Risk factors for oral cancer

The process of the digestion starts with the formation of the complex of the food which is done by the chewing of the food with the teeth and the chemical action of the saliva and the composite of the food is otherwise known as the bolus. The process of swallowing the food is known as Deglutition and the mouth plays a vital role by receiving the food, changes the basic form of the food in to the complex form by means of chewing, initiates the process of digestion through mastication and creates the essential forms for the flow of the speech. Mouth is otherwise known as the secondary air canal of the respiratory system.

Pharynx is located in the posterior region of the mouth and it is a pathway for both the air and food. Thus, it is associated with both the respiratory and the digestive system. The moisture in the lining of the pharynx and mouth is maintained by the action of saliva. The lining of both the structures are created by the non-keratinized stratified squamous epithelium.

Oral cavity

Oral cavity is basically same as the mouth and the cavity is made up of the cheeks, soft and hard palates and the lips which act as the vestibule for the oral cavity. The vestibule is positioned between the gums and the cheeks. The opening of the oral cavity is the oral orifice which is commonly called as the mouth and the fauces is the opening between the pharynx and the oral cavity [1].

Cancer of the oral cavity is the development of the tumors in the inner lining or the buccal mucosa of the lips and cheeks, oral tongue which is the front two-thirds of the tongue, the bottom of the mouth below the tongue, hard

palate which is the bony roof of the mouth and the retromolar trigone which is the space behind the wisdom of the wisdom teeth. The tumors are found to be maliganant. The uncontrolled proliferation of the cells results in the development of the cancers of the mouth and the throat. The most common cancer found in the oral cavity is the Squamous cell carcinoma.

Oropharyngeal cancer is the formed in the back part of the mouth or the upper region of the throat which includes the base (rear one-third) of the tonsils, tongue, tonsillar pillars, soft palate and the posterior pharyngeal wall which is in the back of the throat. The posterior pharyngeal wall makes up the oropharynx. Cancers of this region is found to develop the open sores which is otherwise known as the ulcer and the cancer spreads locally or to the organs that are placed distantly in the entire body.

The cancer of the tongue includes the uncontrolled proliferation of the cells in the tongue and about 90% of the cancers in the tongue are the squamous cell carcinoma. Based on the anatomy, the tongue is divided in to two different areas namely:

- Oral tongue and
- The base of the tongue

The oral tongue is a part that can be “ stuck out” and it elongates back to a v-shaped group of lumps on the back of the tongue which is the specialized taste bud and the base of the tongue that is just behind the taste buds. Almost all the cancers of the tongue are found on the lateral margin (side) which is the middle third of the oral tongue and the ventral aspect which is the extension from the bottom of the tongue whereas the 20% of the cancer

occurs on the dorsum (top surface) or on the tip of the oral tongue. The tongue has an wide circulatory and lymphatic supply and the cancer of the tongue very easily but the prognosis in individuals with the advanced stage of the cancer is deprived.

Cancer of the oropharynx (oral cavity) which includes the tongue is treated based on the stage of the cancer. TNM (tumor/node/metastasis) is the staging system which is used for the oral and oropharyngeal cancer that includes the base of the tongue. The system was invented by the American Joint Committee on cancer and progression of the cancer is indicated as:

- T1 tumor may be 2cm or less in size.
- T2 tumor is greater than 2cm but not more than 4cm.
- T3 tumor is greater than 4cm.
- N1 has metastasis to a single lymph node which 3cm or less in size.
- N2 has a metastasis for a single node which is greater than 3cm but not more than 6cm.
- N3 has a metastasis in a lymph node which is greater than 6cm.
- Mx is the distant metastasis which cannot be assessed.
- M0 stands for no metastasis and
- M1 is used when the metastasis are confirmed.

Oropharngeal cancer has number of stages. Stage I is a tumor which is of 2cm or less in size; the size of the tumor in stage II is greater than 2cm but less than 4cm; stage III tumor is larger than 4cm in size; tumor developed in the stage IV is of the advanced form and it can be further divided as IV A, IV B and IV C. Stage IV A is an invasive tumor in which the lymph node does not get involved or the spread of only one lymph node in the same side or the

lymph node is involved without the metastasis. IV B is the tumor in which the lymph node gets involved but there is no metastasis. IV C can be clearly defined as the spreading of the tumor. In the stage I and II, the tumor does not spread to the lymph nodes and there is no metastasis. The stage III is a smaller tumor which spreads to the lymph nodes but there is no metastasis.

