Pathol. Oncol. Res. (2013) 19:353–363
DOI 10.1007/s12253-013-9628-y

REVIEW

An Analysis of the Epidemiological and Etiological Factors of Oral Tumors of Young Adults in a Central-Eastern European Population

K. Túri · P. Barabás · K. Csurgay · Gy. Léhner · Á. Lőrincz · Zs. Németh

Received: 6 February 2013 / Accepted: 18 March 2013 / Published online: 6 May 2013

Abstract The etiology of tumors in young age is not precisely known yet, but studies on the topic generally agree that in this group of patients the traditionally known behavioural risk factors (tobacco and alcohol abuse) play no or a significantly less important role. Oral squamous cell carcinoma occurring at a young age is a topic of utmost importance that is extensively and intensively researched as, while the overall incidence of oral cancer is decreasing worldwide, that of squamous cell carcinoma diagnosed in young adults is steadily increasing. The present article aims at presenting the main questions and characteristics of tumors in young adults in Central-Eastern Europe and in developed West European countries as contrasted to tumors found in middle aged and elderly patients. Factors influencing the development of oral cancer include regulatory factors of the cell cycle, the inherited vulnerability of the genetic code of certain proteins and the presence of HPV infection with an oncogenic genotype. The connections of HPV infection and genetic damages are studied intensively. It is known that the prevalence of oral HPV infections is growing with a background of potentially changing sexual habits. It is debated, however, whether smoking and alcohol consumption could have a connection to HPV associated oral cancer and whether the spread of HPV in itself could be an explanation for the growing occurrence of young-age tumors. There is no consensus in the literature as to the prognostic significance of age. Some research groups have found a better life expectancy for young patients, while other authors found a worse prognosis for these patients. It is known that the prognosis of head and neck tumors, the prevalence of HPV infections as well as genetic mutations show regional and ethnic variations. This might be explained by differences in the degree of development of a preventive system, in the quality of care and in the attitudes of young patients towards visiting a doctor. The study is made difficult by incomparable patient selection criteria as well as by the question of the intraoral localisation of tumors as an independent risk factor.

Keywords Young adult · Oral cancer · Epidemiology · Etiology · Human papilloma virus

Abbreviations

Akt	Protein kinase B, serine/threonine protein kinase
Bcl-2	B cell lymphoma 2
CCND1	Cyclin D1 coding gene
DHAS	Dehydroepiandrosterone-sulphate
EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
FSH	Follicle stimulating hormone
hMSH2	MutS homolog 2
hMLH1	MutL homolog 1
HPV	Human papilloma virus
IRF6	Interferon regulating factor 6
LH	Luteinizing hormone
LI	Leukocyte-interleukin
MAPK	Mitogen activated protein kinase
MTHFR	Methylene tetrahydrofolate reductase
NF-κB	Nuclear factor-kappa B
PCNA	Proactive cell nuclear antigen
PIK3CA	Phosphatidylinositol −4,5-bisphosphate 3 kinase catalytic subunit alpha
PR	Progesterone receptor
PRL	Prolactin
PTEN	Phosphatase and tensin homolog
TE	Testosterone

K. Túri · P. Barabás · K. Csurgay · G. Léhner · Á. Lőrincz · Z. Németh (✉)
Department of Oro-Maxillofacial Surgery and Stomatology, Faculty of Dentistry, Semmelweis University, Budapest, Mária str. 52, 1085 Budapest, Hungary
e-mail: nemeth.zsolt@dent.semmelweis-univ.hu

XRCC1 DNA repair protein= X-ray repair cross-complementing protein 1
5-FU 5-fluorouracil

Introduction

Oral cancer mortality rate for 100.000 inhabitants is extremely high in the Central-Eastern European region. 30–40 years ago most of the patients were elderly men. Smoking and alcohol abuse were the main etiological factors.

15–20 years ago the ratio of female patients grew and it can be said that nowadays overall the 45–65 age group is the one mostly struck by the disease. Today - mostly in the economically developed countries (US, Western Europe) - the occurrence of oral cancer is decreasing due to prevention campaigns and the reduction in smoking and alcohol consumption. In contrast, there is a worldwide growth in the incidence of oral squamous cell carcinoma diagnosed at a young age (<50 years) and it seems more and more likely that these patients form a homogeneous group separate from others in a number of aspects (etiology, prognosis).

Epidemiology

The incidence of oral squamous cell carcinoma occurring at a young age is on the rise in contrast to oral squamous cell carcinoma with a traditional etiology [1]. The positive international statistics for the older population did not manifest in Hungary for a very long time, but in the past few years a slow but constant tendency of decrease is seen in the incidence of oral cancer (Fig. 1a and b).

According to international literature 4–6 % of oral tumors occur in young patients, i.e. in patients whose age at diagnosis is less than 40 years [2–5]. According to the data of the *National Cancer Registry* for 2010 in Hungary 12.8 % of oral tumors occurred in patients between 14 and 50 years of age and 78 % of the patients were males. One year earlier, in 2009 the figures were similar: 13.7 % and 75 % respectively. Counting for all localisations (i.e. not just oral and not just squamous cell carcinoma) three times more tumors occur in young males than in women. (Figure 2) [6].

