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## Assessment of Head and Neck Cancer Patients of Chhattisgarh Institute of Medical Science (CIMS), Bilaspur, Chhattisgarh

ORIGINAL ARTICLE



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### Abstract

Head and neck cancer in India are emerging as major public health problems, which are lifestyle related. In India 6.5% of the total population is represented by older persons. In India this cancer has distinct demographic profile, risk factors, food habits, family and personal history. Overall 57.5% of cases occur in Asia especially in India for both sexes. It is the seventh most frequent cancer and the ninth-most frequent cause of death from cancer. In the present study, a total of 30 patients from Chhattisgarh Institute of Medical Sciences (CIMS) Bilaspur, Chhattisgarh were studied with the aim of assessment of the major risk factors and their association with behavioral and environmental factors, if any. The disease was seen highly prevalent in age group of 50- 59 years among males (63.3%) who were indulged in smoking Bidi (30.0%), Khaini (43.3%), Gurakhu (30.0%) and alcohol drinking (43.3%). Low

income groups like farmers were more affected with stage III (56.6%) of mouth and tongue cancer.

### Key Words

Head and Neck Cancer, Risk Factors, Signs and Symptoms, Prevalence.

### Introduction

Cancer is defined as group of diseases which involves abnormal cell growth having potential to invade or spread to other parts of the body (WHO, 2018; NCI, 2007). Its possible sign and symptoms include lump, abnormal bleeding, prolonged cough, unexplained weight loss and a change in bowel movement. While these symptoms may indicate cancer, they can also have other causes (NHS, 2014). Over approximately 100 types of cancers affect humans (NCI, 2007). Cancer is generally caused by accumulation of mutation they are common in higher vertebrates, but many other organisms do not manifest cancer because they do not live long enough. Cancer is well studied in animals, but tumours also occur in plants. (Twyman & Wisden 1998).

### Classification of Cancer

S.N.	Category	Description
1	Carcinomas	Arise from epithelial cells lining the internal surfaces of the various organs (e.g. mouth, oesophagus, intestines, and uterus)
2	Sarcomas	Arise from mesodermal cells constituting the various connective tissues (e.g. fibrous tissue, bones).

3	Lymphomas	Myeloma and leukaemias arising from the cells of bone marrow and immune systems
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The term “primary Tumour” is used to denote cancer in the organ of origin, while “secondary Tumour” denotes cancer that has spread to regional lymph nodes and distant organs. When cancer cells multiply and reach a critical size, symptoms and signs of invasion and distant metastases become clinically evident.

The present study has been undertaken with the aim to assess major risk factors of head and neck cancer, and its probable association with behavioral and environmental factors, if any among patients of Chhattisgarh Institute of Medical Science, (CIMS) Bilaspur, Chhattisgarh.

## Head and Neck Cancer

It is a group of cancers that starts in the mouth, nose, throat, larynx, sinuses, or salivary gland. It is most commonly of the squamous cell carcinoma type. The diagnosis is confirmed by tissue biopsy. The degree of spread may be determined by medical imaging and blood tests. Symptoms for it may include a lump or sore that does not heal, a sore throat that does not go away, trouble swallowing, or a change in the voice. There may also be unusual bleeding, facial swelling, or trouble breathing. About 75% of this cancer is caused by the use of alcohol or tobacco (WHO 2014). Other risk factors include betel quid, human papillomavirus, and certain workplace exposures. In 2015, HNCC globally affected more than 5.5 million people (mouth 2.4 million, throat 1.7 million, and larynx 1.4 million), and it has caused over 379,000 deaths (mouth 146,000, throat 127,400, larynx 105,900) (GBD et al. 2016). Together, they are the seventh most frequent cancer and the ninth-most frequent cause of death from cancer.

In the United States of America, about 1% of people are affected at some stage in their life, and males are affected twice as often as females. The usual age at diagnosis is between 55 and 65 years old. The average 5 year survival following diagnosis in the developed countries is 42-64% (Beyzadeoglu et al. 2014).