Risk of the cancer of the oral cavity

The usage of tobacco is the greatest risk factor of the oral cavity cancer which also includes the smokeless tobacco. About 90% of the oral cancer is developed because of the usage of the tobacco. The risk of the squamous cell carcinoma depends on the number of the cigarettes smoked per day. The caricinogenic effect of the smoking is increased in the smokers who consume alcohol and they develop the oropharyngeal cancer 35 times more than the people who do not drink and smoke. The individuals who use smokeless tobacco are found to develop the cancer of the orl cavity four times more than the individuals who do not use the smokeless tobacco. The other risk factors of the cancer of the oral cavity includes poor hygiene of the oral cavity which includes the bacterial irritation, poor nutrition and the immunosuppressed states that includes the long-term usage of the immunosuppressive drugs after the transplantation or to treat the autoimmune disease such as infection of Human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS). It is found that the Human Papilloma Virus (HPV) may play a vital role in the growth of the oral and oropharyngeal cancer. Individuals who are exposed to ultraviolet light showed 30% risk to the lip cancer. The cancer is also caused by the exposure of the individuals to the vitreous or wool fibers such as the fiberglass and

blown-in insulation, mustard gas, isopropyl alcohol, hexavalent chromium, tannin extract, vinyl chloride polymers, aryl hydrocarbon hydroxylases and azo dyes. Some of the other risk factors include Plummer-vision syndrome which is the mucosal atrophy of the mouth, pharynx and oesophagus, achlorhydria and iron deficiency anemia, chronic syphilis and the poorly fitting dentures. Mutation of the gene is related to the loss of the molecular signaling mechanism which controls the growth of the cell and the mutation of the specific genes which leads to the development of the cancer of the oral cavity in some individuals and the example for this is the ras family which is linked to the HPV infection. Even if the oral and oropharyngeal cancers are found in the adults of all ages, races and ethnic groups, they are found to be common in blacks than in whites. They are generally found in persons above the age of 35 and the average age of diagnosis is of 62. Oral cancer is rare among the childrens and the cancer of the tongue is found in the older adults who have the history for the usage of alcohol and tobacco. The tongue cancer is also increased by the nutritional deficiencies and the infectious agents such as HPV and fungi.

Incidence and Prevalence

It has been predicted by the American Cancer Society that by 2009 that 35, 720 new cases which includes 25, 240 men and 10, 480 women with 7, 600 deaths with the risk of the cancer of the oral cavity and oropharyngeal cancer will be diagnosed. The diagnosis and the death of the individuals with oral cavity and oropharyngeal cancer are found to be decreased for the past 20 years because of the reduced usage of the tobacco in US. The oral and oropharyngeal cancer incidence vary in countries around the world and they

are associated with the environmental risk factors. The highest incidence of the cancer was found in the Hungary and France and it has lowest incidence in Mexico and Japan [1].

Reference for the cancer of oral cavity

http://www. mdguidelines. com/cancer-oral-cavity-and-oropharynx

Genetic level understanding of smoking induced oral cancer

Findings

Independent carcinogenic effects of tobacco smoking and the alcohol drinking and their interaction is studied n the population of the heavy smokers and drinkers. The individuals who use filtered cigarette had an increased risk to cancer when compared to that of the individuals who use unfiltered cigarettes.

Reference

Mashberg. A, Boffetta. P, Winkelman. R and Garfinkel. L., " Tobacco Smoking, Alcohol Drinking and Cancer of the Oral Cavity and Oropharynx among US. Veterans"

Findings

The risk of the oral cavity is increased by the bidi smoking. Meta-analysis implies that the bidi smoking has 3. 1 fold increased risk of oral cancer when compared to that of the non-smokers.

Reference

Rahman. M, Sakamoto. J and Fukui. T., (2003). " Bidi Smoking and Oral Cancer: A Meta-Analysis", Int. J. Cancer, 106, 600-604.

Findings

The main risk factors of the cancers oral cavity and pharynx include the alcohol and cigarette smoking. GSTM1, GSTM3, GSTP1 and GSTT1 are some of the subtypes of the GST superfamily which gets involved in the detoxification of the carcinogens like benzo[a]pyrene, ethylene oxide and monohalomethanes which is commonly known as the polycyclic aromatic hydrocarbons. Matthias et al reported that the polymorphism of GSTP1 has 2 fold increased risk of cancer.