Müller et al. did a retrospective study of 34 years of the oral squamous cell carcinoma patients at Emory University Hospital in the United States. 5 % of the patients were younger than 40 years of age at the time of diagnosis and the male:female ratio was 1.7:1 [7].

Annertz et al. found different results in their study of 5.024 tongue cancer patients in a Scandinavian population between 1960 and 1994. The ratio of young patients (20–39 years) was 5.5 %, the male:female ratio was 1:1.6, i.e. they had more young women with tongue cancer than men

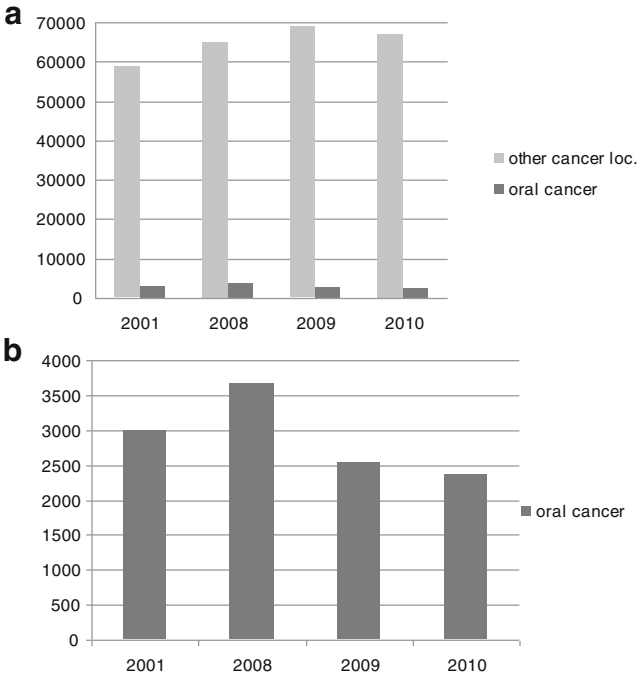

Fig. 1 **a** Morbidity data for oral cancer in contrast to cancer of other localisation **b.** Morbidity data for oral cancer showed a slight but constant decrease in the past years (based on data from the National Cancer Registry)

[2]. A significant male dominance was found in young oral squamous cell carcinoma patients (4:1) in a Sri Lankan population [8]. According to a recent comparative study done in the US there are 2–4 times more male patients in the overall oral and oropharyngeal cancer population than women. That study showed a decreasing tendency in all ethnic groups in all the tumor localisations that is due to the significant decrease in tobacco and alcohol consumption. HPV associated oral cancer, however, showed a growing tendency (3 times more common in men than women), as well as the number of young (25 to 44 years) patients with a cancer of the tongue, with an especially rapid rise in female lingual cancer cases [9]. In childhood oral tumors are

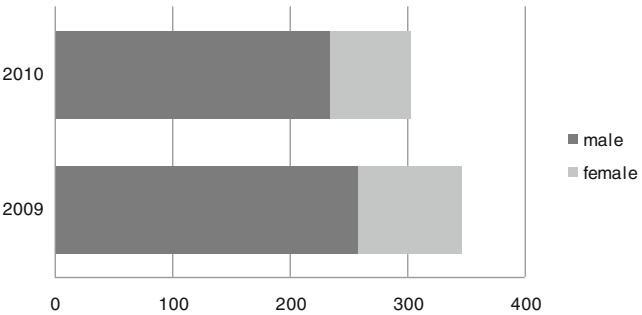

Fig. 2 The gender distribution of tumors of the oral cavity appearing at a young age (14–50) show a male majority in Hungary (based on data from the National Cancer Registry), in contrast to international literature, where this distribution is equal

rare entities. 7–9 % of these are malignant and these mostly (40 %) occur in the age group of 5 to 9 years [10].

Etiology

A close connection is known to exist between behavioural factors and cancer morbidity in general and oral tumors in particular. The two determining etiological factors are smoking and alcohol consumption. The presence and role of these etiological factors is much less in young patients [11]. In young patients, who do have these risk factors it is debatable whether the time of exposure is sufficient to cause enough damage to result in the development of a tumor [12]. It seems that the main etiological factor for oral tumors in the young population is neither extreme alcoholism nor tobacco abuse. *Llewellyn et al.* have shown that behavioural risk factors are present in the young population as well, and these did have an elevated risk of developing the disease (an analysis of 53 patients under 45 years of age vs a matched control group). The short exposure time due to young age and the high number of patients in whose cases 'classical' risk factors are not present, show that other etiological factors also play a role in the pathogenesis of young-age oral tumors [3].

In view of this some Hungarian data might be of interest concerning young-age tobacco and alcohol consumption customs. According to 2009 data from *Eurobarometer*, 46 % of men and 32 % of women above 15 smoke regularly. The high number of smokers in the young (15–24 years) population is especially worrying. 39 % of the 15–24 age group, and 50 % of the 25–39 age group are smokers [13]. This places Hungary to fifth place among EU countries. Among young boys only the Estonians, whereas among young girls the Austrians and Brits smoke more. The ratio of young smokers has shown a slow decrease since 2000; in 2003 39 % of young people smoked regularly, whereas in 2007 this was 'just' 33 % . This was unchanged for young women. According to a survey done in early 2012 32.3 % of men and 23.5 % of women were daily smokers. The number of cigarettes smoked decreased by 8 % compared to 2009, but the ratio of hand-rolled cigarettes increases and accounts for one third of all cigarettes smoked [13, 14].

