1. Introduction

1.1 Background

Cancer is a group of disease categorized by uncontrolled growth and proliferation of cell, where damaged cells divide uncontrollably to form lumps or masses of tissue known as tumors. Tumors that stay in one spot and exhibit limited growth are generally considered to be benign. The successful spread of cancer to other parts of the body, invading and destroying other healthy tissues, it is referred to as metastasis. Cancer mostly initiates in one part of the body before spreading to the rest of the body [1, 2].

1.2 Present scenario

Cancer is one of the most common causes of morbidity and mortality today; with more than 10 million new cases and 7 million deaths from cancer in 2000 [3]. According to International Agency for Cancer Research (IARC), WHO in the year 2012, there were an estimated 8.2 million cancer related death and 14.1 million new cancer cases around the world as compared with 7.6 million and 12.7 million, respectively, in 2008 [4]. The most commonly diagnosed cancers worldwide were those of lung (1.8 million, 13.0%), breast (1.7 million, 11.9%), colorectum (1.4 million, 9.7%), lip, oral cavity (0.30 million, 2.1%) and pharynx (0.14 million, 1.0 %). The most common causes of cancer death were cancers of the lung (1.6 million, 19.4%), liver (0.8 million, 9.1%) stomach (0.7 million, 8.8%), lip, oral cavity (0.14 million, 1.8 %) and pharynx (0.09 million, 1.3 %) [4].

In India cancer is a dreaded disease with an estimated of 2.5 million victim patients. About 0.8 million new cancer cases are registered every year, with an annual of about 0.55 million [5]. In India the most prevalent cancers are breast, cervical and oral. The three most common mortal cancer are oral (including lip and pharynx) (22.9 %), stomach (12.6%) and lung (11.4%) in men; and cervical (17.1%), stomach (14.1%) and breast (10.2%) in women. Tobacco-related cancers described 42.0% of male and 18.3% of female cancer deaths and there were two fold as many deaths from oral cancers as lung cancers in 2010 [6]. Almost 70 % of cases which report for diagnostic and treatment facilities are in the higher stages of the disease, thereby leading to poor survival and high morality in India [4].

The North-Eastern region of India has the highest incidence of cancer in the country according to the Indian Council of Medical Research (ICMR). In male, age-adjusted incidence rate (AAR) of all types of cancers is highest in Aizawl district of the state of Mizoram followed by East Khasi Hills (Meghalaya). In female, the highest incidence is in Aizawl district (Mizoram) followed by Kamrup urban district (Assam). According to a publication of the National Cancer Registry Program (NCRP), the northern and western Assam (Darrang, Kamrup, Dibrugarh, Barpeta and Nalbari districts) have the highest incidence of cancer [7, 8]. In the NE population of India the leading sites of cancer are oesophagus (14.3 %), hypopharynx (8.9 %), lung (8.4 %), stomach (6.7%), and mouth (5.2%) in male and breast (17.5%), oesophagus, (10.2%), gall bladder (9.3%), cervix uteri (8.6%) and ovary (5.5%) in female [9].

Despite the dreaded mortality of cancer, the level of awareness among the general public is surprisingly low. Incompetent socio-economic condition and the accessibility issue for cancer diagnosis and treatment, 80% patients come to the hospital at a very late stage, when there are no chances of recovery. Besides, affordability of cancer precaution remains a major challenge in India for effective cancer control [10].

1.3 Head and Neck Cancer (HNC)

HNC commonly originate from the mucosal lining (epithelium) of these region [11]. These regularly spreads to the lymph node of the neck which is frequent (and sometimes only) indication of the disease at the time of diagnosis [12, 13]. The term head and neck cancer (HNC) arises as a broad spectrum of anatomical site covering in the oral cavity, oropharynx, larynx or hypopharynx and vast majority of them; more than 90% are squamous cell carcinomas that originate from epithelium lining [13, 14].

The HNC is a very common tumor worldwide. It represent the sixth most frequent and seventh leading cause of cancer death worldwide [15]. It is estimated that approximately 0.65 million cases will arise annually and 0.35 million death annually worldwide [16]. Only 40–50% of patients with HNC will survive for 5 years [13]. HNC represent approximately 3 % of all cancer in the United States whereas, these HNCs are much more prevalent in the other areas of the world, such as Brazil, Thailand and India [15, 17, 18].

In India, HNC contribute about 30-40% of cancer at all sites [19]. HNCs are common in India and account for about 30% of cancers in males and about 13% in females. In males pharynx and oral cavity are the usually affected sites, followed by larynx. In females, oral cavity is the dominant site [20]. India has the world's highest reported incidence of HNC in female [20, 21]. Among HNC, oral cavity is the most common sites for developing cancer in India subcontinent and Southeast Asian countries. This can primarily be attributed to their regular habit of betel quid chewing and exposure to tobacco [22, 23].