Reference

(1999). " Glutathione S-transferase GSTM1, GSTM3, GSTP1 and GSTT1 genotypes and the risk of smoking-related oral and pharyngeal cancers", Int. J. Cancer, 81, 44-48.

Findings

Reference

(1977). " Quantification of the Role of Smoking and Chewing Tobacco in Oral, Pharyngeal and Oesophageal Cancers", Br. J. Cancer, 35, 232.

Findings

Polymorphism of the gene GSTP1 in smokers results in the change of an amino acid from isoleucine 105 to valine which is accompanied by the reduction in the catalytic activity of the enzyme.

Reference

Katoh. T, Kaneko. S, Takasawa. S, Nagata. N, Inatomi. H, Ikemura. K, Itoh. H, Matsumoto. T, Kawamoto. T and Bell D. A., (1999). " Human glutathione S-transferase P1 polymorphism and susceptibility to smoking related epithelial

cancer; oral, lung, gastric, colorectal and urothelial cancer”, Pharmacogenetics, 9 (2), 165-169.

Findings

P53 mutations have the highest risk for the oral cavity squamous cell carcinoma. Moderate and the heavy smokers has the 6 fold increased risk to the OCSCC when compared to that of the light or the non-smokers.

Reference

(1996) “ Relationship between p53 mutation incidence in oral cavity squamous cell carcinomas and patient tobacco use”, Carcinogenesis, 17 (4), 733-739.

Findings

GSTM3 and GSTT1 genotype does not have any influence on the buccal mucosa cancer susceptibility while the GSTM1 which is a null genotype showed an increased risk in the bidi and the cigarette smokers and the GSTM1 null genotype had 6 times increased risk when compared to that of the GSTM1 protective genotype. The risk of the cancer is related to the higher amount of the benzo[a]pyrene in bidis and cigarettes.

Reference

(2002). “ Polymorphism at GSTM1, GSTM3 and GSTT1 gene loci and susceptibility to oral cancer in an Indian population”, Carcinogenesis, 23 (5), 803-807.

Findings

The carcinogens are metabolized by xenobiotic metabolizing enzymes and it involves two steps namely, phase I and Phase II. The phase I metabolism was carried out by the Cytochrome p450 (CYPs) whereas the phase II metabolism was mediated by the glutathione S-transferases and N-acetyltransferases. In the Phase I, the functional group of the substrates are exposed which produces the highly reactive metabolites. The intermediates formed in the phase I acts as a substrate for the phase II reaction which gets involved in the conjugation with the molecules which are endogenous like glutathione and this leads to their elimination. The exposure of the carcinogen is determined by the coordinated expression and regulation of the phase I and II metabolizing enzymes. The expression, function and the activity of the gene is altered by the variation in the sequence or the gene polymorphism which leads to the development of cancer. CYP1A1 codes for the enzyme aromatic hydrocarbon hydroxylases. It catalyzes the conversion of PAHs to phenolic metabolites or diol epoxide. An example for this is the conversion of the benzo[a]pyrene (B[a] P) to benzo[a]pyrene-diol-epoxide (BPDE). Transistion of T to C in the 3′ noncoding region increases the risk of the cancer. GSTT1 gets involved in the detoxification reactive diol epoxides and monohalomethanes while the GSTM1 involves in the conjugation of GSH which is a tripeptide to the PAH diol epoxides. Deletion in the structure of the genes symbolizes a null genotype which is associated with the increased risk of the cancer. The cancer risk is also increased by the combination of the CYP1A1 homozygous variant and the GSTM1 null genotype.

Reference

(2007). “ Susceptibility to oral cancer by genetic polymorphisms at CYP1A1, GSTM1 and GSTT1 loci among Indians: tobacco exposure as a risk modulator”, Carcinogenesis, 28 (7), 1455-1462.

Findings

It occurs in the parotid gland and it is found that the smoking increases the Warthin’s tumor.

Reference

“ Cigarette Smoking and Warthin’s Tumor”, American Journal of Epidemiology, 144 (2).

Findings

In betel quid chewers, the risk of the oral cancer is reduced by the deletion of the gene CYP2A6.