**Table 1: Types of HNCC**

Category	Parts affected	Symptoms
Mouth (oral cavity)	the lips, gums, inside lining of the cheeks and lips, front two-thirds of the tongue, floor of the mouth under the tongue, bony roof of the mouth (hard palate), and the small area of gum behind the wisdom teeth	<ul style="list-style-type: none"> <li>• mouth pain or pain when swallowing</li> <li>• a persistent sore or swelling in the mouth</li> <li>• unusual bleeding or numbness in the mouth</li> <li>• red or white patches on the gums, tongue or mouth</li> <li>• bad breath</li> <li>• changes in speech or difficulty pronouncing words</li> <li>• difficulty chewing or swallowing food, difficulty moving the tongue or limited chewing</li> <li>• weight loss</li> <li>• a lump in the neck</li> <li>• loose teeth, or dentures that no longer fit</li> <li>• earache</li> </ul>
Throat (pharynx)	<ul style="list-style-type: none"> <li>• Nasopharynx—called nasopharyngeal cancer</li> <li>• Oropharynx –called oropharyngeal cancer</li> <li>• Hypopharynx or hypopharyngeal cancer</li> </ul>	<ul style="list-style-type: none"> <li>• Throat pain or difficulty in swallowing</li> <li>• bad breath</li> <li>• a persistent sore throat or cough</li> <li>• weight loss</li> <li>• coughing up bloody phlegm</li> <li>• voice changes or hoarseness</li> <li>• dull pain around the breastbone</li> <li>• numbness of the face</li> <li>• pain in the ear or frequent ear infections</li> <li>• feeling that your air supply is blocked</li> </ul>

Voice box (larynx)	<ul style="list-style-type: none"> <li>• glottis</li> <li>• epiglottis</li> <li>• subglottic</li> <li>• thyroid gland</li> </ul>	<ul style="list-style-type: none"> <li>Swelling or a lump in the neck or throat</li> <li>• a persistent sore throat • constant coughing</li> <li>• a persistent change in the voice, including hoarseness</li> <li>• difficulty swallowing or pain when swallowing</li> <li>• difficulty breathing • weight loss</li> </ul>
Salivary glands	<ul style="list-style-type: none"> <li>• Parotid gland – in front of the ears</li> <li>• Sublingual gland - under the tongue</li> <li>• Sub-mandibular gland - under the jawbone.</li> </ul>	<ul style="list-style-type: none"> <li>Swelling or a lump near the ear, jaw, lip, or inside the mouth</li> <li>• different appearance on each side of the face or neck</li> <li>• difficulty swallowing or opening mouth widely</li> <li>• drooping, numbness or muscle weakness on the face (palsy)</li> </ul>
Nasal cavity and Para nasal sinuses	<p>The Para nasal sinuses</p> <ul style="list-style-type: none"> <li>• maxillary sinuses – under the eyes and in the cheek area</li> <li>• frontal sinuses – behind the forehead</li> <li>• ethmoid sinuses – above the nose and between the eyes</li> <li>• sphenoid sinuses – behind the nose and between the eyes.</li> </ul>	<ul style="list-style-type: none"> <li>• a persistent blocked nose, particularly in one nostril</li> <li>• decreased sense of smell • pressure or pain in the ears</li> <li>• frequent nose bleeds • difficulty in swallowing</li> <li>• excess mucus in the throat or back of the nose</li> <li>• frequent headaches or sinus pressure</li> <li>• loose or painful upper teeth</li> <li>• a lump on/in the face, nose or mouth</li> <li>• numbness of the face, upper lip, or within the mouth or upper teeth</li> <li>• a bulging or watery eye • double vision</li> <li>• complete or partial loss of eyesight.</li> </ul>

## Head and Neck Cancer in India

Head and neck cancer in India are emerging as major public health problems, which are lifestyle related. In India 6.5% of the total population is represented by older persons (60 years and above) (Shah et al. 2006). In India it has distinct demographic profile, risk factors, food habits, family and personal history (Mishra A, Sing VP., Verma V., 2009). Overall 57.5% of global head and neck cancers occur in Asia especially in India for both sexes (Chaturvedi P. 2009).

As per the GLOBOCAN (2012) survey more than 200000 cases of HNCC occurs and 80000 oral cancer cases are diagnosed each year in India. Whereas around 40000 cases of pharyngeal cancers excluding nasopharyngeal cancers (31% of global cases) and nearly 29000 cases of laryngeal cancers (18% of global) occur in India every year. India stands second place in prevalence of oesophageal cancers (77,000) after China. It is the third most common cancer in India with 52067 deaths and 77003 cases diagnosed in 2012.

