Chapter 1

Introduction
Physicians of the Utmost Fame
Were called at once; but when they came
They answered, as they took their Fees,
“There is no Cure for this Disease.”

- Hilaire Belloc

Despite the tremendous advancements in clinical research and medical facilities, diseases like cardiac vascular diseases, cancer, diabetes, AIDS and malaria, etc. are the most dreaded enemies of the human beings, contributing a significant number to the world wide mortality and a still higher percentage of handicapped survivors. With a rapid increase in new incidences and mortality rate of about eight million people a year, cancer has emerged as a chief cause of death worldwide.

Cancer dates back to the earliest human beings. Hippocrates (460 BC – 370 BC) was the first person to describe several kinds of cancer and referred to them with the Greek word *carcinos* which means crab based on the appearance of the dissected view of a solid malignant tumour, with "the veins stretched on all sides as the animal the crab has its feet, whence it derives its name". Celsus (25 BC - 50 AD) translated *carcinos* into the Latin *cancer*, also meaning crab. Galen (130 AD – 200 AD) called benign tumours *oncos*, Greek word for swelling, reserving Hippocrates' *carcinos* for malignant tumours (Raven, 1990).

**1.1 GLOBAL BURDEN OF CANCER**

**1.1.1 Incidence**

Incidence is the number of new cases arising in a given period in a specified population. Cancer is one of the major diseases all over the world. In 2008, an estimated 12.7 million new cases of cancer were diagnosed worldwide (Figure 1).

Lung (12.7%), female breast (10.9%), colorectal (9.8%) and stomach (7.8%) cancers were found to be the four most common cancers worldwide accounting for about 40% of all the cancers diagnosed (Figure 2).

Lung cancer is the most common cancer type in men with more than 16.5% share of all new cancers cases diagnosed in men followed by prostate, colorectal and
stomach cancers with 13.6%, 10.0%, and 9.7% shares of the new cases, respectively (Figure 3).

In women, cancer of breast leads the number of new cancer cases with about 22.9% of all the new cancers cases diagnosed followed by colorectal, cervix uteri and lung cancer at 9.4%, 8.8% and 8.5%, respectively (Figure 4) (Ferlay et al., 2010).

If recent trends in major cancers are projected for future, the incidences of cancer are estimated to rise about 75% from 12.7 million in 2008 to 22.0 million in 2030 (Bray et al., 2012).

1.1.2 Mortality

Mortality is the number of deaths occurring in a given period in a specified population. Cancer mortality is a key measure of cancer burden in a given country and provides an important basis for implementing public health preventive measures. In the majority of developed countries, cancer is the second leading cause of death following cardiovascular disease. A similar trend is seen to be emerging in the less developed world too, especially, in countries in transition from under developed to developed, such as countries in South America and Asia. About 70% of all cancer cases occur in developing countries (WHO, 2013).

Cancer caused 7.6 million deaths (~13% of all deaths) worldwide in 2008. Lung (18.2%), stomach (9.7%), liver (9.2%), colorectal (8.1%) and female breast (6.1%) cancers are the most common causes of cancer deaths worldwide, accounting for more than 50% of all cancer deaths (Figure 2). Lung cancer alone causes about one fifth of all cancer deaths.

In men, the cancers of lung (22.5%), liver (11.3%) and stomach (11.0%) are the three leading killers (Figure 3) while breast (13.7%), lung (12.8%) and colorectal (8.6%) cancers are cancers with the highest death toll in women worldwide (Figure 4).

The number of global cancer deaths is projected to increase almost 74% from 2008 to 2030 (from 7.6 million to 13.2 million deaths), partly because of an increasing and aging global population (Ferlay et al., 2010).

1.1.3 Prevalence

The prevalence of a particular cancer is the number of persons in a defined population who have been diagnosed with that type of cancer during a fixed time in the past, and who are still alive at the end of a given year. Approximately, 29 million
people diagnosed with cancer within the five years earlier were alive at the end of 2008, worldwide. A majority of them were women after their breast cancer diagnosis (17.9%) followed by men and women after their colorectal cancer diagnosis (11.4%), and men after their prostate cancer diagnosis (11.0%) (Bray et al., 2012, 2013). Figures 5 and 6, show the most prevalent cancer by country in men and women, respectively.

1.2 INDIAN SCENARIO

Increasing life span and progressive control of communicable diseases have led to the rise of cancer and other non-communicable diseases as a major health issue in India and other developing countries.

1.2.1 Incidence

There were 948,900 new cancer cases in 2008 of which 430,100 were men and 518,800 were women. Cancers of cervix (14.2%), breast (12.1%), oral cavity (7.4%), and lung (6.2%) were the most common types of cancer diagnosed in the country (Figure 7).

The most common cancer types in men were the cancers of lung, oral cavity, pharynx, oesophagus and stomach of which cancers of lung (10.9%), oral cavity (10.6%) and pharynx (8.5%) accounted for almost one third of the newly diagnosed cases (Figure 8).