According to the *INHANCE* study (International Head and Neck Cancer Consortium; 17 European and North American centres, 11,221 patients vs. 16,168 healthy control persons) alcohol and tobacco are responsible for 72 % of head and neck cancer (61–79 %): in 4 % alcohol consumption in itself, in 33 % smoking in itself and in 35 % tobacco and alcohol abuse combined. Out of head and neck cancer in tumors localised in the oral cavity these etiological factors are present in 64 % of the cases. Risk factors and the development of oral cancer showed a correlation of 74 % for males and 57 % for females. The risk rate is of just 33 % if the patient is under 45 years of age at the time of diagnosis [15]. *Llewellyn et al.* compared data of patients with oral squamous cell carcinoma under 45 years of age (n=116) with those of a matched healthy control group with regard to risk factors. Calculated risk was quite low both for smoking and alcohol consumption and no etiological factor was identified in 36 % of young female cancer patients and in 18 % of young male cancer patients. Additionally, only smoking for at least 21 years was associated with a higher risk [16]. *Bachar et al.* analysed the data of 291 israeli oral squamous cell carcinoma patients. No tobacco or alcohol abuse was found in the histories of 116 patients (39 %). A significantly worse survival rate was found in patients under 40 who neither drank nor smoked, which also shows that there is a separate homogeneous group of young patients, where new etiological factors need to be researched [17].

Genetic Risk

The exact importance of the numerous genetic lesions seen in the background of oral cancer is not known yet. Usually there is a superimposed damage to two big gene families behind malignant transformation: proto-oncogenes and tumor suppressor genes.

Proto-oncogenes include genes that initiate proliferation and inhibit cell death which are very important phylogenetically conservative elements of normal control. Damage to growth factors, growth hormone and their receptors and elements of the receptor signal transduction cascade results in an uncontrolled multiplication of cells [18].

Activation of the c-erbB2/H-ras/c-myc cascade is very often seen in tumor cells, also in oral squamous cell carcinoma. *Popovic et al.* found an amplification of c-erbB2 in 32 % of oral squamous cell carcinoma. A more advanced stage of disease (more positive cervical lymph nodes) and a less differentiated tumor was found in association with this genetic phenomenon in this study, in accord with other authors as well. It was also associated with worse survival rates. Mutation of the H-ras oncogene was described in 22 % of the cases, and similarly to c-erbB2 it is associated with more lymph node metastases and less 5 year survival. Interestingly the prevalence of H-ras mutation grows from West to East both in respect of continents and countries (5–35 %) [19, 20].

The EGFR - Ras - Raf - mitogen activated protein kinase (MAPK) signal cascade plays an important role in tumor formation [21]. Out of the mutation of the EGFR gene amplification, mutation of the tyrosine kinase domain, deletion in the sequence coding the extracellular part (vIII EGFR), or mutation of codon 12 of the K-ras that plays a role in the signal cascade may happen. *Szabó et al*. found gene amplification in 11.3 %, and mutation in vIII EGFR in 21 %, both of which are negative prognostic factors [22].

Interestingly no vIII EGFR mutation was found in a Japanese study, which might call attention to ethnic differences [23]. In another Japanese study not a single EGFR, Erb2, K-ras mutation was found in 91 patients with oro-pharyngeal cancer, but EGFR expression was present in all the samples and it was overexpressed in 68 %. Compared to Western patients mutation was very rare in Japan, thus overexpression plays a rather important role in tumorigenesis there [21].

EGFR is an important therapeutic target and prognostic factor in oral cancer. Several studies have been made concerning the connection between EGFR expression and mutation and response to anti-receptor therapy. In a European randomised phase III study the effectiveness of anti-EGFR Cetuximab and 5-FU/platinum combination therapy was studied versus platinum/5-FU treatment alone as a first line therapy in recurrent or metastatic oral cancer. Mildly elevated EGFR transcription was found in all tumors but significantly increased amplification was only found in 11 %. No significant correlation was found between the degree of amplification and survival, but better progression-free survival and better response rates were described with treatment including Cetuximab [24]. According to another study EGFR amplification might be an independent indicator of the therapeutic response to combined Cetuximab and radiotherapy, while no significant differences were found in therapeutic response in EGFR and K-ras mutations [25].

The other major gene family is that of tumor suppressor genes that inhibit proliferation. The most important members of the family are p53 and pRb. A number of authors describe a significant correlation between p53 mutation and tumor stage, which suggests that p53 might rather play a role in tumor progression [26].