The world's highest incidence of cancers of the lower pharynx (11.5 per 100,000 people) and tongue (7.6 per 100,000 people) in men are reported in Aizawal district of northeast India. One of the highest incidence rates of mouth cancer among men is found in Pondicherry (8.9 per 100,000 people). In paediatric age group incidence is quite rare (0.25% with the ratio of 1:8:1 in males and females (Sinha et al. 2003). In childrens lymphomas are commonly found (43.39%) followed by the rhabdomyosarcoma (20.75%). The malignant lesions were largely seen above 5 year of age (69.81%) maximum occurring in the age group of 10 to 12 years (47.17%) (Sengupta et al. 2009).

**Table 2:** Causative Agents of Head & Neck cancer

Alcohol and Chewing Tobacco	oral cavity, oropharynx, hypo pharynx, and larynx	75% HPV type 16	Gandini et al. (2008), Hashibe et al. (2009), Gillison et al. (2008)
Pan (betel quid)	oral cancer		Ho et al. (2007)
Preserved or salted foods	nasopharyngeal cancer		Yuan et al. (2006).
Oral health	oral cancer		Mayne et al. (2009)
Occupational exposure	nasopharyngeal cancer, laryngeal cancer	wood or nickel dust or formaldehyde	Berrino et al., (2003), Luce et al. (1993).
Radiation exposure	salivary glands		Martin et al. (1988), Horn-Ross et al. (1997).
Epstein-Barr virus infection	nasopharyngeal cancer, salivary glands		Chen et al. (2001).

## Materials and Methods

The study group comprised 30 patients of Head and Neck cancer being treated at Chhattisgarh Institute of Medical Sciences (CIMS Bilaspur). Purposive random sampling method was applied for collecting data in the field. Causative factors and socio-demographic profile were collected from the study population.

The causative factors of head and neck cancer included in the study are:

- **Bidi:** A Bidi is a thin cigarette or mini cigar field with tobacco flake and commonly wrapped in a tendu or Piliostigmaracemosum leaf tied with a string or adhesive at one end. It originates from the Indian subcontinent.
- **Cigarette:** A cigarette is a narrow cylinder containing psychoactive material, usually tobacco that is rolled into thin paper for smoking.
- **Khaini:** A form of chewing tobacco containing slaked lime. It keeps in lower gingivolabial sulcus and sucked. Its having higher chances of effecting with lip cancer.
- **Gurakhu:** Gurakhu is a paste like tobacco and molasses preparation.
- **Pan Masala:** Pan Masala is a mixture of areca nut with slaked lime, catechu and other flavouring agents, many brand of pan masala have tobacco in it.
- **Pan:** There are main four contain in pan those are areca nut slaked lime Nitrosomines are found in areca nut so that this is carcinogenic. By chewing pan there are maximum chances of affecting with mucosa, cheek and gingival groove cancer.
- **Alcohol:** A drink that contains ethanol produced by fermentation of grains, fruits or other source of sugar. Drinking alcohol plays an important social role in many cultures.

## Collection of Socio-Demographic Data

A set of socio-demographic data was collected in a consistent way from all individual patients.

- **Personal Information:** Name, age, sex, date of birth, caste, religion and ethnicity were recorded from each patient.
- **Occupational Status:** Patient occupation and their spouse occupation (Farmer, Wage Labour, Service and Other)

- **Educational Status:** Primary, Secondary, Higher Secondary, Undergraduation, Postgraduation and others).
- **Source of Drinking water:** Tubewell in household, Dug/open well in household, Tap in household, Public tubewell/well/tap.
- **Other Socio-Economic variables:** Sanitation, Family income, Total family members, Food type (veg/ Non-veg) etc.
- **Tools and Techniques** - This study included primary and secondary sources for data collection. Primary data were collected in the field and secondary data was collected from internet, books, literature work and journals. Socio-demographic data was collected through interview schedule.
- **Statistical Analysis:** All the data was recorded and subjected to statistical analysis. Percentage was calculated to find the frequency of use of causative things and derived variables. All statistical analyses and graphical representation of figures were performed using the Microsoft Office Excel (MS Office 2010).