The cancers of cervix, breast, ovary, oral cavity and oesophagus were the most common cancer types in case of women, of which cancers of cervix (25.9%) and breast (22.2%) accounted for about half of all the new diagnosed cases in women (Figure 9) (Ferlay et al., 2010).

While the age adjusted incidence rate of oesophageal cancer (8.3 per 100,000) in women of Bangalore and gall bladder cancer (10.6 per 100,000) in women of Delhi are amongst the highest in the world, the highest incidence rate (8.8 per 100,000) of cancer of tongue in males in the world is found to be in Bhopal (Rao et al., 2002).

1.2.2 Mortality

In India, cancer is the fourth major cause of death after cardiovascular diseases, respiratory diseases and trauma. It accounted for an estimated 555,000 deaths in 2010 (Dikshit et al., 2012), which was roughly 6% of all the deaths
occurring that year. In 2008, out of the total 633,500 cancer deaths, 321,400 were men and 312,100 were women. Cancers of cervix (12%), breast (9%), lung (8%) and oral cavity (8%) were the most common causes of cancer deaths. The major causes of cancer deaths in men were the cancers of lung (13%), pharynx (11%) and oral cavity (10%) while in women, cancer of cervix (23%), breast (17%) and ovary (6%) amounted to half of the cancer deaths (Figures 7, 8, 9) (Ferlay et al., 2010).

1.2.3 Prevalence

In India, at the end of 2008, about 1.71 million people (adult population), diagnosed with cancer within the five years earlier were alive. While 1.09 million of them were women, 0.62 million were men (Figures 7, 8, 9) (Bray et al., 2012, 2013).

1.3 CAUSES OF CANCER

According to WHO (2009), cancer is the result of the interaction between a person's genetic factors and three categories of external agents, called carcinogens.

1.3.1 Genetic Factors

Alteration in certain important genes results in production of faulty proteins which may directly or indirectly lead to cancer. These genes can be broadly classified into the following categories:

1. Oncogenes: These are the genes which promote cell proliferation and stop cell death. Defects in their regulation result in cancer.

2. Tumour suppressor genes: These genes are protective in nature and normally limit the development and/or growth of tumours; when a tumour suppressor gene is mutated, it may fail to prevent a cancer from growing.

3. DNA mismatch repair genes: These genes maintain integrity of the genome and the fidelity of information transfer from one generation of cells to the next. Loss of function of DNA mismatch repair genes could make a cell error-prone and lead to cancer.

Some examples of genes involved in cancerous development are: BRCA1 in inherited breast and ovarian cancer; colon cancer and prostate cancer; BRCA2 in inherited breast cancer in women, also male breast cancer; HER2/neu/ERBB2 in non-hereditary breast cancer; p53 in leukaemia, breast carcinomas, sarcomas, brain
tumours, head and neck squamous carcinomas and Barrett’s adenocarcinomas; P65 in breast and prostate cancers, CDK4 in certain non-hereditary cancers, Rb1 in retinoblastoma, etc. (WHO, 2009).

1.3.2 Carcinogens
Exposure to certain environmental factors can cause mutations which may lead to cancers. These may be broadly classified as:

1. **Physical carcinogens:** Physical agents such as ultraviolet and ionizing radiations are reported to cause cancer on excessive exposure.

2. **Chemical carcinogens:** Chemicals like asbestos, components of tobacco smoke, aflatoxin (a food contaminant) and arsenic (a drinking water contaminant) also increase the risk of cancer development.

3. **Biological carcinogens:** Biological agents of cancer include viruses, bacteria or parasites. Some examples of infections associated with certain cancers are:
   a. **Viruses:** Hepatitis B and liver cancer, Human Papilloma Virus (HPV) and cervical cancer, and human immunodeficiency virus (HIV) and Kaposi sarcoma.
   b. **Bacteria:** *Helicobacter pylori* and stomach cancer.
   c. **Parasites:** *Schistosomiasis* and bladder cancer.

1.3.3 Other Factors
Apart from genetic and environmental factors, some lifestyle factors also influence the risk of cancer a person has. Some of these factors are:

1. **Ageing:** Incidences of non-communicable diseases, especially cancer, increase with the percentage of aged population of a country, most likely due to a buildup of risks for specific cancers that increase with age. The overall risk accumulation is combined with the tendency for cellular repair mechanisms to be less effective as a person grows older. Control of communicable diseases and alterations in lifestyles have increased the life expectancy of the population and, thus, more of the population is at risk of developing cancer.

2. **Tobacco use:** Tobacco consumption is the world’s most avoidable cause of cancer. In most developed countries, smoking is the cause of up to 30% of all cancers. Globally, it is responsible for more than 80% of lung cancers in men.
and 45% in women. It also causes cancer of throat, mouth, pancreas, bladder, stomach, liver and kidney (Stewart & Kleihues, 2003).

3. **Alcohol use:** Excessive consumption of alcohol increases the risk of cancers of oral cavity, pharynx, larynx, oesophagus, liver and breast.