Due to carcinogenic exposure probably all the oral cavity gets into a precancerous condition and synchronous or metachronous multiplex tumors can develop anywhere. Due to this supposition the 'p53 status' of visibly healthy mucosa might be a possible means of the early detection of recurrence Correlations were also found between gene mutations and the tumor's tendency to recur and to give metastases. Apart from p53 mutation Bcl-2, Cadherin E, Cyclin D and p16 also play a role in recurrence. The expression of Bcl-2 is fourfold in tumors with metastasis compared to those without metastases, while the level of Cadherin E is one third. A correlation was found for two proteins enabling cell proliferation: the levels of the E2F1 transcription factor and Cyclin D were higher in recurrent oral cancer than in primary tumors. In contrast to this, the level of expression of p16 that inhibits cell proliferation is higher in primary tumors. The overexpression of Bcl-2 regulating apoptosis and Cadherin E down regulation facilitate metastasis formation in head and neck cancer [3, 27].

Cyclin D overexpression and p16 gene inactivation call the attention to head and neck cancers' tendency to recur [27]. The correlations of genetic damages in smoking and non-smoking head and neck cancer patients were also studied with a view to enable individual cancer risk assessment. DNA repair genes might play a role in damage caused by smoking. The TT genotype of the XRCC1 (codon 194) only occurs in healthy subjects and protects against tumor formation. CC genotype is present in 89.2 % of cancer patients, whereas the AA genotype only occurs in cancer patients (lip, oral cavity, pharynx). 1298 CC polymorphism of the MTHFR gene is less frequent in non-smokers and in healthy control subjects (6.7 %; 3.4 %), than in smokers (10.4 %; 12.1 %). There is a higher occurrence of XRCC1 cd399 AA polymorphism in smokers (13.5 vs. 6.7 %) [28]. The mutations of DNA mismatch repair genes, also responsible for genetic instability along with p53 were studied (25.6 %) and hMLH1 mutation occurred in 17 %, and hMSH2 mutation in 8.6 %. In studies of various other genes that play a role in the control of the cell cycle it was found that the promoter regions of these have various methylation patterns in various anatomic localisations of tumors, therefore tumor development is highly individual and so must therapy be [27].

A high number of copies of certain genes (e.g. subunits p15 and p65 of NF-κB) also increase risks. The lack of the suppressor gene PTEN is a bad prognostic factor for lingual carcinoma, and the high expression of epidermal growth factor receptors (EGFR) and proactive cell nuclear antigens (PCNA) are also bad prognostic factors. A high number of copies of the Cyclin D1 regulating factor in histological samples obtained from squamous cell carcinoma also indicated a highly aggressive form with quick recurrence. Interestingly radiotherapy is more effective in these cases than in other genetic damages, thus Cyclin D1 expression might be a prognostic factor for the efficacy of radiotherapy [28].

Alvasiri et al. studied PTEN and Akt activation in the histological samples of 146 oral squamous cell carcinoma patients fixed in formaldehyde. A decreased PTEN expression and the resulting increased Akt activity induced increased cell proliferation and decreased apoptosis. In that study a lack of PTEN activation was found in 61 % of the samples together with an Akt activation in 68.5 % of the samples that also showed correlation with tumor stage. A low apoptosis index (AI) was found in 72 % of the samples [29–31].

Wang et al. studied the effect of p53 gene polymorphism in HPV16 associated oral cancer. Low, medium and high risk groups were established based on the combinations of gene polymorphisms. According to the results a combined genetic risk especially in young non-smoking patients increased the risk of the occurrence of an HPV16 associated tumor [32].

Inactivation of the p16 gene is very often seen in oral cancer. *O'Regan et al.* studied the variations of damage to the p16 gene in relation to age, localisation and HPV status. In their earlier study it was shown that p16 deletion has a strong correlation with age. In their later study it was found

that in younger patients the post-methylation inactivation of p16 was more common, whereas deletion occurred more often in elder patients [33].

Harris et al. studied 25 patients under 40 years of age with a cancer of the tongue. p16 (INK4a), EGFR, and p53 expressions were studied. An increased expression of p16 was found in 44 % of the samples (the samples were HPV negative), in which group the patients had a significantly better relapse-free and overall survival rate [34].

It is interesting to note that even though millions of people worldwide are subject to the adverse effects of smoking and alcohol consumption the majority of them never develop oral cancer. It was suggested that a polymorphism in the enzymes responsible for the metabolism of the carcinogens in alcohol and tobacco smoke might be in the background of the vulnerability to oral cancer as carcinogens might accumulate due to the inadequacy of their metabolism. It was shown that the presence of some alcohol-dehydrogenase polymorphisms increase the chance of the subject developing cancer in his or her lifetime if he or she abuses alcohol.

There are at least 400 various carcinogens in tobacco smoke. The polymorphism of certain genes coding proteins responsible for the metabolism of xenobiotics (e.g. cytochrome p450 1A1, glutathione S transferase, glucosyltransferase 1A7) indicate a higher risk for smokers [27]. One family of catabolic proteins often studied is glutathione S transferase M1 and T1, the polymorphism of which can be connected to the oral cancer of smokers. *Zhang et al.* performed a meta-analysis of 28 studies on the topic. It was found that the glutathione S transferase M1 0 genotype showed a correlation to oral cancer of smokers in an Asian ethnic group, but this correlation could not be established in a Caucasian population. According to their results glutathione S transferase T1 plays no role in carcinogenesis [35].