## Results

Age group-wise distribution of patients both male and females frequency shows that patient belonging to age group 50-59 year (33.3%) are more affected by head and neck cancer followed by patients within the age range of below 30 years and within 60 – 69 years (13.3% both), Patient within the age group of 30-39 years and d'70 year (6.6% both) are less affected by head and neck cancer. Sex-wise distribution shows males (63.3%) to be having higher tendency towards head and neck cancer as compared to females (36.6%). However, this variation may be attributed to low sample size of the study population.

The patients having below Rs.5000/- monthly income are more affected (76.6%). 36.6% of the patients were using public well/tube well/tap as a source of drinking water. Patient using Bidi (Smoke tobacco) were more (30.0%) affected than patients using cigarette (10.0%). The frequencies of smokeless tobacco use by patients like Khaini (43.3%) and Gurakhu (30.0%) were also observed to be high. The frequency of alcohol taken by patients was 43.3%. Occupation distribution of patient frequency shows that most of the patients (39.2%) were engaged in agriculture (farmer). 30% patients were illiterate, 43.3% were primary educated, and 13.3% were graduates. 80.0% patients were observed to be non-vegetarians. 40% patients were from urban habitat and 60% of patients were from rural habitat. 3.3% have Kutcha house, 30% have pukka house and 66.6% have semi-pukka house.

Mouth and Tongue cancer patients were showing equivalent frequency of occurrence (23.3%) while percentage frequency of patients of nasopharyngeal cancer was 3.3%. 20.0% patients have Buccal Mucosa cancer, 10.0% Neck cancer, 6.6% throat cancer and 6.6% lymphoma in neck. The distribution of stages showed that 56.6% patients are in stage-III. Stage I frequency was 6.6%, in stage-II it was 3.3%, and in stage-IV 33.3% patients were observed. Highest frequency of symptoms like mass in the head or neck area was reported in 86.6% patients. 70.0% have swelling in neck, 6.6% have red or white patches, 46.6% have harness or change in voice, 6.6% have difficulty in breathing, 46.6% have blood in saliva and 50.0% have weakness of a body part in head and neck area.

## Discussion

The HNSSC stands 5<sup>th</sup> in rank causing worldwide deaths with an incidence of 500,000 new cases per year (Chuang et al. 2012). Apart from smoking and drinking, other factors are also responsible for occurrence of HNSSC thus the disease needs to be properly investigated early in every patient resulting in specific treatment choice for every patient.

Multifactorial interaction of environmental and genetic inheritance is the causes of HNSCC development. Major risk factors being smoking (Hashibe et al. 2007) and alcohol abuse (Haddad & Shin, 2008) in addition

to HPV human papilloma virus contributing about 25% of the disease. HPV infection is directly associated to oropharyngeal carcinogenesis, tonsillar cancer in particular having strong independent prognostic. Additionally, not all smokers and drinkers show HNSCC development, showing the role of variability in genetic susceptibility to be critical (Liang et al. 2012). The most effective measure is prevention and early diagnosis. Late diagnosis of tumor owes to ignorance and non-compliance of symptoms and lack of routine examination by health professionals (Galbiatti et al. 2013).

Petersen (2009) worked with reference of tobacco and oral disease and found that 43% of cancer death worldwide is due to tobacco, unhealthy diet, physical inactivity and infections. Hobbs et al. (2006) carried out a meta analysis on Human Papillomavirus and Head and Neck cancer and found that the association between HPV16 and cancer was strongest for tonsil (OR: 15.1, 95% CI: 6.8-33.7), intermediate for oropharynx (OR: 4.3, 95% CI: 2.1-8.9) and weakest for oral (OR: 2.0, 95% CI: 1.2- 3.4) and larynx (OR 2.0, 95% CI: 1.0-4.2). Tachezy R et al. (2009) studied on demographic and risk factors in patients with head and neck tumours. He found that the high risk HPV DNA was detected in 43% of oral washing of cases and 4% of controls ( $P < 0.0001$ ) for head and neck cancer. Rekha et al. (2013) carried out epidemiological study of head and neck cancer in south Indian population and found that the highest incidence of Head and neck squamous cell carcinoma (HNSCC) was among both males and females within the age group of 51-60 ( $P < 0.001$ ) and also reported that major risk factor for the disease were combination of smoking and alcohol (22.61%) habit in males, whereas in females, the major risk factor was only alcohol (6.39%) consumption. Kulkarni MR (2013) studied head and neck cancer burden in India and found that 57.5% of global burden occurs in Asian region especially in India which accounts for 30% of all cancers.