The NE region has very high prevalence of head and neck cancers (HNC), particularly oropharynx carcinoma is higher as compared to other sites of cancer. The incidence of head and neck cancer is alarmingly increasing in developing countries and in North East India. The prevalence is found to be significantly high at 54.48%, affecting males more than females in the age group of 40–69 years [19].

It is estimated that around 85% of HNC are associated with tobacco/betel quid chewing and 47% population of NE region use tobacco/betel quid in one form or the other [24]. In North East, in Kamrup metro district the leading sites of tobacco related cancer (TRC's) among men were oesophagus (18.3%) followed by hypopharynx (11.0 %) and lung (6.9 %) and in women oesophagus was the commonest (11.7%) followed by mouth (4.2 %) and lung (2.9%) [25].

In Indian context by the year 2020, the cases of HNC are estimated to be approximately around 218,421 (19.0% of All sites cancers) and consumption of alcohol and tobacco will remain as the main risk factor for the development of HNC [26].

1.4 Etiological factor of Cancer

The etiology of cancer is caused by both endogenous factors (such as inherited mutations, immune conditions and hormones) and exogenous/environmental factors (such as betel quid, tobacco, smoking, alcohol, diet, sun exposure and infectious organisms, stress, obesity and physical activity). Only 5-10 % of all cancer cases can be detected which occur due to genetic defects, whereas, the remaining 90-95% are due to environment and life style. The life style factor includes BN, tobacco, smoking, diet

(fried foods, red meat), alcohol, and sun exposure etc. [27]. According to previous studies all cancer related deaths are either due to endogenous or exogenous factors. Due to endogenous factor such as infection are about 15-20% and exogenous are almost 25–30% due to tobacco and 30– 35% are related to diet and the remaining percentage are due to other factors like physical activity, stress, radiation and environmental pollutants etc. [27].

The causes of cancer are lifestyle factors such as dietary habits of betel nut, tobacco and alcohol consumption, smoking habits, infection with Human papillomavirus, Epstein Barr virus, Kaposi's sarcoma-associated herpes virus, Human T-lymphotropic virus 1, HIV, HBV, and HCV, hormonal imbalance, stress, obesity etc. As the hereditary factor cannot be modified, the life style and environmental factors can be manipulated to reduce the burden of cancers [27].

Epidemiological studies show that there is a wide variety of betel nut, tobacco and related product and alcohol consumption habits prevalent in the NE region of India that might be responsible primarily for the occurrence of oral cancer. Among them betel quid chewing, bidi, cigarette, and traditional hukka smoking accounts for a majority of these cancer cases [28, 29]. In addition, alcohol and some aspects of the regional Indian diet have been suspected to contribute to carcinogenesis. Previous reports have shown that betel quid, tobacco smoking and alcohol intake are major risk factors for HNC in Taiwan [30], and NE India [28, 29].

Extensive studies have revealed that the association between tobacco and smoking gives rise to numerous types of cancer. According to WHO Global Burden of Disease project, alcohol consumption is also associated with a high risk in number of cancer [24]. The International Agency for Research on Cancer (IACR) has recognized betel quid (BQ) products with and without tobacco and alcohol as group I human carcinogens which are associated with increased risk of many types of cancers [24]. The carcinogenic components present in betel nuts, tobacco and smoking are polycyclic aromatic hydrocarbons (PAHs), benzo (alpha) pyrene, heterocyclic aromatic amines, and N-nitrosamine, ethylene oxide, 4-aminobiphenyl, and N-nitroso compounds (NOCs) [24, 28,29]. These promote cellular and tissue damage via

cytotoxic effects, or the rise in genotoxic events, or the cohort of reactive oxygen intermediate and DNA adduct [31]. The ethanol present in alcoholic beverage may facilitate absorption of other carcinogens and may play carcinogenic or genotoxic role as acetaldehyde, the major metabolite of ethanol [29].

Human papilloma virus (HPV) associated Head and Neck Cancers (HNCs) have generated significant amount of research interest in recent times [32]. The HPV is a DNA virus from the papillomavirus family that have been found to have productive infections only in keratinocytes of the skin or mucous membrane [33]. Previous reports have demonstrated that the HPV can exist as more than 200 related viruses. More than 40 of which are usually transmitted through sexual contact. Other HPV types are responsible for non-genital warts, which are not sexually transmitted. Persistent infection with high risk HPV (hr-HPV) infection is nearly associated with all cancer cases of cervical cancer [34, 35]. In typing, the most prevalent are HPV 16 and HPV 18 known to cause around 70% of cervical cancer cases and 15-25% of cancers of the HNC, especially oropharyngeal cancer [36, 37]. However, the most common site of HPV DNA is found in oropharynx. HPV is especially common in carcinoma of the lingual and palatine tonsil were reported 45 to 67% of the cases; less frequently found subsequently in hypopharynx (13%-25%), oral cavity (12%-18%) and larynx (3%-7%) [38, 32].