Of even more interest to the present review is the study by *Gawecki et al.,* where the above enzymes were studied together with various other genetic lesions in young patients. The samples of head and neck cancers from 60 patients under 45 years of age underwent genetic analysis and were compared to samples from 72 elderly patients. No differences were found in the number of (induced and spontaneous) chromosome fractures, (induced and spontaneous) DNA damage, DNA repair capacity and glutathione transferase T1 polymorphism. The glutathione transferase M1 0 genotype was present in the younger group in a higher percentage [36].

Toner et al. subjected the samples of 10 young and non-smoking and 10 old and smoking patients to genetic analysis (gene hybridisation) [37]. It is known that tumorigenesis happens according to a relatively constant pattern in elderly smoking patients, and certain steps can be identified that are characteristic of malignant transformation. The loss of chromosome region 3p is a common and early genetic event. Another important 'lost region' is 9p21 that is seen in 70–80 % of head and neck squamous cell carcinoma. These events are not seen in younger patients or are seen in less of the cases. Based on further differences it can be supposed that a completely different model of tumorigenesis might be described for young patients at a molecular level.

The presence of hormone receptors also has to be mentioned in the pathogenesis of oral cancer. *Lukits et al.* found the presence of estrogen (ERα, ERβ) and progesterone (PR) receptors on tumor cells. ERα was mainly found in the kernel, ERβ in the cytoplasm, while PR was found in both localisations. ER has an effect on PR expression and the other way round and as a result of this effect so-called functional ER is expressed (the simultaneous presence of ER and PR), which is independent of the head and neck region and was found to be 40.3 % in that study. It was also stated that the presence of these receptors is not advantageous as far as survival is concerned [38]. *Remenár* found that in 79 % of 33 male head and neck cancer patients an estrogen receptor was present, in 42 % a progesterone receptor and in 60 % a testosterone receptor was found. In 15 cases of healthy intact mucosa 40 % contained estrogen receptors, 15 % progesterone receptors and 20 % testosterone receptors. The difference between healthy and diseased samples was found to be significant. The highest rate of tumor-free survival following postoperative radiation therapy was found in the group with a positive estrogen and negative progesterone receptor result [39]. Knowledge of these receptors might be a help both in estimating prognosis and in therapy. In another study the ER expression in oral cancer was found to be higher than in laryngeal cancer, whereas PR was similar in the two localisations. There was no significant difference in survival according to sex hormone status, but it was slightly worse in ER positive hypopharyngeal tumors [38].

In a later study it was found that in a group of patients thought to have better prognosis, patients with higher FSH, LH and PRL had worse survival rates. The survival of patients with more advanced cancer and low serum TE and DHAS levels was even worse. In the N0 subgroup PRL, while in the N+subgroup TE proved to be independent prognostic factors [46]. The pathologic levels of sex hormones found in head and neck cancer patients in serum hormone level studies could at least in part be attributed to the concomitant liver damage, but elevated LH and FSH levels were only found in cancer patients. Elevated LH and FSH levels may play a special role in tumorigenesis [39].

Tímár et al. studied the tumor and stromal reactions of T2-3 stage oral cancers in a multicentric phase I/II study following the local application of a natural leukocyte-interleukin (LI). The ratio of tumor stroma to tumor cell group changed significantly as a result of the immunostimulant treatment, with a background of intensive stimulation of necrosis. LI induced

the migration of T-cells into the tumor cell groups and accelerated the cell cycle through the expression of the Ki-67 gene, thereby increasing the tumor's sensitivity to chemotherapy and radiotherapy [40].

The damages to the NOTCH protein that plays an important role in tumorigenesis and the defects of its signal transduction mechanism are the targets of intensive research. Their role was not so widely studied in head and neck cancer. NOTCH (4 types) is a membrane receptor responsible for the proliferation, differentiation and even apoptosis of squamous cells. Depending on the signal transduction mechanism and the signal itself it can act as a proto-oncogene or as a tumor suppressor gene.

Stransky et al. in a relatively recent article studied the occurrence of NOTCH and the molecules of the signal cascade that plays a role in cell differentiation in head and neck cancers. Mutation and deletion of NOTCH 1,2,3 was found in 22 %, CCND1 amplification in 22 %, SYNE1,2 mutation in 24 %, CDKN2A mutation/deletion in 25 %, IRF6 mutation in 5 %, H-ras mutation in 4 %, PIK3CA mutation in 8 %, mutation/deletion of TP53 (p53), responsible for apoptosis in 63 %, TP63 mutation/amplification in 8 % and PTEN mutation/deletion in 8 % of the cases. Average HPV positivity was 14 % in the studied tumors (mainly HPV16), and 53 % in pharyngeal tumors. The most characteristic change for malignization was loss of TP53, partly due to mutation and deletion and partly to inhibition due to HPV infection. The role of the PIK3CA gene is to be found in the NOTCH signal transduction system in head and neck cancer. A mutation of PIK3CA that plays a role in the activation of the lipid-kinase pathway and inhibits apoptosis and helps cell proliferation was found in 8–10 % [41]. The role of these molecules in the pathogenesis of oral squamous cell carcinoma needs to be further studied.