## Conclusion

Head and Neck cancer has proved to be one of the major disease leading to mortality with a wide range of causes. The present study population showed results which were in agreement with various other studies showing highest frequency of patients within the age range of 50-59 years. Males were more affected than females with mouth and tongue cancer to be highly prevalent among the population under study. The sources of drinking water used by the population were public well, tube well and tap water. Khaini and alcohol drinking were highly prevalent among the population under study. Occurrence of disease was high among farmers who were majorly primary educated with monthly income d" Rs 5000/-. Third stage cancer with mass in head or neck area is most common among the samples belonging to Bilaspur region.

## References

1. Berrino, F.; Richiardi, L.; Boffetta, P.; Estéve, J.; Belletti, I.; Raymond, L.; Troschel, L.; Pisani, P.; Zubiri, L.; Ascunce, N.; Gubéran, E.; Tuyns, A.; Terracini, B.; Merletti, F. (2003) Occupation and larynx and hypopharynx cancer: a job-exposure matrix approach in an international case-control study in France, Italy, Spain and Switzerland, *Cancer Causes Control*, 14(3): 213–23.
2. Beyzadeoglu, M.; Ozyigit, G.; Selek, U. (Eds.) (2014) *Radiation therapy for head and neck cancers: A case-based review*, Springer
3. Chaturvedi, P. (2009) Head and Neck Surgery, *J Cancer Res Therapeutics*, 5(2): 143.
4. Chen, T.; Yan, W.; Wells, R.G.; Rimm, D.L.; McNiff, J.; Leffell, D.; Reiss, M. (2001) Novel inactivating mutations of transforming growth factor  $\alpha$  type I receptor gene in head and neck cancer metastases, *Int J Cancer*, 93(5): 653-61.
5. Chuang, S.C.; Jenab, M.; Heck, J.E.; Bosetti, C.; Talamini, R.; Matsuo, K.; et al. (2012) Diet and the risk of head and neck cancer: a pooled analysis in the INHANCE consortium, *Cancer Causes Control*, 23(1): 69-88.

6. Galbiatti, A.L.S.; Padovani-Junior, J.A.; Maniglia, J.V.; Rodrigues, C.D.S.; Pavarino, É.C.; Goloni-Bertollo, E.M. (2013) Head and neck cancer: causes, prevention and treatment, *Brazilian Journal of otorhinolaryngology*, 79: 239-47.
7. Gandini, S.; Botteri, E.; Iodice, S.; Boniol, M. (2008) Tobacco smoking and cancer: A meta-analysis, *Int J Cancer*, 122(1): 155-64.
8. GBD et al. (2016) Global, regional and national incidence, prevalence and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study, *The Lancet*, 388(10053): 1545-1602.
9. Gillison, M.L.; D'Souza, G.; Westra, W.; Sugar, E.; Xiao, W.; Begum, S.; and Viscidi, R. (2008) Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers, *J Nat Can Inst*, 100(6): 407-20.
10. GLOBOCAN. (2012) Estimated cancer incidence, mortality and prevalence worldwide in 2012: World Health Organization: Internal agency for research in Cancer.
11. Haddad, R.I.; Shin, D.M. (2008) Recent advances in head and neck cancer, *N Eng J Med*, 359(11): 1143-54.
12. Hashibe, M.; Brennan, P.; Chuang, S.C.; Boccia, S.; Castellsague, X.; Chen, C.; Curada, M.P.; Dal Maso L.; Daudt, A.W.; Fabianova, E.; Fernandez, L.; Wunsch-Filho, V.; Franceschi, S.; Hayes, R.B.; Herrero, R.; Kelsey, K.; Koifman, S.; Vechhia, C.L.; Lazarus, P.; Levi, F.; Lence, J.J.; Mates, D.; Matos, E.; Menezes, A.; McClean, M.D.; Muscat, J.; Eluf-Neto, J.; Olshan, A.F.; Purdue, M.; Rudnai, P.; Schwartz, S.M.; Smith, E.; Sturgis, E.M.; Szeszenia-Dabrowska, N.; Talamini, R.; Wei, Q.; Winn, D.M.; Shangina, O.; Pilarska, A.; Zhang, Z.F.; Ferro, G.; Berthiller, J.; Boffetta, P. (2009) Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium, *Cancer Epidemiol Biomarkers Prev*, 18(2): 541-50.
13. Ho, P.S.; Ko, Y.C.; Yang, Y.H.; Shieh, T.Y.; Tsai, C.C. (2007) Prognostic factors associated with the survival of oral and pharyngeal carcinoma in Taiwan, *BMC Cancer*, 15: 2407-10.
14. Hobbs, C.G.; Sterne, J.A.; Bailey, M.; Heyderman, R.S.; Birchall, M.A.; Thomas, S.J. (2006) Human papillomavirus and head and neck cancer: a systematic review and meta-analysis, *Clinical otorhinolaryngology*, 31(4): 259-66.
15. Horn-Ross, P.L.; Ljung, B.M.; Morrow, M. (1997) Environmental Factors and the Risk of Salivary Gland Cancer, *JSTOR journal*, 8(4): 414-19.
16. Kulkarni, M.R. (2013) Head and Neck Cancer Burden in India, *Int J Head and Neck Surg*, 4(1): 29-35.
17. Liang, C.; Marsit, C.J.; Houseman, E.A.; Butler, R.; Nelson, H.H.; McClean, M.D.; Kelsey, K.T. (2012) Gene-environment interactions of novel variants associated with head and neck cancer, *Head Neck*, 34(8): 1111-8.
18. Luce, D.; Gérin, M.; Leclerc, A.; Morcet, J.F.; Brugère, J.; Goldberg, M. (1993) Sinonasal cancer and occupational exposure to formaldehyde and other substances, *Nat Libr Med*, 53(2): 224-31.
19. Martin, S.P.; Thomas, D.C.; White, S.C.; Cohen, D. (1988) Prior Exposure to Medical and Dental X-rays Related to Tumors of the Parotid Gland, *J Nat Cancer Inst*, 80(12): 943-49.
20. Mayne, S.T.; Morse, D.E.; Winn, D.M. (2009) *Cancers of the Oral Cavity and Pharynx*, *Cancer Epidemio Prev*, Oxford University Press.