4. **Diet:** In developed countries, almost as many cancer cases are attributable to an unhealthy diet and an inactive lifestyle as to smoking.

In high-income countries, tobacco use, alcohol use, and being overweight or obese are major risk factors for cancer while ageing, tobacco use, alcohol use, low fruit and vegetable intake, and chronic infections from hepatitis B virus (HBV), hepatitis C virus (HCV) and some types of Human Papilloma Virus (HPV) are leading risk factors for cancer in low-income and middle-income countries. Cervical cancer, which is caused by HPV, is a leading cause of cancer death among women in low-income countries. Thus, due to these factors cancer has become one of the main health issues in India and other developing countries. Total cancer burden in India for all sites is estimated to increase from 948,900 new cases per year to 1,400,000 cases by 2026 (NCCP, 2001).

### 1.4 EARLY DETECTION: THE KEY TO REDUCING CANCER MORTALITY

Cancer death rates are high as it is usually detected in advanced stages and has metastasized to such an extent that very little can be done to save the patient from their impending death. Treatment is more effective when cancer is detected while it is still in a localized (pre-metastasis) state. Therefore, early detection and treatment is the key to cancer control and can decrease more than one-third of the global cancer burden. The two major components of early detection of cancer are: early diagnosis and screening.

#### 1.4.1 Early Diagnosis

Recognizing the warning signs and symptoms of cancer and taking prompt action can help diagnose and treat the disease before it becomes advanced. Thus, increased awareness of possible warning signs of cancer can have a great impact on controlling the disease burden. Some of the warning signs of cancer are: lumps, sores that fail to heal, abnormal bleeding, persistent indigestion, and chronic hoarseness.
Early diagnosis is especially relevant for cancers of the breast, cervix, mouth, larynx, colon and rectum, and skin (WHO, 2013a). Early diagnosis programmes are quite relevant in low-resource settings where most of patients are diagnosed in advanced stages and where there is no screening.

1.4.2 Screening

Screening refers to the use of simple tests across a healthy population in order to identify individuals who have disease, but do not yet have symptoms or are at a risk of developing a disease. It intends to identify individuals with abnormalities suggestive of cancer or a risk of developing a cancer and refer them promptly for diagnosis and treatment. It is especially effective for frequent cancer types for which a cost-effective, affordable, acceptable, and accessible screening test is available to the majority of the population at risk. Mammography for breast cancer screening and PAP smear test for cervical cancer screening have been very effective tools in reducing the mortality rates of these cancers (WHO, 2013).

1.4.3 Biomarkers for Cancer Screening

While earlier, a lot of emphasis was laid upon finding the cure of cancer, nowadays, attention is being shifted towards the early diagnosis of cancer so that the disease can be nipped in the bud itself. With this new approach biomarkers have come into prominence as the application of cytogenetic biomarkers represents the essential next step of screening of the whole population for individuals at risk of having cancer.

Valid biomarkers may be used for the timely identification of increased cancer risk, and can be used in the prevention or control of disease. The assumption that the observed relationship between exposure and the marker will translate into a similar relationship between exposure and disease supports the use of a biomarker as a surrogate of disease (Schatzkin et al., 1990). Micronucleus (MN) assay and single cell gel electrophoresis (comet assay) are amongst the latest biomarkers employed for the assessment of genetic damage and the identification of possible cancer risk.

India is expected to overtake China to become the world’s most populated country. With an increasing average age of the population, greater exposure to environmental carcinogens, chemicals from industry and continued tobacco use, the number of cancer incidences is expected to rise substantially (Murthy et al., 2008). In spite of this and a large number of cancer casualties every year, there is a wide gap
between the disease burden and the share of research performed in India. Even with large population size, very little is known about the epidemiology of cancer as the data on the prevalence of cancer in India is limited, considering the socioeconomic and rural-urban disparity and the great cultural, geographical and racial diversity of India.

In India, more that 80% of the cancer patients report to cancer care facilities in the advanced stage of disease which makes it incurable. Therefore, early detection is very important to reduce cancer morbidity and mortality. Tests like, Pap smear test for cervical cancer and mammography for breast cancer have shown good results, but due to their high costs and the requirements of skilled professionals and infrastructure, these tests are being employed for mass screening in a few developed countries, only. Therefore, in developing countries like India, it is imperative to have cost effective mass screening tests to identify the individuals at higher risk of developing cancer, who may be further subjected to confirmatory tests.

1.5 OBJECTIVES

Keeping in view the above shortcomings, the aim of the present study was planned to investigate the levels of genetic damage in the peripheral blood lymphocytes (PBLs) and buccal epithelial cells of cancer patients with following objectives:

1. To make an epidemiological survey of the proposed human subjects.
2. To look for DNA damage, if any, in the proposed subjects along with healthy matched controls.
3. To compare the frequency of micronuclei in buccal epithelial cells of the diseased persons with controls.
4. To provide a baseline data for further studies in this field.