Human Papilloma Virus Infection

HPV, a known oncogene is one of the most common pathogens in skin and mucosal pathoses. It can be found in mucosa in the genital tract, the urethra, the skin, the larynx, the nasal cavity, the maxillary sinus and the oral cavity. One possible and intensively studied etiological factor is HPV infection of an oncogenic genotype 16,18. Human papilloma virus (HPV) is a DNA virus of 7,900 bases. Today more than 120 genotypes are known. The genome codes 7 early proteins (E1-7). The currently known HPV viruses differ in their E6 and E7 proteins and they can be classified into groups of low, medium and high oncogenicity based on these proteins. The exact mechanism of the malignant transformation induced by the virus is not yet known. The genomes of viruses in the high risk group are integrated into the host genome under appropriate conditions. The circular viral genome disintegrates and regions E1, E6 and E7 integrate into the DNA of the host cell, regions E2 to E5 are lost and can never be found in tumor cells. Upon virus multiplication these lost regions control E6 and E7 function that are thus exempt from normal control and inhibit the physiological functioning of the p53 and pRb genes of the host cell, thus acting as oncogenes. The probability of malignant transformation caused by an HPV infection depends on the type of virus, the presence of other synergistic mechanisms (alcohol consumption, smoking) and the immune status of the host organism [42].

As mentioned above, HPV is a common pathogen in the oral cavity, and numerous studies have shown its presence in oral lesions. The oral manifestation of verrucous carcinoma is an exophytic, circumscribed, locally aggressive growth. HPV genotypes 6, 11, 16 and 18 have been found in tumor cells. A number of studies have investigated the HPV genotypes present in oral leukoplakia and according to some studies HPV 16 infection was present in more than 80 %, independent of the degree of mucosal dysplasia. Various authors found a degree of 4 to 40 % infection with HPV 6 and 11 in leukoplakias. For squamous cell carcinomas this ratio is between 10 and 100 %. Out of the genotypes most often present (6, 11, 16 and 18) the risk of malignant transformation is highest in genotypes 16 and 18. In more recent studies the presence of HPV 16 was found in 90 % of all head and neck tumors and in 50 % of squamous cell carcinomas of the region [19, 42–57]. Even more interesting is the find of *Smith et al.* that they found a large amount of HPV in head neck tumors that otherwise did not have smoking or alcoholism as risk factors [43].

Oral HPV infection shows a growing tendency worldwide. Similarly to risk factors of uterus cervical carcinoma this is probably due to changing sexual habits, like the spread of oral sex, the early loss of virginity and the rise in the number of sexual partners. According to 2009–2010 data the prevalence of HPV infection in the US was 6.9 %, wherein that of the high malignancy group was 3.7. It was more common in men than women and in smokers than in non-smokers. An oral infection was 8 times more common in adults with an active sexual life as contrasted to those who had no sexual life and its frequency rose with the rise in the number of sexual partners and was more likely in people who started sexual life at an early age (under 18 years) [44].

Because of this some authors classify HPV associated oral cancer as a sexually transmitted disease. A study made at *Johns Hopkins Hospital in Baltimore* (100 oropharyngeal squamous cell carcinoma patients with 200 matched control) found a strong correlation between oropharyngeal cancer, any type of oral HPV infection and sexual habits (high number of sexual partners, oral and vaginal sex). That study found no correlation between HPV infection, smoking and alcohol consumption habits [45]. It is not a decided matter whether smoking is a risk factor for HPV associated oral

cancer or not. Some studies report a positive correlation, while others conclude that HPV associated cancer is the disease of non-smoking, non-drinking young people [46, 47].

The chance of intrauterine infection of children of HPV positive mothers is about 20 %. It can happen by a haematogenous route (transplacental) or following early amniorrhexis as a result of an ascending infection, or perinatal when passing through the infected vagina with infection rates of 20 to 70 % [48, 49].

As contrasted to other head and neck tumors the incidence of HPV associated oral squamous cell carcinoma is increasing. HPV was detected in the highest proportion from tumors of the tonsils and the oropharynx, followed in order of frequency by oral squamous cell carcinoma and laryngeal cancer. The closest association is found in cases of radical tumors of the tongue and of the tonsils. Infection is most commonly caused by genotype 16 of HPV. The ratio of HPV positive tumors is between 20 and 70 % according to various authors. This wide range may be due to differences in HPV detection methods as well as to geographical and ethnic differences.

Kreimer et al. analysed the data from 60 studies done in 26 countries. HPV infection was found in a significantly higher percentage in oropharyngeal squamous cell carcinomas (34 %), than in oral and laryngeal cancers (both 25 %). HPV 16 was the most commonly found infective agent. Prevalence is similar in North America and Europe (about 16 %), but is extremely high in Asia (33 %) [50]. A Croatian group studied 77 head and neck squamous cell carcinoma cases and HPV 6 was found in 60 % of the samples, while high malignancy HPV 16/18 was found in 68 %. It was found in 20 % of tongue and oral cancer [51]. HPV was found in 64 % of 81 patients operated for oral and oropharyngeal cancer in the Czech Republic [52]. This (the presence of HPV 16) was found to be just 10 % of 60 oral cancer patients from Serbia [19]. In Slovenia the data of 62 oral squamous cell carcinoma patients were compared to 62 healthy control cases matched for age, gender, localisation, smoking and alcohol consumption. No significant differences were found between the two groups (8.4 % vs. 6.4 %) as for the detectability of various HPV genotypes [53]. The same group did not find significant differences between 49 patients treated for oral papilloma and matched control groups as far as HPV 6, 11 and 31 are concerned. The presence of the virus was detected in a surprisingly low percentage in oral papilloma patients (9.1 %) [54].

