are part of the same disease group. As regards malignant transformation, the telomeres are repeatedly shortened until they reach a critical length, precipitating a genetic crisis in which the surviving cells acquire genomic instability, allowing progression to neoplasia.

Conclusion

So: a spectrum or a distinct group? It seems more likely these patients they are both, falling into three major groups: (1) those in the 40–45 age group who report a very high level of risk factor exposure, a part of the spectrum seen in older patients; (2) males with oropharyngeal cancer, many non-smokers, some of whom are <45 but most of whom are somewhat older, who are an emerging group related to high risk HPV infection; (3) a third distinct group of <40 year olds, usually female non–smokers, with oral cancer. It had been suggested that HPV must be a factor in the latter group, but El Mofty [8] and O'Regan [17] indicate otherwise. In the midst of the avalanche of HPV literature, it is important to note this group of young patients in whom HPV is not a factor; it may also be important in this context to re-examine the long recognised group of older females, without usual risk factors, with oral cancer, the aetiology of which remains unclear. Closer examination of these separate groups with regard to the roles of environmental smoke exposure, marijuana, anaemia and genetic polymorphisms relating to detoxification of cigarette smoke and alcohol may prove helpful in the future. Early detection of cancers of all sites in young patients would be desirable and may well improve due to recognition of the overall trend for the decreasing age profile in oropharyngeal HNSCC. In part two of this session, the molecular concepts of HNSCC relating to young patients will be discussed.

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