Reference

(http://sciencelinks. jp/j-east/article/200303/000020030302A0896702. php)

Findings

Cigarette smoke contains more than 4000 chemical components which includes 40 carcinogens like nitrosamines, hydroquinone (compound that forms free radical) and the compounds of PAHs which forms the DNA adducts. Due to the lack of the DNA repair mechanism and the protective histone backbone the mtDNA is more prone to the damages created by the reactive oxygen species like hydrogen peroxide, superoxide radical and the hydroxyl radical. The defects in the mitochondria like decreased oxidation of

NADH-linked substrates, abnormal activity of the aerobic respiratory chain subunits, mutations and alteration in the expression of mtDNA at the organelle level is found to be related to the cancer. The mitochondrial genome undergoes the oxidative damage occurs due to the transistion of the AT base pair to GC and GC to AT in the nucleotide position of 4767 and 4853.

Reference

(2006). “ Mitochondrial DNA mutations in oral squamous cell carcinoma”, Carcinogenesis, 27 (5), 945-950.

Findings

Polymorphism of genes XRCC1 at the coding regions of 194 and 399 and XPD has the increased risk of the oral cancer when compared to that of the wild genotype. Increased risk of the oral cancer was found in the betel quid chewers and smokers with the polymorphic variant of XRCC1 at the coding region of 399 and XPD.

Reference

Ramachandrana. S, Ramadasb. K, Hariharana. R, Kumarb R. R, Pillaia. M. R., (2006). “ Single nucleotide polymorphisms of DNA repair genes XRCC1 and XPD and its molecular mapping in Indian oral cancer”, 42 (4), 350-362.

Findings

XRCC1 is found to have two SNPs in its structure which is found at the codon 399 and 194. The coding region 399 includes the substitution of the nucleotide G28152 with A of exon 10 which is accompanied by the change in the residue from Arg to Gln whereas the coding region of 194 includes the base pair change of C26304 with T of exon 6 which is accompanied by the

residual change of Arg to Trp. The higher level of the DNA adducts are formed by the variation in the 399Gln allele of XRCC1 and is found to have higher risk to the DNA damage caused by the usage of the tobacco and the sensitivity of the ionizing radiation.

Reference

Kowalski. M, Przybylowska. K, Rusin. P, Olszewski. J, Morawiec-Sztandera. A, Bielecka-Kowalska. A, Pietruszewska. W, Mlynarski. W, Szemraj. J and Majsterek. I., " Genetic polymorphisms in DNA base excision repair gene XRCC1 and the risk of squamous cell carcinoma of the head and neck"

Findings

It is found to catalyze the hydrolysis of the alkene, arene and the aliphatic epoxides of the PAHs and aromatic amines and is found to involve in the oral and pharyngeal cancers as it is seen in all the tissues including the aerodigestive tract. Polymorphism of the gene includes the substitution of the base pair C with T in the exon 3 which is accompanied by the change in the amino acid from His to Tyr at 113 and this kind of the polymorphism is known as the " slow allele" as the activity of the enzyme is reduced by 40-60% when compared to that of the wild type. The allele is otherwise called as HYL*2. The second polymorphism involves the substitution of G with A at the exon 4 which leads to the replacement of the amino acid His instead of Arg139 and this kind of the polymorphism is otherwise recognized as the fast allele HYL*3 as it increased the activity of the enzyme by 25%. It is found that the risk connected to the consumption of the alcohol and tobacco can be modified by the substitution of the amino acid Arg with His at the position 139 of mEH and null polymorphism of the gene GSTM1. It was reported by

Wenghoefer et al that the risk of head and neck cancer can be modulated in smokers by the heterozygous allele His or Arg at the exon 4 of mEH.

Reference

“ CYP1A1, mEH, and GSTM1 Polymophisms and Risk of Oral and Pharyngeal Cancer: A Spanish Case-Control Study”, Journal of Oncology, Volume 2008, 11 pages

Findings

XRCC1 which is a DNA repair gene is found to play a vital role in the progress of the carcinogenesis of the human as it is required for the stability of the genome. On the other hand, the polymorphic variant of the gene XRCC4 is not associated with the susceptibility of the oral cancer. Polymorphism in the heterozygous allele of XRCC1 in the codon 247 with the change in the base pair from G1394 to T had an increased risk to the oral cancer in the smoking individuals of the Taiwan.

Reference

Tseng. H. C, Tsai. M. H, Chiu. C. F, Wang. C. H, Chang. N. W, Huang. C. Y, Tsai. C. W, Liang. S. Y, Wang. C. L and Bau. D. T., “ Association of XRCC4 Codon 247 Polymorphism with Oral Cancer Susceptibility in Taiwan”

Findings

Met241 which is a homozygous allele of XRCC3 showed increased risk of the second neoplasms.