Szentirmay studied a Hungarian population of head and neck cancer patients and found that HPV positivity was present in 50 % of oral cavity, oropharyngeal and tonsillar tumors, this value was 36.1 % in laryngeal tumors and 39 % in esophageal tumors. HPV genotype 6/11 was found in 12.5 % in the oral cavity and in 15.4 % in the larynx. HPV 16 was found in the oral cavity in 18.8 %, and in 38.5 % in the larynx. According to histological type squamous cell carcinoma was HPV positive in 18.4 % of the cases, hyperplasia and dysplasia in 30.8 %, papilloma in 46.2 %, basaloid carcinoma in 81.8 % and verrucous carcinoma in 100 %. HPV 16 was found in 36.4 % of basaloid carcinoma, 19.2 % of papillomata, 10.5 % in squamous cell carcinoma and in 7.7 % both in dysplasia and verrucous carcinoma. Women had a higher rate of HPV infection [55]. A later study yielded similar results: HPV positivity was found in 48.5 % in the oral cavity and pharynx and in 35.7 % in the larynx. Typical squamous cell carcinoma had 19.6 % positivity, verrucous cancer 100 % and basaloid cancer 87.5 % [22, 55].

According to several studies HPV associated oral cancer is often poorly differentiated, discovered at an advanced stage, positive neck lymph nodes are very often found often signifying poor prognosis. Despite of this patients with HPV associated oral cancer have a significantly better survival rate, than patients with HPV negative cancer. *Joo et al.* studied a large number of patients (n=156) and found a significant correlation between high malignancy HPV positivity, the depth of tumor invasion and the presence of cervical lymph node metastases, still these patients had a significantly better tumor-free survival rate [56].

According to meta-analyses a patient with HPV positive oral cancer has a significantly better life expectancy and less chance of recurrence, but there is no difference in overall survival between HPV positive and negative tumors outside of the oropharyngeal region [47].

Several explanations have been proposed for this phenomenon. One is that virus associated tumors are more sensitive to radiotherapy and chemotherapy [46]. *Lill et al.* studied 29 patients with oropharyngeal carcinoma who underwent radiotherapy and chemotherapy. The patients in whom the HPV genome was detectable showed significantly better survival rates and better disease-free survival [57]. *Klozar et al.* at the university department in Prague found significantly better overall and specific survival rates if HPV was detected in squamous cell carcinoma (oral and oropharyngeal carcinoma, n=81) [52].

Kozomara et al. studied the presence of p53 mutation in HPV positive oral squamous cell carcinoma patients at Belgrade University (n=32). Every patient received postoperative radiotherapy. The patients whose tumor contained p53 mutation and the HPV genome showed a significantly higher recurrence rate and worse five year survival. It was concluded that the simultaneous presence of the p53 mutation decreased the efficacy of radiotherapy. [58]. *Hong et al.* examined 198 patients and found 83 HPV positive tumors (42 %). Patients underwent surgery, had surgical and radiotherapy or had radiochemotherapy only. Better results were found among HPV positive patients in all treatment groups both in respect of recurrence and survival. No significant

differences were found between treatment groups, but surgical therapy meant a slightly, if not significantly better outcome both in the HPV positive and negative groups. The fact that the survival of HPV positive tumor patients is independent of the treatment type does not conrtadict the fact that HPV associated tumors a more sensitive to radiation. Overall positive differences were found in the radiochemotherapy groups as well, in favour of the HPV positive group. It is supposed that the immune system and other hitherto unknown factors also play a role in HPV positive tumorigenesis and radiation sensitivity through virus specific antigens [59]. A further hypothesis is that virus infected cells suffer hypoxia, therefore are more prone to necrosis, or that the genome of the infected cells is less stable [47].

A South Korean group studied the relationship of HPV and EGFR mutation on 108 patients suffering from lingual and tonsil tumors. Only 9 % of the patients were HPV positive and an EGFR mutation was found in 17 %. No HPV positivity was found in a single EGFR mutation case. EGFR mutation showed no correlation with smoking either [60]. *Szabó et al.* had similar results from a study of 71 Hungarian head and neck cancer patients. No EGFR amplification could be detected in HPV positive (19.6 %) samples [22].

Nowadays a vaccine is already available to prevent HPV infection (divalent vaccine against HPV 16, 18, quadrivalent vaccine against HPV 6, 11, 16, 18). Based on theoretical considerations the vaccines are probably effective against oral infections as well, but further studies are necessary. If the efficacy of anti-HPV vaccines could be proven in oral cancer prevention, that would also prove the etiological role of HPV in oral cancer [47].