21. Mishra, A.; Singh, V.P.; Verma, V. (2009) Environmental effects on head and neck cancer in India, *J Clin Oncol*, 27(15): 17059.
22. National Cancer Institute (NCI) (2007). What is cancer?
23. National Cancer Registry Programme (ICMR) (2008). Consolidated Report of Population Based Cancer Registries: 2004-2005. Bangalore, India, 2008.
24. Petersen, P.E. (2009) Oral cancer prevention and control-the approach of the World Health Organization, *Oral Oncol*, 45(4-5): 454–60.
25. Rekha, R.; Reddy, M.V.V.; Reddy, P.P. (2013) Epidemiological Studies of Head and Neck Cancer in South Indian Population, *Research in Cancer and Tumor*, 2(2): 38-44
26. Sengupta, S.; Pal, R.; Saha, S.; Bera, S.P.; Pal, I.; Tuli, I.P. (2009) Spectrum of head and neck cancer in children. *J Ind Assoc Pediatr Surge*.14(4): 200-3.
27. Shah, B.; Kumar, D.N.; Menon, G.R. (2006) Assessment of burden of non-communicable diseases: A project supported by WHO. ICMR.
28. Sinha, R.; Anderson, D.E.; McDonald, S.S.; Greenwald, P. (2003) Cancer risk and diet in India, *J Postgrad Med*, 49(3): 222-28.
29. Tachezy, R.; Klozar, J.; Rubenstein, L.; Smith, E.; Saláková, M.; Smahelová, J.; Ludvikova, V.; Rotnagova, E.; Kodet, R.; Hamsikova, E. (2009) Demographic and risk factors in patients with head and neck tumors, *J Med Virol*, 81(5): 878-87.
30. Twyman, R.M.; Wisden, W. (1998) Advanced Molecular Biology, *Garland Science*, 1: 5-9.
31. World Health Organization (2014) *World Cancer Report*, p. Chapter 4.7. ISBN 978-92-832-0429-9.
32. World Health Organization (2018) Cancer.
33. Yuan, J.M.; Woon-Puay, Koh W.P.; Hin-Peng Lee H.P.; Yu, M.C. (2006) Diabetes Mellitus and Risk of Colorectal Cancer in the Singapore Chinese Health Study, *J Nat Can Inst*, 98(2): 135–38.

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