1.5 Genetic Alterations and Cancer

Change in internal exposure and/or external exposure stuffs including drugs, toxins, and carcinogens directly damage DNA and DNA–binding metabolites and possess mutagenic properties, and can thereby influence intermediate effect markers, such as DNA adducts and eventually risk for cancer [39, 40, 41]. Genetic polymorphisms in genes controlling carcinogen metabolism cause individual variations in cancer risk and provides genetic information that helps in recognizing the effect of xenobiotics on the human body [42]. The development of cancer is influenced by both the genetic and environmental factors. In environment-gene interaction, xenobiotic metabolism enzymes, which are involved in the activation of xenobiotics and conversion of endogenous and/or exogenous xenobiotics compounds, also has role in carcinogenesis

[42, 43]. Phase I xenobiotics metabolism systems which includes cytochrome P-450 (CYP), epoxide hydrolase (EPXH), generally activate carcinogens to highly reactive intermediates and phase II enzymes N-Acetyltransferases and Glutathione S-transferases (ie, NAT and GST) usually catalyze the conversion of reactive carcinogenic electrophiles to inactive metabolic derivatives. Although the cellular balance between phases I carcinogen-activating enzymes and the phase II detoxifying enzymes influences cancer susceptibility. The contribution of genetic background and environment to risk assessment for cancer is significant. [39, 43].

DNA repair systems are crucial for maintaining genomic integrity [44]. DNA in most cells is regularly affected by endogenous and exogenous carcinogens. Unrepaired damage can lead to gene mutation or may cause unregulated cell growth and cancer [39, 45]. If DNA damage is recognized by cell machinery, numerous responses may occur to prevent replication. At the cellular level, checkpoints can be activated to arrest the cell cycle; transcription can be up-regulated to compensate for the damage. The first line of cellular response is repair of damaged DNA by recruiting several enzymes present in the cell [39, 44, 45]. The evolving ability of genetic polymorphisms of DNA repair genes may contribute to variations in DNA repair capacity (DRC), there by contributing towards susceptibility to carcinogenesis [44, 46].

Epidemiological data have indicated the association between the genetic polymorphisms of ADH2 and ALDH2, and the alcohol exposure as high risk factor for HNC and esophagus cancer worldwide [39, 47]. Alcohol intake increases exposure to high levels of acetaldehyde, the principal metabolite of alcohol, which increases risk of cancer such as HNC [32]. Post alcohol exposure, alcohol is mainly oxidized in the liver by alcohol dehydrogenase (ADH) to acetaldehyde and it is subsequently detoxified into acetate by aldehyde dehydrogenase (ALDH)-2. The main enzyme alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) which area multi gene product, is involved in ethanol and acetaldehyde metabolism [48, 49]. However, involvement of these genes occurs in several variant and the enzymes encoded by convinced variants might result in high acetaldehyde levels; the existence of these variants will lead to development of carcinogenesis [48].

With the above background and considering the importance of genetic alterations in xenobiotic metabolizing and DNA repair genes, the present research study is focused on the role polymorphism in genes involved in xenobiotics metabolism and DNA repair on HNC risk and their association with dietary habits such as betel nut and tobacco chewing, smoking and alcohol consumption in the population of NE India.

1.6 Aim and objectives of the present study

The prevalence of Head and Neck cancer in North Eastern region of India is very high. Consumption of betel nut, tobacco and alcohol in this region of India is very significant. But there is lack of enough evidences on the role of betel nut and tobacco and alcohol consumption with polymorphic xenobiotic metabolizing and DNA repair genes on the risk HNC in the population of NE India. So the aim of this doctoral research was to study the association of xenobiotic metabolism and DNA repair gene polymorphisms with dietary habits such as consumption of betel nut, tobacco and alcohol in the development of HNC. It should be of cardinal importance to trace out the role of gene polymorphism and HPV typing with p16 expression status in HNC patients of North Eastern region of India with clinico-pathological characteristics.

The specific objectives of the present study are as follows:

1. To study the association of dietary habits in the risk of head and neck cancer (HNC).
2. To study the polymorphisms in xenobiotic metabolism, DNA repair genes.
3. To study association of the gene polymorphisms with dietary habits such as betel nut and tobacco chewing, smoking and alcohol consumption on the risk of HNC.
4. To study the role of Human Papilloma Virus (HPV) as a risk factor for head and neck cancer (HNC) and correlation of p16 expression and clinico- pathological data.

1.7 Scope of the thesis

An all-encompassing detailed genetic level study (genetic alteration precisely) in patients from larger population will provide better compressive understanding of disease prognosis and subsequent prediction of disease severity. These polymorphic status of the genes and HPV status might serve as possible predictive biomarkers for early detection of HNC. Furthermore, gene-gene and gene-environment interaction between the genetic polymorphism and prospective life style risk factor in particular population would be instrumental in determining the preventable life style factors in order to reduce the burden of HNC. Furthermore, the polymorphic status of particular genes in specific population will provide insight into the development of personalized effective therapeutic regimens based on pharmacogenomics principle for better management of disease severity and treatment.

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