Prognosis

Byers et al. were the first to describe squamous cell carcinoma in young patients in 1975. It was supposed in that early publication that tumors in this group of patients have a more aggressive spread and early recurrence, in other words that age is of prognostic importance [61]. A number of authors have studied the topic.

There is no unanimous view in the literature in the question of prognosis. *Garavello et al.* performed a matched analysis of 48 young patients with lingual tumor and found significantly worse survival and a higher recurrence rate [62]. A group at the *University of Bern* performed a retrospective analysis of patients with tongue tumors and discovered a higher rate of late cervical lymph node metastases, but found no difference in survival [63]. *Sarkaria et al.* recommended aggressive therapy and a close follow-up based on their review of the literature [64]. *Mallet et al.* performed a multicentric retrospective study and analysed data for oral squamous cell carcinoma patients under 35 years of age (n=52) and a very poor prognosis in cases of local recurrence [65]. *Gawecki et al.* compared the data of 95 young patients (<45 years of age) with those of 95 elderly patients treated at the *University of Poznan*. More oral squamous cell carcinomas were found among the young patients and laryngeal carcinoma was more common in the older group. Younger patients presented with more advanced stage disease, but their tumors were better differentiated [66]. *Pytynia et al.* performed a matched retrospective study (n=31) and found no difference in survival if the patients received identical therapy [67]. An Iranian study found no difference in survival between the two age groups [68]. *Annertz et al.* studied a Scandinavian population and examined the data of 276 young patients with lingual cancer and found that they had better prognosis than elderly patients [2]. The *South Korean group* mentioned above described a better survival rate in HPV positive tumors, but EGFR mutation did not prove to be a significant prognostic factor [60]. *Szabó et al.* did not find a more favourable survival rate in HPV positive head and neck cancer patients in contrast to non infected patients, neither could they establish a significant connection between survival, EGFR expression and various EGFR mutations [22].

There are probably multiple causes behind these differing results. On the one hand the quality of life and dental care and patients use of it is highly variable from country to country. There are cultural differences in oral hygiene and patient co-operation. There are significantly worse five-year survival data for all oral cancer patients in Eastern Europe than in Western Europe [69]. The probable cause of this is late diagnosis on the one hand and the inequalities of the health care system on the other. The studies have various patient selection criteria (e.g. some studies only include lingual cancer patients), and this is a further difficulty in finding the causes of the differences as well as the highly divergent numbers of cases examined in each study. Further problems are caused by the fact that at present there is no single definition of a young patient.

Summary

The question of young age oral cancer is of utmost importance and it is also intensively researched. It is known from epidemiological studies that the incidence of oral squamous cell carcinoma diagnosed at a young age is growing worldwide. There is also a growing tendency of the number of HPV associated oral cancers. This presents in men more often than in women. There is a drastic increase in the number of young female patients suffering from tongue tumors.

The etiology of young age tumors is not exactly known. All studies agree that behavioural risk factors (smoking and alcohol consumption) do not play a role in this group of patients or they play a lesser role. One factor could be the

inherited vulnerability of the individual's genetic code and the role of oncogenic genotype HPV infections.

There are two big gene families behind malignant transformation of mucosa in oral cavity: proto-oncogenes and tumor suppressor genes. The EGFR (EGFR, Ras, Raf, Erb2) signal cascade of proto-oncogenes can play an important role in tumor formation. The other major gene family is that of tumor suppressor genes that inhibit proliferation. The members of the family p53, p16, Cyclin D and others are in oral squamous cell carcinoma as well. Various mutations were established in ethnics, and variant outcomes were found between mutations and tumor recurrence, progression. The presence of hormone receptors (ERα, ERβ, PR) also has to be mentioned in the pathogenesis of oral cancer. However knowledge of these mutations and the presence of hormone receptors might be a help both in estimating prognosis and in therapy.

It is known that the prevalence of oral HPV infection is growing, which probably has in its background changes in sexual habits. Oral HPV infection and HPV associated oral squamous cell carcinoma are more common in men and their risk factors are practically identical with those described for the cervical cancer of the uterus, such as sexual activity begun at an early age, a high number of sexual partners and oral sex. It is debated whether smoking and alcohol consumption can have a connection with HPV associated oral cancer, or whether the spread of HPV could in itself explain the growing incidence rate of young age tumors. Several authors studied the correlations of genetic errors of copy number alterations of control factors in cells from HPV infected oral tumors with infection, but no such significant correlation was found.

A hot topic in research on young-age oral cancer is the prognostic role of age. There is no unanimous conclusion in the literature. Some authors found the life expectancy of young patients to be better, others have found it to be worse. It is known that there are territorial differences in head and neck cancer prognosis.

Differences in the health care systems and patients' attitudes to medical visits might be the underlying causes. It was described in Poland that young patients tend to visit the doctor at a late stage despite of clear symptoms. This is indicative of the social acceptance of young age disease. It is known that there is a territorial distribution of HPV infection as well. A further problem in the comparability of studies is that patient selection criteria are not the same. There is no consensus on what the age limit of a young patient is. Another problem is that of localization as it is known that anatomic localization is an independent prognostic factor within the head and neck region

Further standardized multicentric studies are necessary to identify possible etiological factors. Thus more effective treatment protocols and prevention programs could be developed.

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